MITOCHONDRIA AND REACTIVE OXYGEN SPECIES IN AGING AND AGE-RELATED DISEASES

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ABSTRACT

Aging has been linked to several degenerative processes that, through the accumulation of molecular and cellular damage, can progressively lead to cell dysfunction and organ failure. Human aging is linked with a higher risk for individuals to develop cancer, neurodegenerative, cardiovascular, and metabolic disorders. The understanding of the molecular basis of aging and associated diseases has been one major challenge of scientific research over the last decades. Mitochondria, the centre of oxidative metabolism and principal site of reactive oxygen species (ROS) production, are crucial both in health and in pathogenesis of many diseases. Redox signaling is important for the modulation of cell functions and several studies indicate a dual role for ROS in cell physiology. In fact, high concentrations of ROS are pathogenic and can cause severe damage to cell and organelle membranes, DNA, and proteins. On the other hand, moderate amounts of these species are essential for the maintenance of several biological processes, including gene expression. In this review, we provide an update regarding the key roles of ROS-mitochondria crosstalk in different fundamental physiological or pathological situations accompanying aging and highlighting that mitochondrial ROS may be a decisive target in clinical practice.

Key words: mitochondria, ROS, antioxidant defense, aging, age-related neurodegenerative disorders, mitochondrial dysfunction-related pathologies, anti-ROS intervention

ROS and aging

Proposed in 1954, by Denham Harman, the Free Radical Theory of Aging (FRTA) was the first attempt to link aging and oxidative stress (Harman, 1956). Later on, in 1972, this theory was revised, and the same author developed the Mitochondrial Free Radical Theory of Aging (MFRTA) (Harman, 1972; Schriner *et al.*, 2005), which states that mitochondrial dysfunction and consequent increased ROS production results in a vicious cycle contributing to cellular damage and consequent cell death. Although his theory was initially received by his peers with rebuttal, we know nowadays that ROS are important during the aging process. In fact, these highly reactive oxygen-derived molecules produced during aerobic metabolism can interact with cellular components, causing cumulative oxidative damage along time which may thus plausibly reduce lifespan (Harman, 1956). Oxidative damage to DNA genomes, proteins, and lipids has been associated with elevated ROS production, mitochondrial function impairment and ultimately cell senescence or death (Bokov *et al.*, 2004; Sohal , Weindruch, 1996). Of particular importance, the close proximity between ROS production sites and mitochondrial DNA (mtDNA) can favor the accumulation of oxidative stress-associated DNA damages. Elevated ROS production has been correlated with mitochondrial oxidative damage, along with a reduction of mitochondrial copy number (Cocheme *et al.*, 2011; Herbener, 1976; Lambert *et al.*, 2007; Yen *et al.*, 1989). These alterations are associated with an increased mutation rate of mtDNA in brain, liver and muscle fibers of aged individuals (Cahill *et al.*, 2005; Corral-Debrinski *et al.*, 1992; Fayet *et al.*, 2002; Raha , Robinson, 2000; Yen *et al.*, 1991). Interestingly, the establishment of the mutator mouse model allowed the demonstration of a direct correlation between an increased number of mtDNA mutations and a decreased mitochondrial respiratory chain activity (Trifunovic *et al.*, 2004). For instance, these alterations were accompanied by the development of typical symptoms of aging in humans, namely hair loss, weight and fat reduction, decreased bone density and cardiomyopathy (Trifunovic et al., 2004).

Aging has been also associated with a decline of antioxidant defense efficiency, which together with increased ROS production significantly contributes to a manifestation of an oxidative stress state. This in turn can initially disturb enzyme activity through reversible oxidation of thiol groups, but which ultimately can lead to a more profound alteration in biomolecule structure and integrity (Freitas *et al.*, 2016). Consistent with this, overexpression of antioxidant enzymes decreases ROS production and protects DNA from harmful ROS effects, which is associated with a prolonged life span in *Drosophila melanogaster* (Orr , Sohal, 1994; Schriner et al., 2005). Moreover, it has been found that long-lived mice strains possess higher level of antioxidant enzymes and have reduced oxidative damage of proteins and lipids (Pamplona *et al.*, 2002; Rebrin ,

Sohal, 2004). Interestingly, the reduced oxidative damage in long-lived species could be explained by an adaptive mechanism of cysteine depletion in mitochondria (Moosmann , Behl, 2008).

Despite the numerous studies supporting Harman's ROS theory of aging, other discoveries are questioning a direct correlation between oxidative stress damages and the life span. Using *Caenorhabditis elegans* as a model, mitochondrial mutations had no effect on overall ROS despite an increase of mitochondrial superoxide level (Yang , Hekimi, 2010). Surprisingly, the above-mentioned study reported a positive correlation between mitochondrial oxidative stress and the extension of life span (antioxidants supplementation shortened life span of mutants). Similarly, a number of recent works using mice models have also questioned the validity of ROS as the cause of an aged phenotype. Lapointe and Hekimi showed that a reduced level of mitochondrial enzyme MCLK1 causes mitochondrial dysfunction manifested as a reduction of electrons transport through mitochondrial respiratory chain and decrease of tricarboxylic acid (TCA) cycle activity. All these events are accompanied by increased mitochondrial oxidative stress but decreased oxidative damage to cytosolic proteins as well as reduced level of isoprostanes in plasma (systemic biomarker of aging and oxidative stress) (Lapointe , Hekimi, 2008). Additionally, the silencing of antioxidant enzymes such as mitochondrial SOD2 (manganese superoxide dismutase; also called MnSOD) and GPx-1 (Glutathione peroxidase-1), did not affect longevity in spite of increased oxidative stress (Perez *et al.*, 2009a; Zhang *et al.*, 2009). It thus seems that there is not sufficient evidence to undermine credibility of the free radical theory of aging however the contradictory studies have been rather supporting for a new recent theory named mitohormesis. According to this theory, moderate levels of mitochondrial ROS could activate compensatory mechanisms that protect cellular organelles from the deleterious effects of ROS and ultimately, delaying the appearance of an aging phenotype (Ristow , Zarse, 2010). For instance, moderately increased levels of ROS have been linked to an extension of longevity in *D. melanogaster* and in young mice (Copeland *et al.*, 2009) (Basisty *et al.*, 2016; Csiszar *et al.*, 2008). The discovery that the reduction of elevated mitochondrial ROS levels protects against age-related decline in old mice (Basisty et al., 2016) implies that a decrease of ROS levels could be a determinant factor to delay progression of diseases parallel to the extension of life span in mammals in more advanced ages (Schriner et al., 2005). For example, administration of an antioxidant N-acetylcysteine (NAC) has been shown to prevent the loss of activity (observed during aging) of complexes I and IV (Miquel *et al.*, 1995). Moreover, supplementation with antioxidant compounds selegiline and vitamin E (Vit-E) alone or in combined therapy showed to delay Alzheimer disease (AD) progression in human subjects (Sano *et al.*, 1997). In conflict with the mentioned studies, some evidence reported that antioxidant therapies may not be universally beneficial in the prevention of age-related diseases. While Vit-E did not show to

protect or delay Parkinson's disease (PD) progression (Parkinson Study, 1993), this antioxidant compound was even deleterious in AD patients (Lloret *et al.*, 2009). The finding that not all patients respond similarly to the antioxidant therapy is consistent with the requisite of moderate level of ROS to induce stress resistance adaptation. As opposed to the controversial effects of dietary antioxidant compounds, caloric restriction is a promising therapeutic strategy able to retard or prevent aging in several species ranging from worms to humans (Hekimi , Guarente, 2003; Sohal , Weindruch, 1996). The mechanism underlying these effects is not completely understood. Although, evidence supported the role of ROS as inducers of mitochondrial oxidative stress adaptations, including a marked increase in mitochondrial function through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and mitochondrial NAD-dependent deacetylase sirtuin-1 (SIRT1) activation (Nisoli *et al.*, 2005). Likewise, endurance training may cause increased levels of ROS, which induce cellular signaling pathways associated to the function and turnover of mitochondria, hence contributing to the extension of life span (Lanza *et al.*, 2008; Ristow , Zarse, 2010).

Intracellular sources of ROS

Uncontrolled ROS production may lead to the oxidation of fundamental cellular components, such as proteins, phospholipids, and nucleic acids. Ultimately, ROS (hydroxyl radical, •OH; superoxide anion, $O_2^{\bullet-}$; hydrogen peroxide, H_2O_2; alkoxyl and peroxyl radicals, as well as singlet oxygen) can not only modify enzyme activity, but also result in profound alterations in biomolecular structure. Cellular components can be also modified by products of free radical reaction intermediates such as peroxynitrite (formed by the reaction of nitric oxide with superoxide anion) or lipid hydroperoxides (prominent non-radical intermediates of lipid peroxidation produced by the reaction of an hydroxyl radical with unsaturated fatty acids). Although ROS are generally seen as harmful agents that need to be removed by detoxification mechanisms, the truth is that some of these species, most notably H_2O_2, play a physiological role in cell homeostasis, functioning as signaling molecules. This is still a controversial concept since the specificity of ROS action is unclear due to the high reactivity of some of the species towards many macromolecules, the covalent nature of modifications they bring, and the limited (in some cases) spatial effects of some of the species. Nevertheless, it is accepted that some ROS regulate their own demise through up-regulation of ROS detoxification enzymes (D'Autreaux , Toledano, 2007). Under physiological conditions, ROS can act as mediators and regulators of cell metabolism, by interfering with the transmission of signals to and throughout the cell. Specific ROS such as H_2O_2 and $O_2^{\bullet-}$ are important second messengers in growth, differentiation and cell death, activating proteins involved in cell

division (mitogenic activated protein) and participating in the immune response of the organism. By affecting the synthesis, release, or inactivation of the endothelium-derived relaxing factor (EDRF), ROS may cause the relaxation or contraction of the vascular wall. In addition, ROS can increase the permeability of the capillary walls, stimulate transport of glucose into cells and of serotonin into platelets (Droge, 2002). Furthermore, H_2O_2 regulates the expression of many genes, including AP-1, CREB, HSF1, NRF2, HIF-1, TP53, NF-κB, NOTCH, SP1 or SCREB-1 (Marinho *et al.*, 2014; Sies, 2017). Finally, it has been demonstrated that peroxides may regulate the synthesis of prostanoids (Korbecki *et al.*, 2013).

Mitochondria are considered one of the important sources of ROS and these, when produced extensively during pathological conditions, can evoke intracellular oxidative stress, leading to the aforementioned damage. ROS over-production in cells may cause disruption of tissue and organ function, leading to different pathologies or even premature death of the organism. Not surprisingly, mitochondria are both producers and targets of ROS. So far, several distinct sites of ROS production in mammalian mitochondria have been identified. The two sites that have been most extensively studied are complexes I and III of the mitochondrial respiratory chain, with the focus on the mechanistic role of the ubiquinone cycle in promoting univalent oxygen reduction (Brand, 2010; St-Pierre *et al.*, 2002). Traditionally, complex II was not considered a source of ROS *per se*, instead it was described to contribute to their formation via its substrate, succinate. In many tissues, succinate plays a role in reverse electron transfer, the process in which electrons are transferred from succinate to ubiquinone via complex II and then back to complex I (Liu *et al.*, 2002; Yankovskaya *et al.*, 2003). Despite this, it has been suggested that Complex II alterations with tissue aging would be responsible for $O_2^{\bullet-}$ production (Ishii *et al.*, 2011). The hypothesis concerning the involvement of complex II in ROS production is discussed later in the context of diabetes (Nishikawa *et al.*, 2000), and skin aging (Anderson *et al.*, 2014). Moreover, it was suggested that mutation in complex II might also result in $O_2^{\bullet-}$ overproduction (Ishii *et al.*, 2005). Additionally, Paddenberg *et al.* investigated the role of mitochondrial complex II in ROS production, showing that complex II plays an essential role during hypoxia. At reduced oxygen tension, catalytic activity of complex II switches from succinate dehydrogenase to fumarate reductase, with this alteration being associated with increased ROS production (Paddenberg *et al.*, 2003a; Paddenberg *et al.*, 2003b; Yankovskaya et al., 2003). Reports indicate that the magnitude of the transmembrane electric potential regulate ROS generation by the respiratory chain (Korshunov *et al.*, 1998), which has been shown to depend on the AMP-activated protein kinase (AMPK) activity (Weisova et al., 2012), while others presented evidence against this relationship between mitochondrial polarization and ROS production (Shabalina , Nedergaard, 2011).

It is important to note that mitochondria are not the only ROS-producing organelles in the cell. Microsomal enzymes including the cytochrome P450 system (Bhattacharyya *et al.*, 2014), peroxisomal enzymes xanthine oxidase, polyamine oxidase, sarcosine oxidase and different types of acyl-CoA oxidases (Bonekamp *et al.*, 2009), as well as and some enzymes in the plasma membrane (NADPH oxidase and lipooxygenase) (Bedard , Krause, 2007; Shintoku *et al.*, 2017) have been identified as non-mitochondrial ROS generators. Despite the fact that Brown and Borutaite presented a number of examples supporting the hypothesis that mitochondria are not the primary source of ROS (Brown , Borutaite, 2011), oxidative phosphorylation accounts for 90-95% of cellular oxygen consumption. Although it is difficult to make an exact assessment because of frequent artifacts with the use of fluorescence-based redox-sensitive dyes, it is now considered that the initial idea that 1-4% of oxygen consumption is converted into $O_2^{\bullet-}$ is wrong, as most of the original works were performed with mitochondrial inhibitors (Chance *et al.*, 1979). More recent work brought down the value to 0.15%, with $O_2^{\bullet-}$ being generated at distinct topologies at the respiratory chain, notably at Complex I and III (Quinlan *et al.*, 2013; St-Pierre et al., 2002). Although it may seem a very small amount, 0.15% of total oxygen consumed represents a significant amount of $O_2^{\bullet-}$ produced and therefore should not be omitted, when considering mitochondria as a ROS producer under physiological and pathological situations (Fridovich, 2004). Other documented sources of ROS in mitochondria include monoamine oxidase and dihydroorotate dehydrogenase (Cadenas , Davies, 2000; Lenaz, 2001). The former enzyme was previously demonstrated to be involved in oxidative damage in myocytes from patients with collagen V myopathies (Sorato *et al.*, 2014). In addition, the flavoproteins acyl-CoA dehydrogenase and glycerol phosphate dehydrogenase can produce ROS in tissues during the oxidation of lipid-derived substrates (Lambertucci *et al.*, 2008; St-Pierre et al., 2002). Both pyruvate and α-ketoglutarate dehydrogenase contain flavoenzyme-dihydrolipoyl dehydrogenase subunits and are additional ROS sources (Starkov *et al.*, 2004; Tahara *et al.*, 2007). Mitochondria, as both a generator and target of ROS, accumulate some of the damage that can initiate a vicious circle of further ROS formation. The age-dependent handicapping of mitochondrial energetics is related to the accumulation of defective mtDNA as well as defective respiratory chain complexes that are prone to electron leakage (Linnane *et al.*, 1989; Wei, 1992).

Mitochondria as a source and target for ROS in aging: an interventional review

As mentioned above, approximately five decades ago, coincident with the postulation of the "free radical theory of aging", increased formation of ROS was proposed to be the major factor responsible for the aging process and decreased lifespan (Harman, 1956). The continuous

generation of ROS by mitochondria throughout cell life produces an age-related chronic oxidative stress, especially on mtDNA, resulting in oxidative modification of bases or deletions (Santos *et al.*, 2013). As a consequence, mitochondria have been identified as key players in the aging process (Miquel *et al.*, 1980). However, new findings in the last years suggested that ROS generation cannot be the initial trigger of the aging process, providing an alternative point of view to the Harman's hypothesis. One of the stronger evidence in this lack of mechanistical linkage is the lack of effect on lifespan of under- or overexpressing a large number and wide variety of genes coding for antioxidant enzymes (Perez et al., 2009a). Also, a recent study showed that oxidative damage of cardiomyocytes did not positively correlate with age in human beings, although the samples were obtained from a restricted age span (<2 years old) (Huang *et al.*, 2017). In order to have a thorough knowledge on this topic, we refer the readers to very relevant review articles (Gems , Partridge, 2008; Hekimi *et al.*, 2011; Ristow , Schmeisser, 2011). In this section, we want to discuss the "canonical" association between ROS production and aging, with particular relevance on caloric restriction, which represents the most convincing intervention to delay aging and attenuate age-related disease in multiple species.

Mitochondrial function during aging has been described to decrease, especially at advanced ages. Different studies showed a decline at multiple levels, ranging from decreased activity of the respiratory chain and ATP synthase, Krebs cycle fluxes, oxidative alterations of cardiolipin, disrupted regulation and defective mtDNA regulation and activity, among other described effects (de Almeida *et al.*, 1989; Emelyanova *et al.*, 2017; Petrosillo *et al.*, 2009; Rottenberg , Hoek, 2017). A recent model describes a biphasic model in which an initial increase in mitochondrial function in middle-age is followed by a fast decline at older ages (Baker , Peleg, 2017). As already mentioned, a significant number of studies in different model organisms suggest that inhibition of oxidative stress contributes to an increase in lifespan. Administration of Vit-E was previously shown to extend the lifespan of many animals, including the nematode *Caenorhabditis elegans* (Harrington , Harley, 1988); male mice receiving Vit-E from 28 weeks of age showed a 40% increased median lifespan, with a beneficial effect on aging-related decline in neurological performance and mitochondrial function. The activities of mitochondrial nitric oxide synthase and SOD2 decrease with age, whereat these effects are ameliorated by Vit-E treatment (Navarro *et al.*, 2005). A class of Vit-E analogues, called tocotrienols, possess excellent antioxidant activity *in vitro* and have been suggested to suppress ROS production more efficiently than tocopherols (Schaffer *et al.*, 2005); tocotrienols extend lifespan by reducing ROS damage (Collins *et al.*, 2006). Despite this, antioxidants have had limited success in preventing the progression of diseases involving mitochondrial oxidative damage, probably because they distribute around the body, with only a

small fraction being accumulated by mitochondria (Serviddio *et al.*, 2011). To overcome this problem, lipophilic cations have been conjugated with several antioxidants in order to allow their specific accumulation inside mitochondria. MitoVitE is one of the first mitochondria-targeted antioxidants, rapidly taken up by mitochondria (Smith *et al.*, 2003). In cerebellar granule cells, MitoVitE mitigated EtOH-induced accumulation of intracellular oxidants and counteracts suppression of glutathione peroxidase/glutathione reductase functions and overall cellular glutathione levels (Siler-Marsiglio *et al.*, 2005). MitoQ was reported to significantly increase the lifespan of SOD-deficient flies and to improve their tolerance to paraquat stress, but it could neither increase the lifespan nor rescue the paraquat sensitivity of wild type *D. melanogaster* (Magwere *et al.*, 2006). Moreover, MitoQ was shown to be effective as an antioxidant when complex I-derived superoxide generation is already elevated due to disrupted electron flow, whereas it has a pro-oxidant role in intact cells with normal Complex I activity. Consequently, MitoQ may be useful in the treatment of diseases originating from impairment of respiratory chain complex I due to oxidatively damaged mtDNA, when its targeted delivery to pathogenic tissues is ensured (Plecita-Hlavata *et al.*, 2009). SkQ molecules, in which a plastoquinone molecule is bound to a positively-charged carrier, has also been attempted in the context of delaying aging/senescence effects in cells and tissues, with positive effects being obtained in the eye, heart and kidney (Skulachev *et al.*, 2009).

For several years, Coenzyme Q 10 (CoQ10), whose levels are affected during aging and neurodegenerative diseases, has been considered a key factor in the progression of aging-associated complications (Lopez-Lluch *et al.*, 2010). In rats fed a diet enriched in polyunsaturated fatty acids (PUFAs), supplementation with CoQ10 produces significant increases of mean and maximum lifespan, attenuating oxidative alterations related to this specific kind of diet (Quiles *et al.*, 2004). Furthermore, enrichment of cells with CoQ10 resulted in an ordering and condensing effect on cell membranes, leading to a decrease in ROS generation, and to a protective benefit on DNA integrity (Tomasetti *et al.*, 2001). On the other hand, different studies in *C. elegans* demonstrated that lowering CoQ10 content, by inactivating genes involved in ubiquinone biosynthesis (Asencio *et al.*, 2003) or by dietary deprivation (Larsen , Clarke, 2002), induces a significant lifespan increase. This discrepancy may be explained by considering that lifespan extension occurs with moderately low levels of global CoQ10 content (up to 50%), whereas severe CoQ10 depletion leads to developmental and reproductive inefficiency, with no extension in longevity. This interpretation is supported by the observation that the hallmark of CoQ10 deficiency syndrome is, obviously, a decreased CoQ10 concentration (about 30% or lower of the total coenzyme content, compared to healthy individuals) in human muscle and/or fibroblasts (Montero *et al.*, 2007). Moreover, CoQ10

concentration progressively declines after the age of 40, and, in rodents, this drop occurs even under dietary CoQ10 supplementation, suggesting a higher CoQ10 consumption. Thus, although lifelong CoQ10 supplementation did not prolong or shorten the lifespan of either wild type rats or mice (Lonnrot *et al.*, 1998), it may help to prevent lifespan shortening due to cumulative oxidative insults.

Use of antioxidants or targeting antioxidants to mitochondria by conjugation to lipophilic cations are not the only strategies to reduce oxidative damage and prolong lifespan **(Figure 1)**. Dietary factors, including restriction of caloric intake, restriction of protein or methionine intake, or the ingestion of specific nutrients, have been shown to alter mitochondrial redox metabolism, cellular oxidative stress and animal lifespan (Page *et al.*, 2010). An inverse correlation between longevity and mitochondrial ROS generation is demonstrated by three different studies in which H_2O_2 production by mitochondria isolated from liver, skeletal muscle, and brain was reduced in calorie-restricted rats (Bevilacqua *et al.*, 2004; Hagopian *et al.*, 2005; Sanz *et al.*, 2005). In particular, caloric restriction (CR) increased the efficiency of brain mitochondria in electron transfer in complex I, avoiding electron leak in that complex. Superoxide anion generated by complex I is specifically directed to the mitochondrial matrix, with consequent mtDNA damage and resulting bioenergetic deficits (Stefanatos , Sanz, 2011). The relationship between longevity and complex I is described in a report by Ayala *et al.*, in which liver mitochondria of calorie-restricted rats demonstrated reduced levels of complex I (Ayala *et al.*, 2007). Moreover, analysis of rat liver samples revealed a significant change in abundance in specific subunits of respiratory chain complexes I and IV with life-long CR, allegedly to minimize the electron leak and subsequent ROS formation (Dani *et al.*, 2010). Conversely, dietary restriction did not affect the activity of the oxidative-phosphorylation system or the mitochondrial H_2O_2 production in a similar rat strain (Valle *et al.*, 2007). Thus, more work is required to confirm whether modulation of complex I levels represents one mechanism by which mitochondrial ROS production is reduced in parallel with extended longevity.

CR also reduces oxidative stress through a mechanism involving the mitochondrial deacetylase sirtuin-3, SIRT3. Expression of SIRT3 is increased during CR, and SIRT3 reduces cellular ROS levels by regulating SOD2 through deacetylation of two critical lysine residues, promoting its antioxidant activity (Qiu *et al.*, 2010). However, there is some uncertainty regarding which acetylated lysine residue regulates SOD2 activity, and different groups proposed different sites-specific regulation of SOD2 by SIRT3 (for a complete review on sirtuins and redox stressors, see (Webster *et al.*, 2012)). Although the precise site(s) of regulation remains unclear, ROS levels are tightly controlled by SIRT3. Beyond SOD2, another important redox target of SIRT3 activity is

represented by $NADP^+$-dependent isocitrate dehydrogenase 2 (IDH2), found in mitochondria that catalyzes the oxidative decarboxylation of isocitrate to 2-oxoglutarate. In response to CR, SIRT3 activates IDH2, thereby increasing NADPH levels in mitochondria. This in turn leads to an increased ratio of reduced-to-oxidized glutathione and decreased levels of ROS (Someya *et al.*, 2010). The sites of SIRT3 deacetylation (K211 and K212) were found by Schlicker *et al.*, who showed that in the presence of NAD^+ purified SIRT3, but not SIRT5, deacetylated IDH2 and increased its activity (Schlicker *et al.*, 2008). Importantly, IDH2 deacetylation/activation mediated by SIRT3 has been linked to age-related hearing loss (AHL), whereat a calorie restricted diet reduces the age-related loss of neurons and hair cells, whereas this effect is abrogated in SIRT3-deficient mice (Someya et al., 2010). Association between CR, SIRT3, and IDH2 sustains the concept that oxidative stress is a major component of aging and that nutrient status can regulate the cellular response to degenerative pathologies.

A report by Morselli *et al.*, demonstrates how another component of the Sirtuin family, SIRT1, is required for the lifespan-prolonging effects of caloric restriction and resveratrol, through a mechanism that involves autophagy (Morselli *et al.*, 2010). Dietary delivery of resveratrol increases mitochondrial abundance and aerobic capacity in cultured endothelial cells and mice (Lagouge *et al.*, 2006). Interestingly, resveratrol is able to interact with different components of the respiratory chain: by competition with coenzyme Q, resveratrol is able to decrease complex III activity (Zini *et al.*, 1999), and a binding site on complex V/ATP synthase has been observed (Gledhill , Walker, 2005). In two different cellular settings, cardiomyocytes and dopaminergic neurons, resveratrol protected against oxidative stress and was able to maintain mitochondrial membrane potential (MMP), with both effects directly related to resveratrol-dependent increase in SOD2 activity (Danz *et al.*, 2009; Okawara *et al.*, 2007). In fact, resveratrol supplementation in the context of a high fat diet proved to be effective at elevating antioxidant capacity in the brain, resulting in an increase in both SOD2 protein levels and activity (Robb *et al.*, 2008). Interestingly, recent data showed regulation of SIRT3 activity by SIRT1-mediated de-acetylation, with aging demonstrated to be related with SIRT3 acetylation (Kwon *et al.*, 2017). Considering that SIRT3 regulates several mitochondrial metabolic pathways (Hirschey *et al.*, 2010; Pereira *et al.*, 2012), this discovery sheds light on a cytosolic-mitochondrial sirtuin-based crosstalk with important roles in mitochondrial alterations during aging.

Overexpression of SOD2 confers enhanced oxidative capacity and greater resistance against inducers of mitochondrial permeability transition (Silva *et al.*, 2005). Moreover, flies with severe reductions in SOD2 expression exhibited accelerated senescence of olfactory behavior as well as precocious neurodegeneration and neuronal DNA strand breakage (Paul *et al.*, 2007). Antioxidant

supplementation, such as with Vit-E and Vitamin-C (Vit-C), reduces oxidative stress, improves SOD2 activity, with consequent positive muscle work in chronically loaded muscles of aged rats (Ryan *et al.*, 2010). Furthermore, due to increased SOD2 expression, melatonin-treated animals showed an increase in active mitochondria population and the ability to restore the mitochondrial potential of age-damaged neurons (Garcia-Macia *et al.*, 2011). Interestingly, mice receiving intravenous SOD2-plasmid liposome prior to total-body irradiation show increased survival from the acute hematopoietic syndrome, and males demonstrate improved long-term survival (Epperly *et al.*, 2011). Given these observations, it appears surprising that different publications reported the failure of SOD2 overexpression in prolonging lifespan (Perez *et al.*, 2009b; Zhang et al., 2009), a discrepancy that future research on aging must address. Still, the controversy supports the notion that mitochondrial-produced ROS may have a duality of effects, which are at present difficult to fully understand.

SOD2 expression is also increased in p66Shc knockout mice, which exhibit prolonged lifespan (Haga *et al.*, 2008). Other genetic mouse models of longevity have been reported, such as Ames and Snell dwarf mice and $Igf1r^{+/-}$ female mice (for a review, see (Liang *et al.*, 2003)), and the increased lifespan of these models has been correlated to increased resistance to oxidative stress. To test the causative role of mtDNA mutations in aging, the mtDNA mutator mouse, which accumulates high levels of point mutations due to a proofreading deficiency of the mitochondrial DNA polymerase γ (POLG) has been developed. In this model, mtDNA mutations resulted in a variety of aging phenotypes, i.e. weight loss, alopecia, osteoporosis, anemia, reduced fertility, heart disease, progressive hearing loss and decreased spontaneous activity, but without inducing ROS production or increasing oxidative stress (Edgar , Trifunovic, 2009). This is not the case in p66Shc KO mice, in which oxidative stress play a crucial role. p66Shc is localized to mitochondria in about 20% of fibroblasts of higher organisms, and oxidative stress promotes a translocation of part of the cytosolic pool of p66Shc to mitochondria (Orsini *et al.*, 2004). Within mitochondria, inner mitochondrial membrane p66shc acts as a redox enzyme, with a consequent increment of ROS production and aging. The molecular route that leads to p66Shc activation and mitochondrial import was identified by our group in 2006 (Pinton *et al.*, 2007). p66Shc must be phosphorylated at serine 36 in order to be active (Migliaccio *et al.*, 1999), and this phosphorylation is mediated by PKCβ, a kinase of the PKC family, activated after an oxidative challenge. Once phosphorylated, p66Shc can be recognized by Pin1, a peptidyl-prolyl isomerase that induces cis-trans isomerisation of phosphorylated Ser-Pro bonds, causing mitochondrial translocation of p66Shc (Pinton et al., 2007). At this point, p66Shc can exert its oxidoreductase activity, generating H_2O_2 and inducing the opening of the permeability transition pore (PTP) **(Figure 2)**. In turn, this event perturbs

mitochondrial structure and function (as revealed by the reduced Ca^{2+} responsiveness and the alteration of mitochondrial three-dimensional structure (Pinton , Rizzuto, 2008)). A novel cyclophilin-binding agent, Debio 025, was demonstrated to inhibit cyclophilin D (a component of PTP) without having immunosuppressive effects (Ptak *et al.*, 2008). It has been recently reported that Debio 025 was able to normalize mitochondrial function, muscle apoptosis, and ultrastructural defects in $Col6a1^{-/-}$ myopathic mice (Tiepolo *et al.*, 2009), and it may represent a novel therapeutic opportunity to extend lifespan, minimizing oxidative stress-induced damages typical of aging.

ROS, mitochondrial DNA and aging

Human mtDNA is a circular, double stranded molecule consisting of 16,569 base pairs (for a review see (Lauri *et al.*, 2014)). Thirteen mitochondrial proteins (subunits of the electron transport chain, ETC), 22 tRNA molecules, and 2 rRNA species are encoded in this DNA molecule. Depending on the cell type, there are a few to several hundreds of mitochondria per cell, and from a few to several (on average) mtDNA copies in each mitochondrion. This gives the number of about $10^3 – 10^4$ mtDNA molecules per cell, on average (Lauri et al., 2014). The mtDNA is replicated by DNA polymerase γ that is encoded by the chromosomal *POLG* gene. All mtDNA molecules in one mitochondrion and in the cell can have exactly the same nucleotide sequence, which is called homoplasmy. However, occurrence of different variants of mtDNA (i.e. both wild-type and those containing point mutations or deletions) is referred to as heteroplasmy.

In evolution, mitochondria appeared as a result of a symbiosis between α-proteobacterium and an eubacterium, which was a milestone in the formation of eukaryotic organisms (Otten , Smeets, 2015) and references therein). Creation of mitochondria, which still, after billions of years of evolution, contain their own DNA, allowed producing a large amount of ATP in the cell. However, the price for this advantage is the production of large amounts of ROS, which can be deleterious for mitochondria and the whole cells. Recent analysis (Otten , Smeets, 2015) provided interesting conclusions about differences in evolutionary strategies of mtDNA between plants, fungi and animals. Plants have much larger mtDNAs than animals, with fungal mitochondrial genomes being in between. In plant cells, mtDNA occurs in a low copy number while recombination is quite efficient. Moreover, anti-ROS mechanisms are efficient. Contrary to plants, animals have small mitochondrial genomes, recombination is very rare if any, and mtDNA is prone to mutagenesis. However, relatively high copy number of mtDNA per cell allows to compensate for effects of deleterious mutations in a few mtDNA copies, while providing opportunity to adapt animals, the active creatures, efficiently to various and changing environmental conditions. Nevertheless, the cost of such a strategy is accumulation of mutations in mtDNA during the life. As a consequence,

mitochondrial diseases can appear in further generations. Since such diseases are generally rare, this is an acceptable event for a population, which benefits from increased adaptive possibilities. However, many mutations in mtDNA contribute also to aging of cells and organisms. Again, this is not dangerous for a population, as aging occurs after the time of a reproductive peak, but has a serious consequence for elderly individuals.

The MFRTA has been proposed over 60 years ago, and has been reviewed many times (see, for example (Lee , Wei, 1997; Wei, 1998; Wei *et al.*, 2001)). The main assumption of this theory is that mtDNA is not protected by histones, thus, it is more prone to lesions caused by ROS. Since mitochondria are one major source of ROS, actions of these agents lead to accumulation of mutations in mtDNA. This, in turn, may cause dysfunctions of ETC, which result in even more efficient production of ROS. Such a positive feedback, called also the vicious cycle, has been considered the major cause of mitochondrial destruction, then cell functions' inefficiency, and finally apoptosis of cells and aging of the organism (summarized by (Guest , Russell, 1992; Lee , Wei, 1997; Wei, 1998)). The importance of the role of ROS production in aging may be also supported by the observed age-related decreases in activities of several antioxidant enzymes which could reflect overall accumulation of oxidized proteins with age (Stadtman, 1992, 2006). Nevertheless, even at the mature state of this theory, there were some problems which were difficult to explain. For example, considering that phenotypic manifestation of the mtDNA mutation occurs only when a threshold level is exceeded, usually 60–80% heteroplasmy, depending on the type of mutation (Rossignol *et al.*, 2003), it was difficult to explain how aging can be provoked by mutations in a low fraction of damaged or mutated mtDNA molecules of about 1-5%, which was determined experimentally (Lee , Wei, 1997).

What kind of mutations occurs predominantly in mtDNA? There are both base pair substitutions and deletions (reviewed by (DeBalsi *et al.*, 2017; Lauri et al., 2014)). Molecular mechanisms of appearance of such mutations in mtDNA have been excellently summarized and deeply discussed recently(Szczepanowska , Trifunovic, 2017), thus, they will be mentioned only shortly here. Nevertheless, one should also note that mtDNA depletion (a decrease in the copy number of mtDNA, not necessarily associated with mutations in this molecule; see for example (Weglewska *et al.*, 2005)) may also occur is cells of aging organisms. It was considered that formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), caused by ROS production by Complex I, is the major mutator causing base substitutions in mtDNA. ROS-mediated conversion of guanosine to 8-oxodG appears to be a particularly efficient process, and since 8-oxodG pairs with adenine instead of cytosine, the next replication round results in creation of the G to T transversion. Moreover, ROS cause breaks in DNA strands, which is a prerequisite to formation of

deletions. In fact, early studies on mtDNA in a mouse model indicated that a particular deletion of 4236 base pairs in mtDNA, and 8-oxodG were abundant in mitochondria from old mice while absent in young animals (Muscari *et al.*, 1996). Accumulation of mtDNA deletion of 4977 bp was reported to increase with age (between 32 and 82 years) in neurons from the human brain (Soong *et al.*, 1992). It was supposed that mtDNA should be prone to ROS-mediated mutagenesis more than nuclear DNA since it is not protected by histones, while it is located close to the ROS production site, i.e. Complex I in mitochondrion. However, more recent studies, in which the Duplex Sequencing method was used, allowing to detect one mutation per 10^7 DNA molecules, provided evidence against these early assumptions (Kennedy *et al.*, 2013). When mtDNA was isolated from human brains of old (over 80 years old) and young individuals, the frequency of substitutions in DNA was about 5-fold higher in elderly people. However, the frequency of the G to T transition, which is often used as a marker of ROS-mediated mutations, did not increased with age. On the other hand, in both young and old individuals, transition mutations predominated (Kennedy et al., 2013). Moreover, similar analyses performed in mice indicated that the frequency of mutations in mtDNA appears to be an order of magnitude lower than that reported in earlier studies with the use of significantly less sensitive methods (Vermulst *et al.*, 2007). Such results suggest that errors made by DNA polymerase γ, the only DNA polymerase present in mitochondria (though encoded by nuclear DNA) and responsible for replication of mtDNA, may be responsible for most of the mutations in mtDNA appearing during the whole life.

Other results that are against the early MFRTA theory came from advanced microscopic studies. Contrary to previous assumptions, it appeared that mtDNA is not "naked", but instead, it is covered by the TFAM (transcription factor A) protein which together with DNA forms a nucleoid-like structures (Kukat *et al.*, 2011). Moreover, it was reported that mtDNA may be separated from sites of ROS production in mitochondria due to micro-compartmentalization of the matrix (Appelhans *et al.*, 2012). In fact, by using sensitive methods for detection of mutations, it was found that frequencies of stable genetic changes in mtDNA are similar to those detected in nuclear DNA (Anson *et al.*, 2000; Lim *et al.*, 2005), rather than higher as presumed on the basis of earlier studies in which small amount of mtDNA was a limiting factor for detailed analyses.

The milestone in studies on mutations in mtDNA was construction of mice which produce DNA polymerase γ with deficiency in the proofreading function. Such mice constructed independently by two teams (Kujoth *et al.*, 2005; Trifunovic et al., 2004) accumulate highly elevated number of mutations relative to wild-type animals, which allows detailed studies on mitochondrial mutagenesis *in vivo.* In these animals, no correlation could be found between number of accumulated mutations in mtDNA and oxidative stress markers (Kujoth et al., 2005). Rather, an

increasing number of mutations in mtDNA correlate with aging without influence of the oxidative stress (Trifunovic et al., 2004). Subsequent studies indicated that accumulation of mutations in mtDNA by mice with mutator DNA polymerase γ occurred linearly with age, while production of ROS was at the level comparable to that in wild-type animals (Trifunovic *et al.*, 2005). Therefore, one might suppose that errors made by DNA polymerase γ, rather than ROS-mediated DNA lesions, are the major cause of mtDNA mutations. It was proposed that during aging, their accumulation arise due to clonal expansions of particular mutated mtDNA molecules, rather than due to ongoing ROS-mediated mutation events (Wiesner *et al.*, 2006).

This theory, alternative to MFRTA, received some additional experimental support. Studies on cultured fibroblasts indicated that the T414G mutation in mtDNA has little effect on ROS production and cell aging, which is against the MFRTA theory (Birket *et al.*, 2009). On the other hand, another study on cultured fibroblasts demonstrated that a higher level of a deletion in mtDNA was accompanied with elevated concentrations of ROS (Quan *et al.*, 2015). In fact, there is still an extensive debate on which theory is valid. Still some experimental results might suggest that the old MFRTA is valid, i.e. that ROS cause significant numbers of mtDNA lesions which are accumulated in time due to defects in ETC and result in a constantly increasing ROS production, while other studies indicated that errors made by DNA polymerase γ during replication of mtDNA are the main source of mutations in the mitochondrial genome. The debate is ongoing, and definitely it is not finished. The reader is referred to recent review articles on this topic, for detailed discussions on the mechanisms which lead to accumulation of mutations in mtDNA during aging (Bautista-Niño *et al.*, 2016; Chih-Hao *et al.*, 2013; DeBalsi et al., 2017; Edgar , Trifunovic, 2009; Kim *et al.*, 2015; Kirkwood , Kowald, 2012; Lagouge , Larsson, 2013; Lauri et al., 2014; Lee , Wei, 2012; Pamplona, 2011; Szczepanowska , Trifunovic, 2017; Zapico , Ubelaker, 2013). In addition to the two theories mentioned in the preceding paragraph, a third one has been proposed recently. Studies based on the deep sequence analysis indicated that in the absence of overproduction of ROS and with no accumulation of somatic mutations in mtDNA, the respiration defects associated with aging of human fibroblasts are still evident (Hashizume *et al.*, 2015). Moreover, the previously reduced respiratory function could be restored if aging fibroblasts were reprogrammed by formation of iPSCs (induced pluripotent stem cells). In fact, reprogramming of cells could also recover some other phenotypes related to aging (Lapasset *et al.*, 2011). Therefore, a hypothesis has been published that mitochondrial defects associated with aging may be due to epigenetic changes in nuclear genes, rather than due to accumulation of mutations in mtDNA (Hayashi *et al.*, 2016).

In conclusion, three different theories have been proposed to explain the cause and the role of mutations in mtDNA in aging. It is documented that number of mutations in mtDNA increases

significantly with age. However, it is still unclear whether the major cause of senescence might be: (i) ROS-mediated lesions in mtDNA and the positive feedback leading to enhanced production of ROS and more and more elevated mutagenesis, (ii) errors made by DNA polymerase γ and subsequent clonal expansion of mutated mtDNA molecules, or (iii) epigenetic changes in nuclear genes affecting mitochondrial metabolism, with little contribution of mtDNA mutations. It is still possible that each of these mechanisms may contribute to the total picture of the senescence in relation to mtDNA and ROS.

Intracellular defense mechanisms against ROS: regulation on aging and disease

As protection against the deleterious effects of excessive ROS production, cells developed several enzymatic and non-enzymatic antioxidant defenses. The enzymatic system consists in a number of antioxidant enzymes such as superoxide dismutases, glutathione peroxidase and catalase, localized in distinct cellular compartments. Superoxide anion is a by-product of oxidative phosphorylation, generated by the leak of electrons from the respiratory chain complexes. $O_2^{\bullet -}$, which is generated in the respiratory chain, especially in a pathological state (Ide *et al.*, 1999; Raha *et al.*, 2000) can be converted to H_2O_2 by SOD2 in the mitochondrial matrix, or SOD1 (zinc-copper superoxide dismutase; also called Zn-CuSOD) in the intermembrane space of mitochondria (IMS) and cytosol (Sturtz *et al.*, 2001). Subsequently, H_2O_2 can be converted to water by GPx (a selenocysteine-containing enzyme specific to organic peroxides) and peroxiredoxins (Prx 3 and 5; also controlling the level of peroxynitrite) directly in mitochondria (Cao *et al.*, 2007). Finally, H_2O_2 can diffuse through the mitochondrial membranes to the cytosol, where peroxisomal catalase or cytosolic GPx convert it to water. Besides the antioxidant enzymes, cells and specifically mitochondria also possess other non-enzymatic antioxidant system comprised of small molecules such as ascorbate (Vit-C), glutathione, tocopherol (Vit-E), retinoic acid, uric acid, pyridine nucleotides and thioredoxin, that also provide efficient cellular protection against excessive oxidative stress. These molecules can act directly as free radical scavengers or by modulating the activity of enzymatic systems (Lu *et al.*, 2010). Examples of free radical scavengers include ascorbate and tocopherol (Lu et al., 2010). Ascorbate, present in aqueous phase, becomes a very stable and non-reactive radical and can be subsequently regenerated by pyridine nucleotides-dependent reductases. Tocopherol, present in the cellular lipid phase, is able to neutralise lipid peroxyl radicals, becoming a less reactive phenyl radical (Lu et al., 2010). Tocopherol radicals can then be regenerated by ascorbate. Uric acid is a strong scavenger of peroxynitrite in extracellular fluid, but requires the presence of ascorbic acid and thiols for a complete scavenging (Nimse , Pal, 2015). Reduced glutathione, pyridine nucleotides and thioredoxin work together with antioxidant

enzymatic systems, donating reducing equivalents to neutralize ROS (Lu et al., 2010; Nimse , Pal, 2015). Melatonin, the sleep hormone, produced by the pineal gland, was also demonstrated to have intrinsic antioxidant protective effects on mitochondria, especially by preventing cardiolipin oxidation and limiting the loss of activity of the mitochondrial respiratory chain (Paradies *et al.*, 2017; Paradies *et al.*, 2010; Petrosillo *et al.*, 2008).

The relationship between the mitochondrial membrane potential and mitochondrial ROS production has been described by Korshunov et al. (Korshunov *et al.*, 1997), as a potential mechanism to regulate oxidative stress. Increased ROS production occurring in the presence of mitochondrial hyperpolarisation relates to the higher NADH/NAD ratio indicating a more reduced NADH pool (Adam-Vizi , Chinopoulos, 2006; Aon *et al.*, 2010; Kushnareva *et al.*, 2002). A protection mechanism against excessive ROS production is proposed to be a mild uncoupling of MMP. This process is catalyzed both by a group of uncoupling proteins (UCP2-5) and free fatty acids (FFA). In the case of hyperpolarisation, mitochondrial carriers (*e.g.*, adenine nucleotide translocase, dicarboxylate, and glutamate/aspartate carriers), UCPs and FFA have been shown to be able to partly "discharge" the high proton gradient to a physiological level (Wieckowski , Wojtczak, 1997). It has been demonstrated that (mild) uncoupling of the MMP (by 10%) enables the reduction of ROS generation by approximately 90% (Korshunov et al., 1997). Moreover, superoxide activates UCPs (UCP1, UCP2 and UCP3), causing increased proton leakage, mitochondrial depolarization, and decreased ROS production (Echtay *et al.*, 2002; Mailloux , Harper, 2011). In rat heart and skeletal muscle, UCPs have been proposed to remove the superoxide anion radical from the mitochondrial matrix (Wojtczak *et al.*, 2011). There is an on-going debate regarding the physical and biological functions of UCP proteins, a number of associations of UCPs against ROS production have up-to-date been proposed, elucidating this group of proteins as potentially significant in a number of pathophysiological situations (Bugger *et al.*, 2011; Diao *et al.*, 2008; Prakash *et al.*, 2015). The role of mitochondrial uncoupling in preserving muscle fibers from the aging process was demonstrated by Amara *et al*. In this work, the authors demonstrated that mild uncoupling serves to protect mitochondrial function and contribute to the longevity of the most active muscle fibers, i.e., those with higher oxidative capacity (Amara *et al.*, 2007). Interestingly, opposite effects were found in fibroblasts and yeast cells, where mild-uncoupling led to fibroblast senescence and decrease life-span in yeast (Stockl *et al.*, 2007).

It has been repeatedly demonstrated that a defective antioxidant defense system may lead to serious ROS-related human pathologies, often associated with the aging process, such as AD, PD and diabetes. Oxidative stress caused by disruption of the antioxidant defense and excessive ROS production is closely linked to the pathogenesis of neurodegeneration (Uttara *et al.*, 2009). For

example, the levels of SOD1 in AD patients were significantly decreased. Interestingly, the levels of mitochondrial SOD2 and extracellular SOD3 were not changed (Murakami *et al.*, 2011). These data can be supported by the observations that the antioxidant defense of cells from familial AD patients was weaker than in cells from healthy individuals (Cecchi *et al.*, 2002). In another context, Hwang et al. presented evidence that catalase plays an important role in kidney protection during hyperglycemia. Deficiency of catalase, in catalase knockout (KO) mice accelerated diabetic nephropathy observed in streptozotocin-induced diabetes (Hwang *et al.*, 2012). Liu *et al* (Liu *et al.*, 2017) also demonstrated an increased ROS levels in oocytes from diabetic mice resulting from altered acetylation status of SOD2 in lysine 68. Also, supporting the antioxidant role of UCP and their importance for the development of diabetes, Robson-Doucette *et al*. (Robson-Doucette *et al.*, 2011) demonstrated that UCP2 regulates ROS production and affects insulin and glucagon secretion by pancreatic cells. Broche *et al.* (Broche *et al.*, 2018) demonstrated that UCP2 regulates pancreas development during embryogenesis through ROS-AKT mediated signaling pathway, evidencing the importance of the antioxidant role of the UCP in the development of diabetes.

Increased ROS formation is also a common intracellular stress that effectively leads to induction of autophagy, which acts as a protective mechanism, at least up to a certain degree (Martinet *et al.*, 2009). The principal link between ROS and autophagy is the cysteine protease Atg4 (autophagy-related gene 4), which is a direct target of H_2O_2. Oxidation of cysteine promotes lipidation of LC3 (MAP1 light chain 3)/Atg8, essential for autophagosome maturation (Scherz-Shouval *et al.*, 2007). On the other hand, it has been demonstrated that autophagy can be a crucial mechanism for preventing the accumulation of ROS by removing damaged mitochondria (Kroemer *et al.*, 2010). This mitochondrial quality control is named mitophagy and serves to eliminate the fraction of damaged mitochondria normally suffering from mitochondrial membrane permeabilization. The recognition of this subset of mitochondria is provided by the involvement of the mitochondrial kinase PINK1 (PTEN-induced putative kinase protein 1). When mitochondria lose membrane potential, PINK1 rapidly accumulates on the mitochondrial surface, leads to the recruitment of the cytosolic protein Parkin, that mediates the ubiquitination of mitochondrial protein with consequent engulfment of damaged mitochondrial by membranes that then fuse with lysosomes (Narendra *et al.*, 2010), a process called mitophagy. In fact, mitophagy has been considered a process by which mitochondrial quality is maintained during the course of aging, avoiding excessive oxidative damage to these organelles (Shi *et al.*, 2017).

Although it exceeds boundaries of this review, it is worth to mention that a number of regulatory programs exist capable of modulating the intrinsic antioxidant defenses. Calorie restriction is known to be one of the strongest life span extending interventions and to have a

positive impact in different pathologies (Colman *et al.*, 2009). However, the mechanisms underlying CR remain largely elusive and have become the point of interest of many research groups. Among the proposed mechanisms, the activation of members of the Sirt2 family proteins has gained much interest (Rogina , Helfand, 2004). There is a number of experimental works that associate the activation of Sirt2 orthologs with up-regulation of cellular antioxidant defense systems (Qiu et al., 2010; Rahman *et al.*, 2009). Interestingly, the positive effects of CR were mimicked in mice through the administration of low dosages of the protonophore 2,4-dinitrophenol, suggesting that mild uncoupling (see above) can indeed be a protective strategy by up-regulating the antioxidant network (Caldeira da Silva *et al.*, 2008). In addition, it has been proposed that CR is able to activate the Nrf2/antioxidant response element (ARE) pathway, inducing ROS detoxification systems, exert anti-inflammatory effects, and, thereby, suppress initiation/progression of vascular disease (Ungvari *et al.*, 2008). Next to CR, another important anti-oxidative intervention is physical activity. It is believed that the two mechanisms together are capable of restoring age-dependent reductions of critical endogenous protective mechanisms such as ischemic preconditioning (Abete *et al.*, 2011). This adaptive mechanism in response to brief episodes of myocardial ischemia enables the reduction of cellular damage due to a prolonged ischemic insult (Murry *et al.*, 1986). Increased ROS production observed upon physical exertion may induce compensational increase of the antioxidant defense efficiency (Ji, 1993). Growing evidence indicates that exercise training can result in an elevation in the activity of antioxidant enzymes. Similarly, long term physical activity is related to the increase of catalase, SOD and glutathione peroxidase activities in muscles of trained animals (Ascensao *et al.*, 2013; Goncalves *et al.*, 2013; Ji, 1993; Laughlin *et al.*, 1990; Powers *et al.*, 1999).

Dietary antioxidant supplementation is another strategy to boost antioxidant defenses in different cell types, with possible positive impacts during aging. Phenolic and thiol compounds, flavonoids, and carotenoids are examples of antioxidant compounds that can be obtained from fruit, vegetables, spices, grain, and herbs (Nimse , Pal, 2015). A well-known dietary antioxidant supplement is resveratrol. Resveratrol is a stilbenoid phenolic compound, with its antioxidant capacity giving it several possible therapeutic applications (Cho *et al.*, 2017b; Ko *et al.*, 2017) (Li *et al.*, 2017; Sawda *et al.*, 2017; Truong *et al.*, 2017), including age-related diseases (Lange , Li, 2017; Li et al., 2017; Navarro-Cruz *et al.*, 2017), and cancer (Deus *et al.*, 2017). In fact, resveratrol appears to improve mitochondrial function and biogenesis in skeletal muscle of aged animals (Muhammad , Allam, 2017). Also, due to its beneficial effects on mitochondria, resveratrol was proposed as a promising nutraceutical supplement in the treatment of mitochondrial disorders (De Paepe , Van Coster, 2017). Also, due to its antioxidant properties, flavonoids have demonstrated

neuroprotective actions against neurodegeneration (Frandsen , Narayanasamy, 2018). Equally, high dietary intake of carotenoids appears to reduce the risk of stroke and stroke mortality (Bahonar *et al.*, 2017). The effects of some approaches have been summarized in a recent review by Suski *et. al* (Suski *et al.*, 2011). However, although having good antioxidant properties, some compounds are not able to reach mitochondria, where the majority of ROS are formed. Thereby, in order to observe any effect, a larger amount of those compounds is required, which may lead to undesirable side effects. Thus, new strategies are required to improve the delivery of those compounds.

Another interesting antioxidant strategy can be assigned to heme oxygenase-1 (HO-1) (Otterbein , Choi, 2000). The expression of this enzyme is increased as a response to oxidative and heat stress and its role is to degrade free heme, originating from the denaturation and proteolysis of hemoproteins, to release biliverdin, carbon monoxide and iron (Baranano *et al.*, 2002; Liu *et al.*, 2006; Morse , Choi, 2005). The iron released by HO-1 increases the synthesis of ferritin, what minimizes the probability of Fenton reaction initiation. Furthermore, biliverdin can be converted by the enzyme biliverdin reductase into bilirubin, a potent antioxidant, capable of protecting cells from 10,000-fold higher concentrations of H_2O_2 ((Morse , Choi, 2005)). Activation of HO-1 was described already as a possible mechanism by which different natural compounds delay skin aging (Park *et al.*, 2016).

In summary, although cells possess several mechanisms of protection against oxidative stress, impairment in mitochondrial function and antioxidant defenses systems during the normal aging phenotype promote an imbalance between ROS formation and cleansing, increasing cellular oxidative stress. It remains to be determined which are the best strategies to decrease cell and mitochondrial oxidative stress that accompanies the aging process without disturbing the physiological role of ROS. Such strategies may pass through the modulation of intrinsic antioxidant mechanisms.

Mitochondrial morphology, calcium homeostasis and dynamics in aging

Mitochondrial dynamics

Unlike ROS, mitochondrial dynamics has only recently been studied as a possible player in aging, and specific links between these three processes have been scarcely documented. Thus, here we will give only a brief overview of the studies giving insight to the relationship between mitochondrial dynamics and aging and attempt to highlight the possible trends, underlying mechanisms and links with ROS production. Mitochondrial morphology in living cells is heterogeneous and can range from small spheres to interconnected tubules (Rizzuto *et al.*, 1998) **(Figure 3)**. Growing evidence indicates that mitochondrial morphology is critical for the

physiology of the cell and changes in mitochondrial shape have been related to many different processes such as development, neurodegeneration, calcium (Ca^{2+}) signaling, ROS production, cell division, and apoptotic cell death (Cereghetti , Scorrano, 2006). Mitochondrial dynamics in a broad sense involves the processes of fission, fusion, mitochondrial movement or transport and interactions with other organelles (Benard , Rossignol, 2008). Mitochondrial fission and fusion regulates mitochondrial morphology, branching and network formation and also determines individual mitochondrion size. Mitochondrial transport determines mitochondrial localization and overall distribution within the cell, this is especially important in highly polarized and large cells, such as neurons or oocytes (Barnhart, 2016; Frederick , Shaw, 2007; Mishra , Chan, 2014; Pernas , Scorrano, 2016). In the last two decades, we have learned intricate molecular details about these processes as well as their regulation, which now appears to be concertedly controlled by cellular activity. Mitochondria can associate with different cytoskeletal filaments to facilitate intracellular movement. In mammalian cells microtubule filaments and dynein/kinesin motors are often used for movement purposes, but actin and actin nucleation factors recently emerged as essential players in determining mitochondrial positioning (Barnhart, 2016; Frederick , Shaw, 2007; Kanfer , Kornmann, 2016; Melkov , Abdu, 2018; Pathak *et al.*, 2010). Moreover, mitochondrial interactions with the cytoskeleton are also important to link localization and movement with mitochondrial shape, by interactions with an elaborated machinery on the outer and inner mitochondrial membrane (OMM and IMM) accomplishing the fusion and fission of mitochondria (Chakrabarti *et al.*, 2017; Hatch *et al.*, 2016; Korobova *et al.*, 2014; Korobova *et al.*, 2013; Manor *et al.*, 2015; Prudent , McBride). The cyclic rearrangement of the interconnected dynamic mitochondrial network, by individual mitochondria constantly undergoing fission and then fuse with each other has been studied in much molecular detail, but we still have no consensus on the functional consequences, the purpose and the exact regulation of the entire process (Cho *et al.*, 2017a; Kanfer , Kornmann, 2016; Lee *et al.*, 2016a; Misgeld , Schwarz; Pernas , Scorrano, 2016; Yamada *et al.*). Fusion is an event where the outer and inner membrane of a mitochondrion fuses with the outer and inner membrane of another mitochondrion respectively, allowing the matrix content of the two mitochondria to mix freely and form a single mitochondrion, while fission is the reverse of this event, and the two processes are regulated independently. Intriguingly, fission occurs preferably at sites where mitochondria interact with other organelles, in particular the endoplasmic reticulum (ER) (Friedman *et al.*, 2011). These interactions involve a particular machinery present in subdomains of the ER (mitochondria associated membranes - MAMs), further interacting with the actin cytoskeleton and the fission machinery of the OMM (Cho et al., 2017a; Hatch et al., 2016; Korobova et al., 2013; Kraus , Ryan, 2017; Li *et al.*, 2015b; Manor et al., 2015; Moore *et al.*, 2016).

OMM fission is then promoted by dynamin-related protein 1 (Drp1), a dynamin related GTPase, and Drp1 is recruited to the mitochondria by fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitochondrial dynamics protein of 49 kDa (Mid49) and 51 kDa (Mid51) (Losón *et al.*, 2013). While the molecular details of IMM fission is less known, both OMM and IMM fusion, facilitated by three dynamin-related GTPases, by mitofusin 1 and 2 (Mfn1 and Mfn2) located on the outer membrane, and by optic atrophy 1 (Opa1) located on the inner membrane (Chen *et al.*, 2003; Cipolat *et al.*, 2004), is reasonably well characterized. With interactions with all components of mitochondrial dynamics, the ER-mitochondrial interaction sites thus are central hubs for a concerted regulation of both intracellular networks, probably executed by cellular and mitochondrial Ca^{2+} signals (Chakrabarti et al., 2017), and other processes regulating cell activity and shape (Shao *et al.*, 2015; Wales *et al.*, 2016). Here, an important link between local ROS production in this subdomain and mitochondrial dynamics has also been recently demonstrated (Debattisti *et al.*, 2017; Norton *et al.*, 2014). Interestingly, MAMs appointed to the modulation of calcium (Bononi *et al.*, 2017; Kuchay *et al.*, 2017; Marchi *et al.*, 2018) and ROS (Verfaillie *et al.*, 2012) signaling in health and disease, appears to be altered in aged mice hearts in which Ca^{2+} transients, NAD(P)H regeneration, glutathione levels and ER-mitochondria contact sites are significantly reduced compared to the young ones with a concomitant increase in ROS generation and mitochondrial protein oxidation (Fernandez-Sanz *et al.*, 2014). Interestingly, recently it was demonstrated that knockdown of MCU and inositol 1,4,5-trisphosphate receptor type 2 (ITPR2), both involved in the accumulation of calcium in mitochondria, resulted in senescence escape, indicating the role of mitochondrial calcium accumulation in senescence induction (Wiel *et al.*, 2014). Similarly, lower number of contacts between mitochondria and the ER in senescent human fibroblasts **(Figure 4)** can be also responsible for the compromised mitochondrial calcium uptake in senescent cells. However, additional studies are needed to validate the alterations in the number of contacts between mitochondria and ER during aging or senescence to identify which factors have the highest influence of the regulation of Ca^{2+} fluxes through mitochondria-ER contacts sites in aging cells. The structure and function of MAM in the aspect of aging and senescence has been recently reviewed by Janikiewicz *et al*. (Janikiewicz *et al.*, 2015).

Mitochondrial dynamics and lifespan in model organisms

Mitochondrial dynamics has been linked to existing pathways that regulate lifespan in *C. elegans*. It was shown that mitochondrial trafficking in distal neuronal processes decline progressively with age and long-lived daf-2 mutants with reduced insulin signaling (IIS) show resistance to this decline (Morsci *et al.*, 2016). Neuron-specific activation of CREB regulated

transcriptional coactivator 1 (CRTC-1), which promotes mitochondrial network fragmentation, is able to suppresses both AMPK and calcineurin-mediated lifespan extension in *C. elegans* (Burkewitz *et al.*, 2015). Similarly, inactivation of *C. elegans* Drp1 significantly enhanced the ability of IIS to extend lifespan (Yang *et al.*, 2011), suggesting a correlation between increased fusion/fission ratio and life span extension. Certain mutant bacteria of the *C. elegans* microbiome are able to extend lifespan via increased secretion of the polysaccharide colanic acid, this extension is dependent upon Drp1 and mitochondrial fission (Han *et al.*). Thus, existing pathways of lifespan extension such as the AMPK and IIS pathways are closely linked to mitochondrial dynamics but the causative role of any of these processes has not yet been demonstrated, and is being debated. Indeed, it has been suggested that mitochondrial mass and fragmentation do not affect lifespan, and are merely changes associated with aging (Regmi *et al.*, 2014). However, it is still possible that mitochondrial dynamics plays important roles in the regulation of aging when working in coherence with or as part of other aging pathways such as IIS or metabolic regulation of lifespan via the AMPK pathway.

Fusion and fission balance has also been studied in fungal and *Drosophila* models. In *Podospora anserina* and *Saccharomyces cerevisiae*, deletion of dynamin-related protein 1 (Dnm1p), mediating fission, retards aging and extends lifespan (Scheckhuber *et al.*, 2006). A double deletion mutant of *Saccharomyces cerevisiae* where Dnm1 (the yeast orthologue of Drp1) and Mgm1 (the yeast orthologue of Opa1), are both deleted, contain wild-type like filamentous mitochondria, but a decrease in mitophagy and replicative lifespan (Bernhardt *et al.*, 2015). While these models would support a generalization that fusion is associated with increased lifespan, the *Drosophila* model shows opposite trend. Upregulating Drp1 expression in midlife extends *Drosophila* lifespan, this is likely linked to autophagy as autophagy is required for the lifespan extending effect to occur (Rana *et al.*, 2017). Similarly, overexpression of parkin in *Drosophila* extended lifespan and reduced the level of *Drosophila* orthologue of mitofusin, mitochondrial assembly regulatory factor (Marf), which typically increases with age in flies (Rana *et al.*, 2013).

Overall, from these studies it appears that there is no clear association between either fusion or fission and lifespan, and promoting either process will have an effect which depends on the signaling and metabolic context. Importantly, a few studies pointed to the importance of the interplay between autophagy or mitochondrial specific mitophagy in determining cellular homeostasis, affecting lifespan of whole organisms. This suggests that it is rather the homeostatic function of mitochondrial quality control events, mediated by mitochondrial fusion and fission, bearing the importance for determining or influencing the aging process. Indeed, in mammalian models it is now well documented that any disturbance of the homeostatic circuit maintaining the

functional mitochondrial network has a profound effect on the healthy lifespan of the animals. Mice knockouts for essential components of mitochondrial dynamics (Pernas , Scorrano, 2016) develop pleiotropic symptoms in many organ systems reflecting loss of cellular function or the ability to cope with cellular stress, leading to indicators of early aging or leading to at least a reduced healthy lifespan. E.g. Fis1 KO mice develop multiple early aging signs including lordokyphosis, lack of vigor, inability to accumulate fat, reduced ability to tolerate stress, perturbed Ca^{2+} dynamics, and decreased lifespan (Uzhachenko *et al.*, 2017). Transmembrane protein 135 (TMEM135) is a protein likely involved in mitochondrial fission and mice with mutated TMEM135 display abnormal mitochondrial dynamics and accelerated aging in the retina as well as pathologies observed in age-dependent retinal diseases (Lee *et al.*, 2016b). Furthermore, it has been long known that mTOR plays an important role in aging in a range of different organisms (Johnson *et al.*, 2013). mTORC1 has been linked to regulation of mitochondrial dynamics by stimulating translation of mitochondrial fission process 1 (Mtfp1), promoting mitochondrial fission. Potent active-site mTOR inhibitors promotes mitochondrial fusion over fission events (Morita *et al.*).

We have to emphasize, that the cellular consequences of perturbed mitochondrial dynamics are often associated with loss of redox homeostasis (Abeti *et al.*, 2011), and increased ROS production. In this context ROS is often synonymous with cellular damage (Röth *et al.*, 2014; Willems *et al.*, 2015), but mitochondrial or ER stress related ROS production might play a role in negative feedback regulation of organelles homeostasis, e.g. by altering gene expression via mitohormetic and mitochondrial unfolded protein responses (Shpilka , Haynes, 2017; Yun , Finkel, 2014).

Mitochondrial dynamics and age-related diseases in humans

Mammalian models, such as mice with genetically altered mitochondrial dynamics develop symptoms which resemble human age-related disease, affecting critical organs (nervous system, liver and endocrine and cardiovascular systems) or increasing incidence of cancer (Altieri, 2017; Mishra , Chan, 2014; Pernas , Scorrano, 2016; Senft , Ronai, 2016; Youle , van der Bliek, 2012). Most deaths in old age are still due to diseases and it is not possible to extend lifespan without reducing the effects of age-related diseases. Here, we summarize a series of studies that investigated the relationship between mitochondrial dynamics and age-related diseases.

Cardiovascular disease are a range of diseases whose incidence of occurrence increases with age and are one of the leading cause of death in the developed world (Rapsomaniki *et al.*, 2014). In humans and mice, heart failure is linked to decreased mitochondrial fusion, fragmentation of the mitochondrial network and lower levels of Opa1 expression (Chen *et al.*, 2009). In *Drosophila*,

Marf and Opa1 are essential for proper cardiomyocyte function and fusion defects are associated with cardiomyopathy (Dorn , Scorrano, 2010). Opa1 mutation heterozygotes has late-onset cardiomyopathy in mice (Chen *et al.*, 2012a). Furthermore, unbalanced Opa1 processing and a decrease in mitochondrial fusion is linked to fragmentation results in heart failure in mice (Wai *et al.*, 2015). It has been shown that endothelial cells (HUVECs) maintain a tubular mitochondrial network, but senescent cells have more elongated, interconnected mitochondria, and the change in mitochondrial morphology is caused by downregulation of Fis1 and Drp1 (Mai *et al.*, 2010). However, another group found that in HUVECs, mitochondria of old cells showed a significant and equal decrease of both fusion and fission activity (Jendrach *et al.*, 2005). These results are relatively consistent and suggest that mitochondrial fusion, especially Opa1, is vital for proper heart function and preventing heart failure. This seems to be conserved throughout flies, mice and humans. Expanding on this, it would be interesting to see if overexpressing of Opa1 or increasing mitochondrial fusion can improve declining heart function. In addition, differentiation of arterial smooth muscle cells and of cardiomyocytes is dependent of reduction of fusion, thus prone to disorders related to altered mitochondrial fusion/fission ratios (Chalmers *et al.*, 2016; Kasahara *et al.*, 2013). Altered ROS production was also found associated with disturbances of mitochondrial dynamics in this disease (Chen et al., 2012a; Mai et al., 2010).

Neurodegenerative diseases such as AD and PD are probably the most prevalent age-related neurodegenerative diseases whose risks increases dramatically with age (Fjell *et al.*, 2014; Rodriguez *et al.*, 2015). AD and PD have been linked to mitochondrial dynamics and mitophagy, as parts the mitochondrial quality control machinery, and supposed to play important roles in these diseases (Chen , Chan, 2009). The vast literature on the overall importance of mitochondrial quality control in neurodegenerative disease has been recently reviewed, thus here we will focus on the less covered specific functions of mitochondrial fusion and fission. A large number of studies found that increased mitochondrial fission and fragmentation is linked to AD. Tau mice have higher levels of fission proteins Drp1, Fis1 and lower levels of fusion proteins Mfn1, Mfn2, Opa1 compared to WT mice (Kandimalla *et al.*, 2018). In AD, amyloid-β (Aβ) is linked to Drp1-induced excessive mitochondria network fragmentation in AD progression (Reddy *et al.*, 2017). Drp1 interacts with Aβ and phosphorylated tau, leading to mitochondrial fragmentation, abnormal mitochondrial dynamics and synaptic damage (Manczak *et al.*, 2011; Manczak , Reddy, 2012). Aβ precursor protein transgenic (APP) mice have significantly decreased anterograde mitochondrial movement, increased mitochondrial fission and decreased fusion in neurons (Calkins *et al.*, 2011). Furthermore, reducing levels of Drp1 decreases the amount of soluble Aβ production in AD progression, and protects against Aβ induced mitochondrial and synaptic toxicities in AD progression and

pathogenesis (Manczak *et al.*, 2016). However, sporadic AD is associated with a significantly lower level of Drp1 in fibroblasts (Wang *et al.*, 2008a). Decreased Drp1 levels and mitochondrial localization, as well as reduced Stomatin-like protein 2 (STOML2) and Mfn2 fusion protein levels, are observed in the fibroblasts of sporadic AD patients (Martín-Maestro *et al.*, 2017). In cells overexpressing APP, a fragmented mitochondria structure and abnormal distribution is observed. Moreover, levels of Drp1 and Opa1 were significantly decreased whereas levels of Fis1 were significantly increased, and increasing Drp1 and Opa1 were both able to rescue some mitochondrial defects (Wang *et al.*, 2008b). Thus, current evidence fails to reach consensus, but since alterations in ER-mitochondrial contacts, which appear as central organizer of fusion and fission events (see above), are implicated in AD (Area-Gomez , Schon, 2017; Filadi *et al.*, 2017), one can speculate that deregulation of these membrane fusion and fission events are linked to disturbances of the ER-mitochondrial contact sites with variable outcome. Then again, mitochondrial ROS has been described as culprit for neuronal damage (Angelova , Abramov, 2018), but it also appears the local ROS in the contact sites is also a cellular signal at this interface and regulatory hub (Debattisti et al., 2017). Similarly, altered fusion/fission ratios accompany PD. In respiratory chain-deficient dopaminergic neurons fragmentation of the mitochondrial network and impaired anterograde axonal transport of mitochondria have been observed (Sterky *et al.*, 2011). Alpha-synuclein (αS) has an inhibitory function on membrane fusion. Upon increased expression in cultured cells and in *C. elegans*, αS shift mitochondrial shape towards reduced fusion, leading to a fragmented mitochondrial structure (Kamp *et al.*, 2010). Elegant studies demonstrated the ROS dependence of neuronal dysfunction in vivo in dopaminergic (DA) neurons (Guzman *et al.*, 2010).

Another system affected by degenerative age-related symptoms is muscle. Muscle wasting is a hallmark of aging and the primary reason of declining physical abilities with age (Kalyani *et al.*, 2014). Mitochondrial network in skeletal muscle has a complex and seemingly rigid organisation, but it has been shown that mitochondrial fission is important for muscle atrophy to occur (Romanello *et al.*, 2010). However, in aged muscle in mice, inter-myofibrillar mitochondria in skeletal muscle were longer and more branched, suggesting increased fusion and/or decreased fission, and mitochondrial fusion index (Mfn2-to-Drp1 ratio) was significantly increased in aged muscles (Leduc-Gaudet *et al.*, 2015). In human participants, the levels of the fusion protein Opa1 was lower in muscle from elderly subjects; however, no changes were detected in Mfn2, Drp1 or Fis1 among the groups (Joseph *et al.*, 2012). Thus, studies on muscle atrophy do not have consistent results (Joseph et al., 2012; Leduc-Gaudet et al., 2015), and proper understanding of the organisational principles of the skeletal muscle mitochondrial network will be required to reveal the connection between muscle growth and function in aging.

Metabolic disorders are inherently linked to mitochondrial dysfunction, which can follow alterations in mitochondrial dynamics. This can be extended to insulin resistance and type 2 diabetes mellitus which are strongly linked to aging and incidence of occurrence increases with age (Facchini *et al.*, 2001; Meigs *et al.*, 2003). While both pathologies have been linked to mitochondrial dysfunction (Mootha *et al.*, 2003), the participation of mitochondrial dynamics is less known in the pathomechanism. Increased mitochondrial network fragmentation and Fis1 expression is observed in venous endothelial cells of type 2 diabetes mellitus patients compared to control (Shenouda *et al.*, 2011). A shift toward mitochondrial fission with reduction of fusion protein, mainly Mfn2, has been associated with reduced insulin sensitivity and inflammation in obesity and insulin resistance development (Putti *et al.*, 2015), which can be associated with altered ROS production.

Finally, although not primarily caused by degenerative age-related processes such as the above discussed diseases, in cancer, age is a major risk factor. The role of mitochondria in tumorigenesis is extensively researched (Gasparre *et al.*, 2017; Valcarcel-Jimenez *et al.*), and a few studies established links between mitochondrial dynamics and cancer cell biology. Some suggest a link between mitochondrial dynamics and development and metastasis (Altieri, 2017; Caino *et al.*, 2016; Senft , Ronai, 2016), but not cancer causation. As such, the link between cancer and mitochondrial dynamics are less relevant towards aging for the purpose of this review but nonetheless could yield interesting insight into cellular transformation.

Mitochondrial dysfunction and increased ROS-related/accompanied pathologies in the context of aging

In this section we provide some examples of pathological situations illustrating important role of ROS, oxidative stress and mitochondrial dysfunction in the pathogenesis of described below abnormalities in the context of aging.

Liver, mitochondria and aging

The process of aging develops in parallel with a gradual deterioration of cell functions, including the hepatocytes, in the body. The liver is a vital organ with a full battery of crucial functions which include the regulation of cholesterol, bile acid, triglyceride, protein, glucose, and energy metabolism, as well as detoxification, and production of bile. This latter function is essential for digestion and absorption of intestinal cholesterol, triglycerides, and fat-soluble vitamins, as well as is involved in hepatic secretion of three lipid components, i.e., bile acids, cholesterol, and phospholipids, which helps the body to excrete excessive cholesterol into the feces (Di Ciaula *et al.*,

2017a; Wang *et al.*, 2017b). Although the liver has a major capacity to naturally regenerate, aging induces progressive "physiological" changes of the liver in the structural and functional aspects (**Table 1**)**.** Whether the liver function becomes seriously compromised in elderly subjects remains largely contradictory, because few studies have examined the aging process of the liver from a structural and functional point of view (Schmucker, 1998). The aging liver, however, indeed shows an impaired ability to counteract the hepatic insults, which is a situation often experienced by the elderly.

It has been repeatedly demonstrated that mitochondria play a critical role in driving the age-dependent oxidative lesions with reactive oxygen species increase (Ames *et al.*, 1995; Pamplona *et al.*, 1998; Sastre *et al.*, 1996). Liver mitochondria contain *manganese*-dependent superoxide dismutase (SOD) with antioxidant function. With aging, however, endogenous, mitochondria-derived free radicals might overwhelm the endogenous defensive response. Bejma *et al*. (Bejma *et al.*, 2000) investigated the effects of aging and an acute bout of exercise on intracellular oxidant generation, lipid peroxidation, protein oxidation and glutathione (GSH) status in the heart and liver of young adult (8 month), and old (24 month) male rats. In the whole liver homogenates and in the mitochondria (and also the heart), the rate of dichlorofluorescin oxidation, an indication of intracellular oxidant production, was higher in the homogenates of aged rats. Lipid peroxidation was also increased in the aged liver and exercised aged heart. Both electron transport chain and NADPH oxidase were two major sources of the age-related increase in oxidant production. In turn, in the study of Kujoth *et al*. (Kujoth et al., 2005) the aging process was evaluated in mice expressing a proofreading-deficient version of the mitochondrial DNA polymerase γ. Mice accumulated mtDNA mutations while displaying features of accelerated aging. Of note, the accumulation of damage, i.e., mutations and deletions, of mtDNA was not associated with increased markers of oxidative stress in the liver mitochondria (i.e., H_2O_2 production and protein carbonyls, F2-isoprostanes, 8-hydroxy-2'-deoxyguanosine) or a defective cellular proliferation, but was associated with the induction of apoptotic markers (i.e. cleaved caspase-3), particularly in tissues characterized by rapid cellular turnover such as the liver. Notably, caloric restriction is the only nutritional intervention that retards aging, as well as the accumulation of mtDNA mutations (Aspnes *et al.*, 1997) with reduction of mitochondria-mediated apoptotic pathways (Cohen *et al.*, 2004; Shelke , Leeuwenburgh, 2003).

ROS production increases with aging in state 3 when mitochondria isolated from old rats are supplemented with succinate. This finding could be explained by the defective suppression of H_2O_2 production, i.e., an example of mitochondrial ROS production, during the energy transition from state 4 to state 3. Also, levels of 8-oxodG in the biological macromolecule mtDNA increase with

age in old animals. Notably, this increase is abolished by caloric restriction, with a positive effect on the aging rate (Lopez-Torres *et al.*, 2002). In senescent rats from the ages of 28 to 60, and to 92 weeks, the mitochondrial mass of liver remains unchanged throughout ages, but the aging process is paralleled by increased (36–45%) content of the oxidation products, i.e., thiobarbituric acid-reactive substances and protein carbonyls. These changes are associated with a progressive decrease in critical enzymes for mitochondrial function, i.e., -47% mitochondrial nitric oxide synthase, -46% SOD2, -30% complex I, and -24% complex IV, in old rats compared to young adult rats. However, liver mitochondria from young and old rats do not differ for fragility and water permeability (Navarro , Boveris, 2004). Age-associated decrease of mtRNA is another event involving also the liver (Anantharaju *et al.*, 2002), while damaged mitochondrial proteins increase membrane stiffness (Pamplona et al., 1998). In addition, PUFAs could be easily damaged by ROS (Anantharaju et al., 2002). Thus, the accumulation of oxidized and carboxymethylated proteins in the mitochondrial matrix during senescence concomitant with defective degradation of abnormal matrix proteins, affects the ability of aging mitochondria to respond to additional stress (Bakala *et al.*, 2003).

A summary of established damages in the mitochondria of aging liver is depicted in **Table 2**. These changes include oxidative lesions in the mtDNA (Ames *et al.*, 1993), oxidation of mitochondrial lipids, increased levels of long-chain polyunsaturated fatty acid, decreased membrane phospholipid peroxidability and decreased Δ9-desaturase activity coefficient leading to decreased levels of 16:1 and 18:1 fatty acids with less membrane stability. Additional mechanisms include increased apoptotic pathways, and increased inner mitochondrial phospholipase A_2 activity (Laganiere , Byung, 1993; Pappu *et al.*, 1978). The content of cytochrome oxidase is associated with loss of enzymatic activity (Wilson , Franks, 1975), while malondialdehyde accumulation increases (Von Zglinicki *et al.*, 1991).

In all organs of the body, the aging process develops with progressive unbalanced response of the immune system where pro-inflammatory cytokines, chemokines, and ROS are not adequately counteracted by antioxidants molecules. The liver is enriched with enzymes with antioxidative functions like mitochondrial SOD2, SOD1, cytosolic glutathione peroxidase as well as peroxisomal catalase (Anantharaju et al., 2002). As already mentioned, aging has been shown to be associated with increased oxidative stress, likely due to decreased capacity to eliminate toxic substrates, i.e., metabolically generated superoxide radical. In particular, aging is paralleled by increased production of superoxide anion, hydrogen peroxide, and hydroxyl radical, with all these molecules driving the oxidative protein damage in the liver. The mitochondria play a key role in this scenario leading the oxidative lesions with age (Ames et al., 1995; Pamplona et al., 1998; Sastre et al., 1996). Few studies have attempted to link the oxidative stress to cell injury (Zhang *et al.*, 2003)

examined the effects of hypertermic challenge on levels of ROS, oxidative injury, changes in redox status, and DNA binding activation of critical stress response transcription factors, i.e., Activator protein-1 (AP-1) and nuclear factor-kappa B (NF-κB) in old and young rats. Compared to young rats, old rats show greater oxidative damage with sustained ROS levels through 24 hrs, higher malondialdehyde (MDA) and 4-hydroxy-2-noneal (4-HNE) levels as marker of lipid peroxidation products, as well as hepatocyte damage, i.e., monocyte infiltration, sinusoidal congestion, hepatocellular vacuolization, and diffuse necrosis. Moreover, the ratio of GSH to glutathione disulfide (GSSG) as a marker of hepatic redox status is significantly lower in old rats than in young rats. The effect on peroxidation of polyunsaturated fatty acids in old animals might influence the cellular membrane permeability and membrane leakage. Also, aging impairs the intracellular redox buffering mechanisms, e.g., antioxidants and glutathione, which, by definition, prevent ROS accumulation. Additional damage includes age-related decrease in DNA base excision repair in mouse hepatocytes (Intano *et al.*, 2003), and increased level of oxidatively damaged DNA in the livers of old mice and rats in comparison to young animals (Hamilton *et al.*, 2001). Increased oxidative stress in old animals appears to be paralleled by the enhanced induction of the antioxidant enzyme heme oxygenase via the transcription factor NF-kB (Lavrovsky *et al.*, 2000). The study by Ikeyama and colleagues (Ikeyama *et al.*, 2003) showed that aging, in rats aged 24-26 months, is associated with elevated basal H_2O_2 and epidermal growth factor (EGF)-induced gadd153 gene expression, as pro-apoptotic marker, in the livers compared to that in young animals. Moreover, there might be a variable change in the antioxidant family members with aging. Thomas *et al*. (Thomas *et al.*, 2002) used gene array analysis to find that both aged rat and human liver samples display increased expression of redox and detoxification enzymes, i.e., the glutathione S-transferase GST, UDP-glucuronosyltransferase, and cytochrome P-450 enzyme families.

The excision repair cross-complementation group 1 $(Ercc1)^{-/\Delta}$ murine model hosts a rare human progeroid syndrome caused by inherited defects in DNA repair and premature aging (Gregg *et al.*, 2012). In the 5-month-old $Ercc1^{-/\Delta}$ mice that are similarly to the old wild-type group, at the ages of 24-35 months, the livers show architectural and inflammatory damages, elevated liver enzymes, and decreased albumin. Of note, there is a significant increase in oxidative damage in $Ercc1^{-/\Delta}$ and old wild-type liver, with a detection of lipid peroxidation and senescence products, i.e., lipofuscin, lipid hydroperoxides, and acrolein (Gregg et al., 2012) .

Thus, increased oxidative stress and reduced tolerance to oxidative stress with age can initiate the further signaling pathways that drive cellular dysfunction and reduced stress tolerance in older organisms (Schmucker, 2005; Thomas et al., 2002).

Lipids, mitochondria and aging

Lipid accumulation, i.e., triglycerides and cholesterol, greatly promotes aging in the liver, (Ghosh *et al.*, 2012; Petersen *et al.*, 2003; Slawik , Vidal-Puig, 2006) while phospholipids remain quantitatively unchanged (Schneeman , Richter, 1993). A typical scenario in this respect is age-related increase in the metabolic syndrome with age, (Ford *et al.*, 2002), leading to the progressive redistribution of adipose tissue from subcutaneous sites to visceral ones (Tchkonia *et al.*, 2010), and the increased prevalence of non-alcoholic fatty liver disease (NAFLD) as part of the age-dependent process of fat redistribution in non-adipose tissues. The process of ectopic fat deposition and lipotoxicity, therefore, initiates/perpetuates the damage in the liver, heart, skeletal muscle, and pancreas, thus leading to increased cardiovascular risk, the metabolic syndrome and, in turn, to further enhance liver steatosis (Floreani, 2007; Slawik , Vidal-Puig, 2006; Tchkonia et al., 2010; Tran *et al.*, 2008). Of note, this process also referred to as "inflamm-aging", can also develop in lean, but metabolically-obese subjects (Tchkonia et al., 2010; Vecchie *et al.*, 2017). NAFLD refers to the presence of excess fat in the liver, i.e., hepatic steatosis, when more than 5% accumulation of triglycerides occurs in the hepatocytes (Krawczyk *et al.*, 2010). NAFLD encompasses the spectrum of liver abnormalities which range from simple steatosis, i.e., non-alcoholic fatty liver (NAFL), to steatohepatitis (NASH), and to (likely cryptogenic) cirrhosis, and has a potential progress to hepatocellular carcinoma (HCC) (Brunt *et al.*, 2015). NAFLD is one of the most common liver disorders worldwide (Krawczyk et al., 2010), with a 20-50% prevalence according to ultrasonographic and computed tomography (CT) imaging across population studies (Williams *et al.*, 2011; Zelber□Sagi *et al.*, 2006). Pathogenic factors of NAFLD include a genetic background, (Krawczyk *et al.*, 2013), enhanced uptake of free fatty acids (long-chain fatty acids, LCFA), increased *de novo* lipogenesis, decreased fatty acid β-oxidation, and/or decreased synthesis or secretion of very low-density lipoproteins (VLDL) (Cohen *et al.*, 2011).

Overall mechanisms accounting for the age-related increase of hepatic steatosis include: accumulation of ROS and DNA damage (Aravinthan *et al.*, 2013), hypercholesterolemia (Bonomini *et al.*, 2013), decreased autophagy (Amir , Czaja, 2011), activation of NF-κB signaling that is the key regulator of inflammatory responses (Franceschi *et al.*, 2000), metabolic dysfunction (Rodriguez *et al.*, 2007), telomere shortening (Tomás□Loba *et al.*, 2013), sedentary lifestyle (Breitling *et al.*, 2009), and cigarette smoking (Booth *et al.*, 2011). Aging also induces liver damage, increases proinflammatory M1 macrophage polarization, and enhances inflammatory response typical of NASH (Fontana *et al.*, 2012). Notably, NAFLD appears to decline in very elderly subjects (Koehler *et al.*, 2012) and this finding becomes more apparent when liver fibrosis and NASH are more advanced (van der Poorten *et al.*, 2013), as observed in elderly patients

(Koehler et al., 2012; Noureddin *et al.*, 2013). Different protective mechanisms might be responsible for the age-dependent decrease of liver steatosis, and include increased serum adiponectin levels (van der Poorten et al., 2013), the onset of portosystemic shunting (Nosadini *et al.*, 1984), metabolic changes of mitochondria (Caldwell , Crespo, 2004), and inflammatory and catabolic state of cirrhosis (McCullough , Raguso, 1999), as well as collagen deposition in the liver (Noureddin et al., 2013). In the serum, levels of cholesterol, HDL-cholesterol and triglycerides also increase with age. This trend is reverted in individuals older than 90 years old (Tietz *et al.*, 1992). Notably, LDL-cholesterol metabolism rate is decreased by over 30% with age, as a consequence of a decrease in expression of LDL receptors (Miller, 1984). Aging significantly enhances the progression of NAFLD to NASH, and to fibrosis, leading to the conditions that predispose to increase mortality in elderly subjects with NAFLD (Regev , Schiff, 2001). Age-dependent decline of fatty acid β-oxidation and reduced expression of hepatic nuclear receptor peroxisome proliferator-activated receptor may be potential mechanisms (Sanguino *et al.*, 2004). An additional mechanism is the age-dependent increase of the β-adrenergic signaling that is able to drive liver steatosis (Ghosh et al., 2012; Katz *et al.*, 1993). Also, p300-dependent regulation of chromatin structure during aging is responsible for the activation of five key genes that govern triglyceride synthesis in the liver (Jin *et al.*, 2013). Markers of hepatocyte senescence are also associated with NAFLD (Aravinthan *et al.*, 2013; Park *et al.*, 2010). The link between increased intrahepatic diacylglycerol (DAG) and PKCε activation is essential, since LCFA are oxidized at both mitochondrial and extramitochondrial sites in the hepatocytes. Excessive incorporation of LCFA will increase ROS and mediate hepatocellular and mitochondrial injury (Diogo *et al.*, 2011; Grattagliano *et al.*, 2013; Grattagliano *et al.*, 2011; Zhu *et al.*, 2017).

Mitochondria contribute to the progression of liver disease observed in NAFLD (Grattagliano *et al.*, 2004b), a condition characterized by increased predisposition towards pro-oxidant insults (Pessayre , Fromenty, 2005). One pathway that limits excessive fat accumulation in the liver is the increased mitochondrial oxidation of LCFA, a step associated with an impaired respiration (Fromenty , Pessayre, 1995). Fatty degeneration exposes hepatocytes to a higher risk of oxidative damage, although a number of adaptive metabolic mechanisms have been described (Grattagliano *et al.*, 2003; Yang *et al.*, 2000). Mechanisms include expression of intracellular sensors and signaling molecules for lipid metabolism and oxidative stress pathways (Merriman *et al.*, 2006; Sanyal *et al.*, 2001). Impairment of these systems may have important pathogenic roles in NAFLD progression, including disturbed ATP synthesis (Cortez-Pinto *et al.*, 1999). mtDNA levels, protein expression and activity of respiratory complexes are also decreased in liver mitochondria (Haque , Sanyal, 2002; Perez-Carreras *et al.*, 2003), pointing to a role for oxidative stress mechanism.

Hepatic steatosis indeed causes cellular damage and ROS production. Our group has shown that rat hepatoma FaO cells loaded with oleate/palmitate to mimic liver steatosis resulted in higher production of ROS and lipid peroxidation, stimulation of catalase activity and activation of NF-κB. Lipid droplet accumulation also increased levels of peroxisome proliferator-activated receptors (PPARs) and sterol regulatory element-binding protein-1c (SREBP-1c) (Vecchione *et al.*, 2016). In the intact hepatocyte HepG2 cells incubated with saturated fatty acids (a model resembling NASH), mitochondrial function was depressed together with inhibition of mtDNA gene expression and accelerated degradation of respiratory chain subunits (Garcia-Ruiz *et al.*, 2015). In line with these results, we recently showed that sequential exposure of hepatocytes to high concentrations of fatty acids (FAs) and TNF-α mimic in vitro the progression of NAFLD from simple steatosis to steatohepatitis. Several damages were observed at a mitochondrial level and elsewhere in the hepatocyte (reduced hepatocyte viability, increased apoptosis and oxidative stress, reduction in lipid droplet size, and up-regulation of I-κB kinase-interacting protein and adipose triglyceride lipase expressions). Notably silybin, the extract of the milk thistle seeds counteracted the FA-induced mitochondrial damage, increased the mitochondrial size and improved the mitochondrial cristae organization; stimulated mitochondrial FA oxidation; reduced basal and maximal respiration and ATP production in steatohepatitis hepatocytes; stimulated ATP production in steatotic cells, and rescued the FA-induced apoptotic signals and oxidative stress in steatohepatitis hepatocytes (Vecchione *et al.*, 2017). In steatotic livers, ROS formation is increased at the mitochondrial respiratory chain level and determines oxidation of unsaturated lipids (Grattagliano *et al.*, 2008; Grattagliano et al., 2003; Yang et al., 2000). The activity of complex I of the respiratory chain is also reduced (-35%) in mitochondria from fatty livers and is associated with changes in state 3 respiration (Petrosillo *et al.*, 2007); hydrogen peroxide generation and oxidized cardiolipin are significantly increased (Grattagliano et al., 2008; Petrosillo et al., 2007). ROS affect the mitochondrial complex I activity by oxidizing cardiolipin which is required for the function of this enzyme complex (Paradies *et al.*, 2002).

Oxidation, glutathionylation and nitrosylation of mitochondrial proteins occur as a response to oxidative stress and result in post-translational modification of proteins by carbonyl and disulfide formation or by thiol nitrogen exchange. Factors contribute to a block of the electron flow in the respiratory chain resulting in subsequent generation of ROS. This vicious circle involves ROS-mediated antioxidant depletion, and the deficient capacity of mitochondria to inactivate ROS (Grattagliano et al., 2003). Ultimately, protein and lipid oxidation, and cytokine production are increased. Hepatocytes react to fat deposition with an early increase of GSH and thioredoxin to prevent lipid and protein oxidation (Grattagliano et al., 2008). Also, increases of protein mixed

disulfides (PSSG), nitrates and nitrosothiols are consistent with both pro-oxidant protein modifications and increased nitric oxide (NO) synthesis. A critical role for mitochondrial GSH in the development of NASH was in fact proposed (Garcia-Ruiz , Fernandez-Checa, 2006). GSH depletion sensitizes hepatocytes to inflammatory cytokines and TNF-α. Mitochondrial GSH content declines more rapidly than cytosolic GSH, suggesting mitochondria as specific early target for oxidative changes (Grattagliano et al., 2008).

Other pathogenic factors including nitric oxide play a role for the progression of liver steatosis and appearance of fibrosis. Thioredoxin, a redox active protein regulates of PSH/PSSG ratio. Thioredoxin is actively involved in the regulation of NO activity via cleavage of nitrosothiols (Nikitovic , Holmgren, 1996; Stoyanovsky *et al.*, 2005) which are formed by conjugation of NO with free thiols and oppose dangerous reactions such as peroxynitrite formation. Nitrosothiols also act as intracellular messengers that control mitochondrial functions (Arnelle , Stamler, 1995; Grattagliano *et al.*, 2004a). Major alterations of thioredoxin levels have been observed with ongoing liver steatosis and have been associated with PSSG and nitrosothiols formation (Garcia-Ruiz *et al.*, 2006). Increased peroxynitrite formation is associated with a variety of interactions, including protein nitration and generation of nitrotyrosine (Sanyal et al., 2001).

Additional mechanisms of mitochondrial damage include increased production of angiotensin II associated with oxidative stress. Animals with elevated endogenous angiotensin II levels display mitochondrial alterations with reduced β-oxidation and consequent decreased mitochondrial palmitate oxidation, decreased enzymatic activities, and expression of mitochondrial proteins, including cytochrome c, cytochrome c oxidase subunit 1, and TFAM. Administration of angiotensin II receptor blockers or superoxide dismutase/catalase mimetic treatment improves these abnormalities (Wei *et al.*, 2009). Fatty livers show about 35% decrease of catalytic β-F1 subunit of the F0F1-ATP synthase. The process of aging might also influence other pathways in the steatotic liver. Under starvation, mitochondrial oxidative injury is exacerbated to a greater extent in fatty livers. In the steatotic liver, fasting induces a further decrease of the ATP levels which is accompanied by a 70% fall of the catalytic β-F1 subunit. These changes may account for the observed reduction in the synthesis of ATP (Fernández-Checa *et al.*, 1998). Liver steatosis is also favored by prolonged intake of drugs such as amiodarone or valproate (Berson *et al.*, 1998), and aging is a strong risk factor for medication-induced damage. Amiodarone or valproate accumulate in mitochondria and induce inhibition of fatty acid oxidation and electron transfer chain (Berson et al., 1998). In support of the key role of mitochondria in NAFLD, recent data indicated the critical role of the mitochondrial pyruvate carrier MPC, a heterologous complex made of MPC1 and MPC2 proteins in the inner mitochondrial membrane (Colca *et al.*, 2017). The complex is required for the

entry of pyruvate that is synthetized in the cytosol, in the mitochondrial matrix, where it will be further metabolized. MPC might become therefore the target for treatment of several metabolic and inflammatory diseases, namely diabetes (Chen *et al.*, 2012b; Colca *et al.*, 2013; McCommis *et al.*, 2015), and even NASH (McCommis *et al.*, 2016).

Although the above described observations suggest that fatty livers have compromised mitochondrial function, there are several evidences that the initial stages of the NAFLD condition are associated with an increase in mitochondrial mass, with or without increased mitochondrial fatty acid oxidation, and which serves as an adaptation response to excessive accumulation in the liver. This was elegantly demonstrated in human liver biopsies by Koliaki *et al*. (Koliaki *et al.*, 2015). This paper showed that when compared with isolated mitochondria from lean individuals, their counterparts from obese humans with or without NAFLD had 4.3- to 5.0-fold higher maximal respiration rates, despite similar mitochondrial content. In opposition to this, and despite the fact that NASH patients featured higher hepatic mitochondrial mass, a 31-40% lower maximal respiration associated with greater hepatic insulin resistance, mitochondrial uncoupling, and leaking activity was described.

Initial adaptation to a fatty-rich environment contributes to enhance fatty acid oxidation, which means that hypothetically, accelerating the rate of fatty acid burn by mitochondria could be an effective therapeutic strategy. In fact, a liver-targeted mitochondrial protonophore was described to promote a mild depolarization of the inner membrane, contributing to increase electron transfer and fatty acid oxidation. In rodent models for NAFLD and diabetes type 2 (T2D), this approach appears to reverse hypertriglyceridemia, hepatic steatosis, insulin resistance, and hyperglycemia (Perry *et al.*, 2013). Another approach involved Adenovirus-mediated liver expression of a malonyl-CoA-insensitive CPT1A (CPT1mt) in a high fat/high sugar animal model, with the ultimate objective of accelerating mitochondrial fatty acid β-oxidation. This approach was able to reverse insulin resistance and glucose intolerance, although not affecting steatosis (Monsenego *et al.*, 2012). The important role of mitochondria in the context of NAFLD and its progression to NASH is well demonstrated by two recent findings. One of them demonstrates that mtDNA, a pro-inflammatory molecule per se (Boyapati *et al.*, 2017; Zhang *et al.*, 2016), when released from fatty liver hepatocytes, causes liver inflammation by TRL-9 activation (Garcia-Martinez *et al.*, 2016), which can be an important component of the transition between NAFLD and NASH. In another interesting development, it was recently demonstrated that when mitochondria isolated from hepatoma cells were injected into rodents with fatty liver, the phenotype was improved. Since exogenous mitochondria were tagged with green-fluorescence protein (GFP), it was possible to demonstrate accumulation in mouse liver, lung, brain, muscle, and kidney. How mitochondria

entered the different cells and were able to maintain the integrity and restore metabolic activity was not explained.

Bile mitochondria and aging

Bile is an aqueous solution containing organic solutes, inorganic electrolytes, and trace amounts of proteins. The three classes of biliary lipids include unesterified cholesterol, phospholipids, and bile acids (i.e., primary bile acids: cholic and chenodeoxycholic acid; and secondary bile acids derived from 7α-dehydroxylation of the primary bile acids in the liver and by intestinal bacteria in the ileum and colon: deoxycholic, lithocholic, ursodeoxycholic, sulfolithocholic, and 7α-oxo-lithocholic acids) (Di Ciaula et al., 2017a). Earlier studies have shown that hepatobiliary function as assessed by bile flow and bile acid secretion decline with age in male inbred rats (Schmucker *et al.*, 1985). Moreover, a number of liver enzymes are involved and affected by aging (Schmucker, 2001). Choi *et al.* (Choi *et al.*, 1987) has found a significant decrease in the enzymatic activity of cholesterol 7α-hydroxylase in rats 5 to 32 weeks of age. In the study by Wang (Wang, 2002), gallstone-susceptible C57L mice and resistant AKR mice of both genders split into young adult, older adult, and aged groups (8, 36, and 50 weeks of age, respectively) were each fed a lithogenic diet for 8 weeks. Increasing age augments biliary secretion and intestinal absorption of cholesterol, while reducing hepatic synthesis and biliary secretion of bile acids. Einarsson *et al*. (Einarsson *et al.*, 1985) analyzed biliary lipid composition in 60 healthy lean and gallstone-free subjects of various ages and both genders. They found a positive correlation between age and cholesterol saturation index and a negative correlation with bile acid synthesis and the pool size of the cholic acid. A role for a decline in the enzymatic activity of cholesterol 7α-hydroxylase and 7α-hydroxylated cholesterol (as a marker of bile acid synthesis) has been advocated in humans by the study of Bertolotti *et al*. (Bertolotti *et al.*, 1993). By contrast, Valdivieso *et al*. (Valdivieso *et al.*, 1978) found increased proportion of biliary cholesterol and lithogenic index in gallbladder bile of elderly female Chilean patients without significant changes in bile acid metabolism.

Additional age-dependent changes in lipid metabolism include a decrease of hepatic clearance of HDL-cholesterol in older rats (Bravo *et al.*, 1994). Lipophilic and secondary bile acids, moreover, are able to change the membrane composition of hepatocyte mitochondria (where the inner membranes harbor the cytochrome P450 oxido-reductase system). Thus, changes in the membrane fatty acid composition leads to a decrease of the activity of the mitochondrial enzyme system; this step makes enzymes, defective in handling free radicals which originate during the normal process of energy production and detoxification. As a consequence, free radicals may attack

membrane polyunsaturated fatty acids to initiate and propagate lipid peroxidation, leading to formation of aldehydic lipid peroxidation products (Pandey , Shukla, 2000).

Gallstones, mitochondria and aging

Increasing age is associated with increased risk of gallbladder stones of either types, i.e., cholesterol and pigment stones (Palasciano *et al.*, 1989; Portincasa *et al.*, 2006; Portincasa , Wang, 2015, 2016). It is estimated that the prevalence of gallstone disease is about 50% in females aged 70-75 and in males aged 80-85 (Diehl, 1991; Sama *et al.*, 1990). Pigment stones account for about 20-25% of all gallstones, and form as a consequence of abnormalities in bilirubin metabolism arising in the gut-liver axis. The most common risk factors are hemolytic anemias, liver cirrhosis, Crohn's disease, or extended ileal resection, biliary infection, cystic fibrosis, vitamin B12/folic acid deficient diets, and genetic factors due to UGT1A1 mutation. Age *per se* represent a risk factor for such biliary diseases. Cholesterol gallstones represent about 75-80% of all gallstones in western societies, and are due to at least five pathogenetic defects: 1) genetic factors and *LITH* genes; 2) hepatic hypersecretion of biliary cholesterol, leading to non-physiological and sustained supersaturation of gallbladder bile with cholesterol; 3) accelerated phase transitions of cholesterol in bile; 4) hypomotile gallbladder harvesting the immune-mediated inflammation, as well as hypersecretion and accumulation of mucin gel in the lumen; and 5) increased absorption of cholesterol at the small intestinal enterocyte level (Wang *et al.*, 2017a; Wang et al., 2017b; Wang *et al.*, 2017 pp. 1-676).

A more detailed analysis of the elegant study by Wang (Wang, 2002) found that on the lithogenic diet, cholelithiasis prevalence, gallbladder size (i.e., a marker of gallbladder hypomotility and stasis), biliary lipid secretion rate, and HMG-CoA reductase activity (i.e., a marker of cholesterol biosynthesis in the liver) are significantly greater in C57L mice of both genders compared to those in AKR mice. The activity of cholesterol 7α-hydroxylase (i.e., a marker of hepatic bile acid synthesis) is significantly lower in C57L mice than in AKR mice. Of note, increasing age augments biliary secretion and intestinal absorption of cholesterol, while reducing hepatic synthesis and biliary secretion of bile acids, and decreasing gallbladder contractility. Putting these data together, it is clear that all the above-mentioned age-dependent factors greatly increase susceptibility to cholesterol cholelithiasis in C57L mice. Mitochondria might play a role in some steps of lithogenesis. Biliary proteins and their redox status have been demonstrated by our group in gallstone patients undergoing cholecystectomy and serial analyses of bile composition and crystallization (Grattagliano *et al.*, 2009). The role of gallbladder contractility during fasting and postprandially is essential in preventing stasis of cholesterol supersaturated bile and precipitation of

either cholesterol crystals or bilirubinate pigments (Di Ciaula *et al.*, 2017b; Portincasa *et al.*, 1994; Portincasa *et al.*, 2004; Portincasa et al., 2006). Mitochondrial Ca^{2++} handling is implicated in spontaneous rhythmic activity in smooth muscle and interstitial cells of Cajal. Indeed, disruption of the mitochondrial membrane potential (by carbonyl cyanide 3-chlorophenylhydrazone, carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone, rotenone, and antimycin A) reduced or eliminated action potentials, Ca^{2++} flashes, and Ca^{2++} waves in typical of the gallbladder smooth muscle. Data suggest that mitochondrial Ca^{2++} handling accounts for spontaneous electrical activity, a step involved in gallbladder tone and motility (Balemba *et al.*, 2008). Gallbladder mitochondria are also involved in other pathways such as drug-mediated effects on apoptosis during tumorigenesis in cells and mice (Bao *et al.*, 2014; Li *et al.*, 2015a; Liu *et al.*, 2013; Shu *et al.*, 2014; Wang *et al.*, 2014; Weng *et al.*, 2014) and treatment with oxysterols causing cytochrome c release in the dog (Seo *et al.*, 2004). Both aspects are potentially linked to the aging process of the gallbladder with or without stone-formation ability. Accumulation of gut-microbiota-derived secondary bile acids in the aging, hypomotile gallbladder, moreover, by virtue of their lipophilic action, might change the membrane composition of and contribute to gallbladder carcinogenesis (Pandey , Shukla, 2000).

Epidemiological and clinical investigations have clearly demonstrated that during the aging process, a person progressively loses the ability to maintain normal physiological functions due to structural alteration of cells or dysfunction of vital organs such as the liver. Aging is a major risk factor for most chronic hepatobiliary disorders because the volume and blood flow of the liver progressively reduce with age. As the elderly population is increasing due to an extended lifespan, the number of elderly patients with complicated hepatobiliary diseases has grown in the past decades. New and effective strategies for enhancing liver functions should be extensively investigated to improve life quality of human beings.

Copper toxicity in age-related diseases and Wilson disease

The redox active transition metals copper and iron are fundamental for vital enzymes (Festa, Thiele, 2011; Winter *et al.*, 2014). However, upon overload they might become cell-toxic if uncontrolled redox activity occurs. Here we restrict ourselves to the detailed discussion of copper. Aqueous free copper (and iron) may catalyze the formation of hydroxyl radicals ($OH^{\cdot}$) via Fenton- and Haber-Weiss-based chemistry causing the subsequent damage to proteins, DNA and lipids that result in cell death **(Figure 5)** (Leonard *et al.*, 2004). However, under physiological conditions, this redox activity is prevented by the tight incorporation of copper into the active sites of various vital enzymes that results in the absence of intracellular free copper pools (Kaim , Rall, 1996; Lippard, 1999; Rae *et al.*, 1999; Rubino , Franz, 2012). At present, 54 copper-binding or transporting

proteins have been identified in the human proteome. Together they ensure the safe transport of the transition metal to the target enzymes (Blockhuys *et al.*, 2017). Protein copper binding occurs mainly via cysteine residues (*e.g.*, metallothionein), but can also be performed by histidine (*e.g.,* ceruloplasmin) or methionine (*e.g.,* copper transporter Ctr1) residues (Koch *et al.*, 1997). In cells, the most important copper dependent enzyme resides in mitochondria, the cytochrome c oxidase (complex IV) that is responsible for proper cell respiration and oxidative phosphorylation (Wainio *et al.*, 1959). In serum, the transition metal is mainly present tightly bound to the ferroxidase ceruloplasmin (around 70%), with a small part (around 30%) available as so called "free" or "loosely bound" copper associated to amino acids or albumin (Linder, 2016).

Under pathological situations, the tight regulation of copper uptake, distribution and excretion can be disturbed leading to increased free copper levels that are highly detrimental to cells. Age-related diseases like AD, PD, diabetes, cardiovascular diseases and cancer have been suggested to be associated with increased serum free copper levels (Brewer, 2010). For example, in AD, high free copper serum levels (e.g., due to increased copper uptake via drinking water) were linked to an increased risk for cognitive decline (Sparks , Schreurs, 2003; Squitti , Polimanti, 2013). It was shown, that copper interacts with the characteristic beta-amyloid plaques resulting in increased ROS production and neuronal death (Huang *et al.*, 1999). Besides this "direct" impact of copper on AD progression, copper was also found to oxidize low-density lipoprotein receptor-related protein responsible for the efflux of beta-amyloid from the brain (Singh *et al.*, 2013). However, there are also conflicting studies reporting a reduced beta-amyloid production by addition of dietary copper in mice (Bayer *et al.*, 2003) and a correlation between cognitive decline and low copper plasma concentrations in patients with mild to moderate AD (Pajonk *et al.*, 2005). Additionally, high serum copper levels may be associated with an increased risk for several types of cancer, e.g., lung cancer, neoplastic kidney tissue, leukaemia and hepatocellular carcinoma (Hrgovcic *et al.*, 1973; Karcioglu *et al.*, 1978; Mateo *et al.*, 1979; Poo *et al.*, 2003). Though, whether high copper levels are a cause or "bystander" effect of these malignancies is still under investigation. Thus, at present, future studies have to further substantiate the link between free copper and age-related diseases.

In contrast to the mentioned diseases, copper overload (especially in the liver) is a well-established cell-death causative feature in Wilson disease (WD) (Bearn, 1953; Cumings, 1948). In WD, the hepatocyte demise is linked to copper induced mitochondrial dysfunction. WD is an autosomal inherited disorder caused by mutation(s) in the gene encoding for the copper transporting ATPase ATP7B (Gitlin, 2003; Tanzi *et al.*, 1993). In hepatocytes, this protein facilitates the transport of excess copper into the bile (Bull *et al.*, 1993). In WD patients, the dysfunction of

ATP7B results in the accumulation of massive amounts of copper, primarily in the liver and brain. If untreated, WD is fatal (Liver., 2012).

Mitochondria were identified as first responders in WD patients as well as in WD animal models. In WD, mitochondria present with dramatically increased copper levels (humans (Sokol *et al.*, 1994), animal models (Lichtmannegger *et al.*, 2016; Zischka *et al.*, 2011)), structural abnormalities ranging from distorted cristae structure to electron-dense inclusions and detachment of the inner and outer membrane (humans (Sternlieb, 1968, 1992; Sternlieb , Feldmann, 1976), animal models (Huster *et al.*, 2006; Lichtmannegger et al., 2016; Roberts *et al.*, 2008; Sternlieb *et al.*, 1995; Yurkova *et al.*, 2011; Zischka et al., 2011)), decreased ETC complex activities (humans (Gu *et al.*, 2000), animal models (Roberts et al., 2008; Sauer *et al.*, 2011)) and a reduced ATP production capacity (animal models (Lichtmannegger et al., 2016)).

These structural and functional alterations are accompanied by the direct attack of copper on mitochondrial protein/peptide thiol residues (Nakamura , Yamazaki, 1972; Zischka et al., 2011). Moreover, treating intact liver mitochondria with copper (in the presence of reducing agents like DTT or GSH) resulted in WD mitochondrial phenotypes (Zischka et al., 2011). This latter finding questions the hypothesis that ROS (resulting from copper-based Fenton reaction) are primarily causative for mitochondrial structure changes, although such ROS might be relevant in subsequent mitochondrial destruction (Lichtmannegger et al., 2016; Zischka et al., 2011). It rather appears that thiol-residues in scavenging proteins like metallothionein but also in vulnerable enzymes like the ATP synthase (complex V) are prime copper targets (Duncan *et al.*, 2006; Yagi , Hatefi, 1987). Detrimental outcomes by such mitochondrial functional depletion together with persistent copper overload may consequently pave the way for further mitochondrial and subsequently cellular destruction.

Studies in WD patients described a reduced antioxidative defense system (reduced GSH, GST, SOD1/2) (Bruha *et al.*, 2012; Nagasaka *et al.*, 2006; Summer , Eisenburg, 1985), decreased levels of Vit-E in the serum (that correlated with free copper serum level) (von Herbay *et al.*, 1994) and mitochondrial DNA deletions (Mansouri *et al.*, 1997). Additionally, aconitase activity, a classical mitochondrial marker for ROS damage to proteins was reduced (Gu et al., 2000). These findings were further confirmed by studies in WD animal models. Here, an increased lipid peroxidation (Kumar *et al.*, 2016; Ohhira *et al.*, 1995; Rui , Suzuki, 1997; Samuele *et al.*, 2005; Yamada *et al.*, 1992; Yamamoto *et al.*, 1999), DNA damage (Chung *et al.*, 1999; Nair *et al.*, 1996; Yamamoto *et al.*, 1993; Yu *et al.*, 2016), decreased anti-oxidative defense system (GPx, GSH) (Kumar et al., 2016; Samuele et al., 2005; Yamamoto et al., 1999) as well as reduced free protein thiols were described (Samuele et al., 2005; Zischka et al., 2011). Thus, oxidative damage is clearly

associated with WD. However, it needs to be emphasized that these features mostly appear in WD patients or animal models at severe liver damage, i.e., at late disease stages.

Importantly, diverse therapy strategies addressing increased oxidative stress in WD were evaluated in animal models, in particular the LEC rat. Here, a surplus of Vit-E resulted in later onset of hepatitis and reduced lipid peroxidation in male rats compared to control animals (Yamazaki *et al.*, 1993). In contrast, Hawkins et al. described no effect of Vit-E and β-carotene, but a delayed onset of jaundice and decreased mortality in animals with enforced administration of proline (80%) and Vit-C (65%) (Hawkins *et al.*, 1995). Another strategy used by Yamashita and colleagues was the use of the spin-trapping antioxidant phenyl butyl nitrone that resulted in reduced lipid peroxides and delayed hepatitis and mortality (Yamashita *et al.*, 1996). This finding was further underlined by studies of Asanuma et al., who described delayed hepatitis, reduced lipid peroxidation and decreased oxidative DNA damage in treated animals, while the liver copper level was unaltered (Asanuma *et al.*, 2007). Additionally, unsaturated fatty acids, e.g. linolenic acid and linoleic acid, reduced the incidence and onset of hepatitis (Shibata *et al.*, 1999) and increased animal survival by stimulation of bile acid synthesis (Du *et al.*, 2004). However, curcumin (Frank *et al.*, 2003), quercetin and phytic acid (Kitamura *et al.*, 2005) failed to increase survival or reduce liver damage. In contrast, DL-alpha lipoic acid, a dithiol containing cofactor of the pyruvate dehydrogenase complex of mitochondria, reduced liver damage and increased the anti-oxidative defense capacity by upregulation of glutathione peroxidase and reductase (Yamamoto *et al.*, 2001). Additionally, NAC, a prodrug to cysteine and therefore a precursor for glutathione, reduced liver copper and overall liver damage mainly due to metal chelation rather than ROS scavenging (Kitamura et al., 2005). Additionally, fermented brown rice (Shibata *et al.*, 2006) and coffee (Katayama *et al.*, 2014) were tested to reduce liver damage in LEC rats. Both treatment options were able to prolong survival. Whereas fermented brown rice reduced the incidence of hepatitis, coffee delayed the onset of hepatitis in treated animals compared to untreated rats.

In conclusion, the redox active transition metal copper may be highly detrimental to cells upon toxic overload. While such a role is currently under debate in age-related diseases like AD, there is ample evidence of its destructive power on hepatic mitochondria in WD. With respect to the toxic mode of action of copper on mitochondria, susceptible thiol residues appear as early copper targets. In agreement, treatment regimens that affect the intracellular thiol status (DL-alpha lipoic acid, N-acetylcysteine) were able to increase survival by delaying hepatitis onset or decreasing hepatitis incidence. In contrast, radical scavengers that would counteract a (Fenton chemistry based) ROS burden (e.g., Vit-E, phenyl butyl nitrone) only showed slight effects on WD progression.

Nevertheless, such oxidative stress damage may be present in WD patients and animal models with late stage disease.

Mitochondria, Mitochondrial Associated Membranes, ROS and diabetes in aging

Type 2 diabetes is multifactorial disorder characterized by chronic hyperglycemia due to impaired insulin secretion from pancreatic β-cells and insulin resistance in target tissues. Nowadays it is estimated, that up to 70-90% of patients with T2D are overweight or obese with aging being an important contributing factor (Al-Goblan *et al.*, 2014). Particularly, excessive lipid intake or age-related prolonged ectopic fat deposition in tissues is believed as the primary reason for insulin resistance development, the islet dysfunction and disease progression (Janikiewicz et al., 2015; Szymanski *et al.*, 2017). There is now ample evidence that diabetes and obesity-related metabolic dysfunction can accelerate the progression of other age-related diseases and pathologies in both mouse models of disease as well as normally aging mice (Butterfield *et al.*, 2014; Farr *et al.*, 2008; Morrison *et al.*, 2010). For example, several reports have shown high fat diets, or insulin resistance, can accelerate learning and memory loss as well as neurodegeneration in different mouse models of AD (Kadish *et al.*, 2016; Knight *et al.*, 2014; Maesako *et al.*, 2015; Morrison et al., 2010; Petrov *et al.*, 2015). It is thus possible that obesity-related insulin resistance may be accelerating the aging progression (Salmon, 2016), and mitochondria and oxidative stress may play important role in this process.

Mitochondria associated membranes are important hubs for insulin signaling due to several proteins that were detected at the MAM location, including protein kinase AKT, mTORC2, phosphatase and tensin homolog deleted on chromosome 10 (PTEN) (Tubbs , Rieusset, 2017); however such interconnection awaits further investigations. Since T2D is associated with alterations in lipid metabolism and ER-mitochondria contact sites foster lipid species exchange between these organelles, it is a favorable hypothesis that MAM integrity and action participate to lipotoxicity in diabetes. In fact, MAM integrity was required for insulin signaling and it was altered in palmitate-induced insulin resistant HuH7 hepatic cells, as well as in liver of leptin-deficient ob/ob mice and high-fat and high-sucrose fed mice. Furthermore, disruption of MAM integrity by genetic or pharmacological inhibition of MAM-residing protein cyclophilin D induced insulin resistance in animals, and led to aberrant insulin signaling in human primary hepatocytes. Enhancement of MAM formation restored hepatic insulin signaling and action of HuH7 cells and in diabetic mice (Tubbs *et al.*, 2014). In addition, an abnormal increase in MAM formation was reported in livers of ob/ob, and high-fat fed mice, alongside mitochondrial calcium overload, compromised mitochondrial capacity and augmented oxidative stress (Arruda *et al.*, 2014).

Oxidative stress is considered one of the major risk factors in the onset and progression of T2D. Since the 1960s (Giugliano *et al.*, 1996) hyperglycemia has been hypothesized to contribute to oxidative stress either by direct production of ROS (Nishikawa *et al.*, 2000) or by altering the redox balance. It has been demonstrated that hyperglycemia induces an increased polyol pathway flux and increased intracellular formation of advanced glycation end-products, and contributes to an oxidative stress environment by activating PKC and causing overproduction of superoxide via mitochondrial ETC (Brownlee, 2001). As emphasized in this review, mitochondria play an important role in the maintenance of cellular redox status, thereby acting as a ROS and redox sink and limiting NADPH oxidase activity. The main sources of mitochondrial ROS under physiological conditions are complexes I and III, which produce $O_2^{\bullet -}$ mainly on the matrix side, where it is rapidly transformed into H_2O_2 by SOD2. Brownlee and colleagues proposed that the mitochondrial transport chain plays a key role in hyperglycemia-induced overproduction of superoxide and in the development of secondary complications such as endothelial dysfunction (Brownlee, 2005). Using ρ^0 cells lacking functional ETC, they demonstrated that the effect of hyperglycemia on ROS production was completely lost. Another study by Nishikawa discovered that T2D alters the primary site of superoxide generation such that complex II becomes the primary source of electrons contributing to superoxide formation under diabetic conditions (Nishikawa et al., 2000). Yoon and colleagues (Yu *et al.*, 2006) found that dynamic changes in mitochondrial morphology are an important factor contributing to ROS overproduction under high glucose (HG) conditions. Mitochondria become rapidly fragmented in HG concentrations with a concomitant increase of ROS. These findings suggest that mitochondrial dynamics may influence ROS overproduction in diabetes, obesity, and other related disorders.

Conventional antioxidants neutralize ROS on a one-to-one basis, while hyperglycemia-induced overproduction of superoxide is a continuous process. Riley (Salvemini *et al.*, 1999) proposed a novel type of antioxidant, a catalytic antioxidant, such as SOD/catalase mimetic, which works continuously, similar to the enzymes for which these compounds are named. However, SOD is not yet in widespread use in human clinical medicine due to some obstacles: none of the three human SODs possess the necessary pharmacological properties to make it a clinically useful therapeutic agent (McCord , Edeas, 2005).

Another source of ROS in diabetes is NADPH oxidase. This enzyme has been implicated as a major source of ROS generation in the vasculature in response to high glucose and advanced glycation end-products (Thallas-Bonke *et al.*, 2008). This study suggests that blockade of NADPH oxidases is a valid intervention to consider for combating established diabetic nephropathy. A study by Li & Shah (Li , Shah, 2003) supports the theory that NADPH is a mediator of diabetic

complications and its action can be suppressed by a variety of PKC inhibitors, implicating this family of kinases in the regulation of hyperglycemia-induced NADPH oxidase activity. Production of ROS from mitochondria has received great attention, and it is now becoming clear that it may be regulated under physiological conditions and plays and important role in redox signaling. A recent work by Darley-Usmar and colleagues (Chacko *et al.*, 2010) hypothesize that MitoQ, the most-studied mitochondria-targeted antioxidant, decreased mitochondrial ROS production and showed beneficial effects in diabetic nephropathy. In this study, $Ins2^{+\backslash\text{-AkitaJ}}$ mice were selected as a model of diabetes, showing a dysfunction in pancreatic β-cells, to test the potential benefits of MitoQ therapy. This mouse model develops insulin resistance over time and has many of the characteristics of chronic hyperglycemia (Barber *et al.*, 2005; Bugger *et al.*, 2008). Of the potential compounds available, the ubiquinone analogue MitoQ has received particular attention, since it is orally bioavailable, has low toxicity and reaches concentrations of 200-700 pmol/g of weight in the tissue of a number of organs, including the kidney. The treatment seems to protect mitochondrial redox signaling from hyperglycemia-induced alterations and would thereby ameliorate diabetic nephropathy. Another study by Wang and colleagues proposes the use of vanadium compounds in therapeutic treatment of diabetes and in cancer prevention (Zhao *et al.*, 2010).

Mitochondria also play an important role in β-cell function as insulin release in response to glucose levels and in the sensing of oxygen tension in the carotid body and pulmonary vasculature, two events involved in diabetes pathologies (Duchen, 2004). One of the hypotheses for induction of β-cell dysfunction focuses on changes in the expression and function of UCP2. The inner mitochondrial membrane UCPs are thought to be major facilitators of uncoupled respiration and may modulate the pathophysiology of diabetes (Sack, 2006). It has been proposed that UCP activity and expression contribute to an increase in superoxide formation under diabetic conditions (Krauss *et al.*, 2003). UCP2 is thought to negatively regulate glucose-stimulated insulin secretion by reducing the amount of ATP produced **(Figure 6)**. Another member of this family, UCP3, seems to have a positive role in T2D. This isoform, very enriched in skeletal muscle, is downregulated in pathologic condition and conversely increased in response to exercise training. UCP3 confers resistance against oxidative stress and the genetic deficiency of UCP3 in primary skeletal myocytes results in excess ROS levels under normoxic and hypoxic conditions (Lu , Sack, 2008). To test whether the induction of UCP3 could modulate insulin sensitivity, a skeletal muscle transgenic mouse line harboring the human UCP3 gene was created (Clapham *et al.*, 2000). These mice are hyperphagic and lean with diminished adipose tissue mass, a phenotype consistent with uncoupled mitochondrial oxidative phosphorylation. Despite this, knock-out mice for UCP3 showed some divergent effects, i.e. glucose tolerance improvement, suggesting how the beneficial role of UCP3

may be skeletal muscle specific (for an intriguing discussion on molecular manipulation of mitochondrial metabolism and diabetes, see (Pagel-Langenickel *et al.*, 2010)).

Cells and tissues contain antioxidant defense mechanisms, which maintain their redox balance and aid in preventing the accumulation of ROS. T2D is associated with reduced levels of antioxidants such as GSH, Vit-C, and Vit-E (Jain, 1998). Thus, antioxidant therapy has been of great interest as a means to combat oxidative stress in diabetic patients. However, these treatments lack broad therapeutic effect across the patient population (Ceriello , Testa, 2009). Nevertheless, the current data rise an important, and rather unexplored, question of whether antioxidant treatment could be used in obese patients with metabolic dysfunction to prevent the progression of additional co-morbidities or slow the acceleration of the aging process caused by insulin resistance and chronic inflammation.

Mitochondria, ROS, cardiovascular pathology and aging

Cardiovascular diseases (CVDs) are multifactorial, but several lines of evidence suggest that mitochondrial dysfunction contributes to their pathophysiology. The underlying mechanisms appear to involve not only damage to the organelle and loss of bioenergetic function, but also disruption of mitochondrion-dependent redox-signaling pathways. Mitochondria are considered a major source of ROS and loss of control of their formation leads to mitochondrial oxidative damage and dysfunction; mitochondria are also important targets for ROS. ROS can lead to the activation of pathways that control cell differentiation and apoptosis, both of which are mechanisms of particular relevance to CVDs. Indeed, mitochondrial oxidative damage has been implicated in a range of degenerative conditions that include CVDs, namely atherosclerosis, hypertension, heart failure and ischemia/reperfusion (I/R) injury **(Figure 7)** (Delles *et al.*, 2008; Di Lisa , Bernardi, 2006; Madamanchi , Runge, 2007; Misra *et al.*, 2009).

Some of the most compelling evidence that mitochondrial ROS is a causative agent in the development of CVDs *in vivo* comes from experiments using transgenic mice to alter expression of mitochondrial antioxidant proteins. Initial experiments using genetic knockouts showed that mice lacking SOD2 produce huge amounts of mitochondrial ROS and develop cardiomyopathy within the first weeks of birth (Li *et al.*, 1995; Schriner et al., 2005). Nowadays it is widely accepted that deficiencies in mitochondrial antioxidants and/or regulatory proteins that modulate mitochondrial oxidant production promote the onset of CVDs. In a recent work Nox4, a member of the NADPH oxidases (Nox) family expressed primarily in the mitochondria in cardiac myocytes, was reported to be a major source of superoxide production in the cardiovascular system. Nox4 mediates cardiac hypertrophy and heart failure in response to pressure overload. Upregulation of Nox4 increased

mitochondrial superoxide thereby directly mediating oxidative stress, mitochondrial dysfunction and myocardial cell death during pressure overload-induced cardiac hypertrophy. Since expression of Nox4 is upregulated by cardiac stress, including pressure overload, heart failure and aging, it could become an ideal target for pharmacological interventions to in the heart (Kuroda *et al.*, 2010). Another study shows sex differences in the phosphorylation of mitochondrial proteins, including aldehyde dehydrogenase 2 (an enzyme that detoxifies ROS-generated aldehyde adducts) and α-ketoglutarate dehydrogenase (one of the major source of ROS generation), resulting in a reduced production of ROS and cardioprotection in females (Lagranha *et al.*, 2010). In addition, mtDNA damage is increased in cardiovascular tissues of CVD patients, and it has been established that mtDNA mutations lead to increased ROS production (Aliev *et al.*, 2002).

ROS may be both a cause and an effect of hypertension, since increased blood pressure has been associated with an excessive endothelial production of superoxide and H_2O_2 in both animal models and humans with increased blood pressure (Puddu *et al.*, 2008). The participation of mitochondria in the pathogenesis of hypertension is also suggested by the involvement of UCPs in experimental and human hypertensive states (Table 2). In mice with doxycycline-inducible expression of UCP1 in arterial walls, UCP1 expression increases superoxide production and decrease the biological availability NO, causing increased blood pressure (Bernal-Mizrachi *et al.*, 2005). Also, a common polymorphism of the UCP2 gene has been associated with hypertension (Ji *et al.*, 2004); however, since the hypertension-associated allele was reported to increase transcription of the UCP2 gene, and UCP2 is known to diminish ROS production and emission from mitochondria (Teshima *et al.*, 2003), oxidative stress seems unlikely to be a link between the polymorphism and hypertension. ROS also underlie much of the endothelial cell (EC) damage related to heart disease (Davidson, 2010). Damage to the endothelium contributes to the development of atherosclerosis, and hence to possible myocardial infarction and subsequent heart failure. EC have relatively little dependence on oxidative phosphorylation for ATP production, however endothelial mitochondria are centrally involved in maintaining the fine regulatory balance between mitochondrial Ca^{2+} concentration, ROS production, and NO. Moreover, a general principle appears to be emerging in which mitochondrial ROS signals to other cellular sources, triggering ROS production from these. For example, angiotensin-II, hyperglycemia, or hypoxia, each increases mitochondrial ROS production in EC, which then stimulates NADPH oxidase via activation of mitogen-activated protein kinase (MAPK). Furthermore, a 'reverse' pathway, in which ROS produced by NADPH oxidase leads to increased mitochondrial ROS production (via activation of mitochondrial K_{ATP} channels, matrix swelling and alkalization) may also exist, suggesting a feedback amplification system (Daiber, 2010). These data demonstrate that ROS

production by endothelial mitochondria contribute to heart disease, therefore targeted scavenging of ROS may have various protective and beneficial effects on the heart. Interestingly, ROS play a pivotal role in atherogenesis, which is one of the major factors in the development of heart failure. Oliveira *et al*. (Oliveira *et al.*, 2005) have shown that mitochondria from atherosclerosis-prone hypercholesterolemic LDL receptor knockout mice have oxidative phosphorylation efficiency similar to that of control mice, while their net production of ROS and susceptibility to developing membrane permeability transition are both higher. Indeed, it has been demonstrated that exposure of endothelial cells to oxidized lipids such as oxLDL induces ROS/ reactive nitrogen species (RNS) formation (Zmijewski *et al.*, 2005). Recently, overexpression of mitochondrial thioredoxin (Trx2) in the endothelium has been proven to protect from atherosclerosis (Zhang *et al.*, 2007).

ROS production is also a feature of ischemia and is implicated in the pathogenesis of I/R injury (Misra et al., 2009). In acute myocardial infarction, two distinct types of damage occur to the heart: ischemic injury and reperfusion injury. The first results from the initial loss of blood flow and the second from the restoration of oxygenated blood flow. To maintain the MMP when O_2 is lacking, mitochondria hydrolyse ATP; this activity destroys any available ATP, favors Ca^{2+} accumulation, and increases the generation of ROS. During ischemia, ROS are generated in the myocardium, at complexes I and III of the ETC, and primarily formed by the degradation of adenosine. Increased ROS production (initiated during ischemia and exacerbated upon reperfusion) coupled with increased cellular [Ca^{2+}] are thought to be the main causes of reperfusion injury. The combined effects of ROS and elevated [Ca^{2+}] lead to the opening of the PTP, which ultimately induces apoptosis (Solaini , Harris, 2005). Ischemic preconditioning (IPC) is a very effective way of protecting the heart from reperfusion injury. This process involves one or more short non-lethal cycles of I/R that protect the heart against a subsequent prolonged period of ischemia. It seems clear that IPC protects the heart by reducing oxidative stress during I/R, and that this decreases PTP opening. However, the signaling pathways involved in mediating these effects have yet to be elucidated and several possibilities exist. For example, UCP2 overexpression in rat neonatal cardiomyocytes confers tolerance to oxidative stress by diminishing mitochondrial Ca^{2+} overload and reducing ROS generation, suggesting that UCP2 may mitigate ischemia-reperfusion injury and be a mechanism of cardioprotection (Teshima et al., 2003). Other data demonstrate that Nitrite (NO_2^-), a stable endocrine pool of nitric oxide that is selectively reduced to NO in ischemic conditions, mediates cardioprotection after I/R. The mechanism involves the inhibition of mitochondrial complex I by S-nitrosation, leading to the inhibition of electron transport and subsequent decrease in mitochondrial ROS generation, which limits apoptosis and cytotoxicity at reperfusion (Shiva *et al.*, 2007). Another possible mechanism involved mitochondrial ROS

formation catalyzed by p66Shc; hearts from p66Shc knockout mice display decreased ROS production and decreased myocardial injury caused by post-ischemic reperfusion. In particular the absence of this protein involved in mitochondrial ROS formation prevented the oxidative attack of structural components of cardiomyocytes, such as lipids and proteins (Carpi *et al.*, 2009).

Today, oxidative stress remains an attractive target for cardiovascular prevention and therapy. A general therapy for decreasing mitochondrial oxidative damage should be effective as a future therapy for CVDs. Since the mitochondrial respiratory chain in the IMM is considered as important intracellular source of ROS, a specific action of antioxidants on the mitochondrial respiratory chain may constitute an important mechanism of cardiovascular protection. For example, uncouplers such as dinitrophenol are protective, as they decrease MMP and thus decrease the activity of the mitochondrial Ca^{2+} uniporter, while F1FO inhibitors like oligomycin can decrease wasteful ATP hydrolysis. Unfortunately, these two agents show complementary deleterious effects: uncouplers increase ATP hydrolysis and F1FO inhibitors increase MMP and, presumably, increase mitochondrial Ca^{2+} uptake, thus they are used only as research tools. Other studies seeking to counteract the deleterious effects of ROS have shown that antioxidants such as Vit-E, CoQ10, and NAC decrease mitochondrial oxidative damage in different models. Despite, a number of pre-clinical and clinical lines of evidence, studies testing the effects of classical antioxidants such as Vit-C, Vit-E, or folic acid in combination with Vit-E have been disappointing. Vit-E or CoQ are quite lipophilic and tend to be retained in cell membranes and subsequently fail to achieve significant intracellular concentrations. NAC fails to provide significant antioxidant effect, presumably due to its low lipid solubility and tissue distribution. As these compounds do not significantly accumulate within mitochondria, their effectiveness remains limited. A number of low molecular weight catalytic antioxidants, generally called SOD mimetics, have been shown to provide some protection against I/R injury (Gianello *et al.*, 1996). Unfortunately, again, while these SOD mimetics are cell-permeable, they do not selectively target mitochondria.

Recent drug development efforts have focused their attention on reducing mitochondrial oxidative stress using mitochondrion-targeted antioxidants, which show potential as future therapies for CVDs **(Figure 7)**. MitoVit-E, one of the first TPP^+ (triphenyl phosphonium cation)-conjugates, has been shown to successfully decrease ROS production and apoptosis in bovine aortic EC exposed to oxidative stress (Dhanasekaran *et al.*, 2004), but was ineffective against hypoxic–ischemic striatal injury in neonatal rats (Covey *et al.*, 2006). One disadvantage of Vit-E is that it is not a catalytic antioxidant and its scavenging activity is not regenerated. In contrast, MitoQ consists of a TPP^+ covalently attached via an aliphatic linker to an ubiquinone derivative; after detoxifying an oxidant species, it is regenerated by the respiratory chain. MitoQ concentrates several

hundredfold within the mitochondria, is orally bioavailable, distributes to various organs, including the heart, without adverse effects in rats or humans, and decreases mitochondrial oxidative damage in rodent models of cardiac I/R injury (Adlam *et al.*, 2005). Administration of MitoQ to stroke-prone hypertensive rats improves endothelial function and attenuates cardiac hypertrophy (Graham *et al.*, 2009). Also a cyclosporine A (CsA) derivate, specifically targeted to mitochondria by conjugation to a TPP^+, has been designed (Malouitre *et al.*, 2010); CsA is well known to protect the heart from reperfusion injury by preventing PTP opening, however, side effects associated with PTP inhibitors limit their therapeutic potential. An alternative compound, called SkQ1, when perfused through isolated heart preparations or fed to rats, was able to reduce ischemia-induced arrhythmia and infarct size, despite the use of a concentration that was an astounding six orders of magnitude lower than that of MitoQ (Bakeeva *et al.*, 2008). On the other hand, the accumulation of these lipophilic cations in the mitochondrial matrix can disrupt MMP and inhibit mitochondrial respiration and ATP production. As a result, the therapeutic index of these molecules is rather low, with toxic concentrations being only ~10-fold greater than effective concentrations. The utility of TPP^+-conjugated antioxidants may also be limited by their requirement of MMP for mitochondrial uptake, especially considering that diseased mitochondria are unlikely to have normal MMP. The SS peptides, a novel class of mitochondrial-targeted antioxidant (see above, section vii), appears to hold great promise in the setting of anticipated ischemic intervals and may be used for minimizing I/R injury during angioplasty, coronary bypass surgery, cardiac surgery, and organ transplantation. SS-02, SS-31, and SS-20 have been reported to reduce myocardial ischemia-reperfusion injury in *ex vivo* and *in vivo* studies, and *in vivo* studies showed that SS-02 and SS-31 both reduced cardiac infarct size. A recent study showed that mitochondrial targeted peptide SS-31 ameliorates angiotensin-induced cardiomyopathy through the reduction of mitochondrial ROS, and provide a strong rationale for investigating the clinical application of SS-31 for treatment or prevention of hypertensive cardiovascular diseases (Dai *et al.*, 2011).

Furthermore, physical activity is another condition that increases antioxidant capacity in the heart by augmenting ROS scavenging enzymes such as catalase, superoxide dismutase, and glutathione peroxidase (Linke *et al.*, 2005; Powers *et al.*, 1994; Roh *et al.*, 2016; Somani *et al.*, 1995). Heat shock proteins (HSPs) plays important role in cellular defense against oxidative stress. It was shown that physical training induced HSP70 and HSP27 expression in trained old rats compared to sedentary old and young rats partially counterbalanced the heart age-related effects in the antioxidant system without altering peroxidation levels (Rinaldi *et al.*, 2006). The antioxidant action of exercise seems to be dependent on exercise protocol. While endurance exercise exacerbates oxidative stress and cardiac remodeling, acute or moderate aerobic exercise training

preserves cardiac health and prevents remodeling by maintaining myocardial defense system through stabilizing NRF2-antioxidant signaling (Narasimhan , Rajasekaran, 2016). Although aging hearts exhibit reduced NRF2-dependent antioxidant mechanisms, exercise training in aged mice increases NRF2 activity and induces of its electrophile-responsive/antioxidant-responsive elements (EpRE/ARE) target pathway to near-normal levels seen in young counterparts (Gounder *et al.*, 2012; Narasimhan , Rajasekaran, 2016). NRF2 also *trans*-activates genes of the antioxidant response (Kang *et al.*, 2005) and is coactivated by PGC-1α during oxidative stress (Aquilano *et al.*, 2013). Long- and short-term endurance exercise increases PGC-1α expression in cardiac muscle (Bayod *et al.*, 2012; Safdar *et al.*, 2011) and induces mitochondrial biogenesis (Chinsomboon *et al.*, 2009; Safdar et al., 2011). Besides these, cardioprotective effects of PGC-1 are mediated through its ROS-lowering effects, because PGC-1α induces glutathione peroxidase 1 and superoxide dismutase 2 and protects neural cells in culture from oxidative-stressor-mediated death (St-Pierre *et al.*, 2006). Moreover, (Ferrara *et al.*, 2008) demonstrated that exercise training, which significantly increases activity of SIRT1, a factor that plays important role in antioxidant pathways, could counteract age related systems impairment, by activation of antioxidant systems and DNA repair and disability (Cacciatore *et al.*, 2004), suggesting therefore a possible role of exercise training in conditioning lifespan. Like SIRT1, SIRT3 protects against oxidative stress, in large part through FOXO3a-dependent mechanisms that induce superoxide dismutase and catalase (Sundaresan *et al.*, 2009). Notably, these two sirtuins are upregulated during exercise in the heart and are positive modulators of PGC-1α activity (Palacios *et al.*, 2009; Planavila *et al.*, 2011). The enriched oxidative status caused by exercise training leads to number of beneficial effects, e.g. decreased arterial stiffness, improved endothelial function and metabolic and clotting setting, and reduced body weight (Corbi *et al.*, 2012). Other findings derived from clinical studies show that regular physical activity decreases cardiovascular comorbidity and mortality in adult and in elderly by restoring the protective effect of ischemic preconditioning and partially contrasting loss of antioxidant defense in the aged heart (Corbi et al., 2012).

Mitochondria, ROS, inflammation and aging

Recent studies highlight the important role of mitochondria, especially mitochondrial ROS (mtROS) production, as an upstream messenger in the induction of pro-inflammatory signaling. Inflammation initiates as a defensive immune response to pathogenic stimuli. This inflammatory response is a protective mechanism induced by the organism to remove the injurious stimuli and to promote the repair of damaged tissues. Dysregulation of the inflammatory response is observed in a variety of human diseases, including diabetes, neurodegeneration and cancer. Activation of

inflammatory processes start through the formation of the inflammasome: a high molecular weight multiprotein complex consisting of scaffold proteins and the adaptor protein ASC that recruits and binds caspase-1 (the initiator inflammatory caspase-1. There are four subfamilies of inflammasomes depending on the sensor molecule: NLRP3, NLRP1, NLRC4 (NLR family, CARD domain containing 4) and AIM2 (absent in melanoma 2) (Schroder , Tschopp, 2010). Upon activation, inflammasomes trigger the proteolytic maturation of pro-inflammatory cytokines, such as the potent IL-1β, to engage the immune defenses. Due to its association with numerous inflammatory diseases, the NLRP3 inflammasome is currently the most fully characterized (Martinon *et al.*, 2009).

A variety of danger signals, exogenous as well as endogenous, can activate the NLRP3 inflammasome, although the mechanisms of activation are poorly understood (Baroja-Mazo *et al.*, 2014; Tschopp, 2011). Recent evidence suggests that mitochondria may integrate these distinct signals and deliver information to NLRP3 inflammasomes. Zhou *et al*. found that mtROS are key signals that directly trigger NLRP3 inflammasome activation. These authors artificially induced mtROS production, either by blocking key enzymes of the respiratory chain (complex I or complex III) or by inhibiting mitophagy/autophagy, and demonstrated an increased amount of IL-1β secretion (Zhou *et al.*, 2011). In accordance with these findings, Nakahira *et al*. observed the fundamental role of autophagy in regulating mtROS production, demonstrating that decreased autophagy impairs mitochondrial homeostasis, increases mtROS levels and leads to NLRP3 inflammasome activation and IL-1β production (Nakahira *et al.*, 2011). Moreover, treatment with the antioxidant 4-amino-2,4-pyrrolidinedicarboxylic acid (APDC) blocked NLRP3 inflammasome activation and IL-1β secretion (Zhou et al., 2011). Consistent with these observations, defective mitophagy seems enhancing inflammasome activation. In fact, macrophages treated with 3-methyladenine (3MA) or silenced of the autophagy regulator Beclin 1 and autophagy protein 5 (ATG5) showed an hyper-activation of NLRP3 and IL-1β release upon stimulation with monosodium urate (MSU) crystals and nigericin due to the accumulation of damaged mitochondria and increased ROS generation, while Resveratrol treatment attenuated this effect (Wu *et al.*, 2016).

The link between NLRP3 inflammasomes and mitochondria is further confirmed by the subcellular localization of NLRP3 and ASC. Under resting conditions, NLRP3 is localized in the ER but relocates to MAMs and mitochondria after inflammasome stimulation. Similarly, ASC proteins translocate from the cytosolic fraction to mitochondria and MAM after stimulation (Zhou et al., 2011). Based on these findings, Zhou, *et al.* proposed a model in which NLRP3 acts as a sensor of mitochondrial status. This model was confirmed by evidence that NLRP3 and ASC are required for the release of mtDNA into the cytosol, a key step for caspase-1 activation and IL-1β

secretion (Nakahira et al., 2011). Additional evidence of the intimate relationship between mitochondria and inflammasome is sustained by the role of mitochondrial Ca^{2+} uniporter (MCU). Modulation of MCU expression has been shown to regulate the activation of NLRP3 inflammasome induced by Complement complex (Triantafilou *et al.*, 2013) or by Pseudomonas aeruginosa in lung epithelial cells, preventing mitochondrial ROS production (Rimessi *et al.*, 2015).

In contrast, other data reveal a distinct role for ROS in inducing inflammatory cytokines through a transcriptional-dependent mechanism, rather than through direct activation (van de Veerdonk *et al.*, 2010). Following this theory, Bulua *et al*. demonstrated that mtROS influence the transcription of pro-inflammatory cytokines through the regulation of the MAPK pathway (Bulua *et al.*, 2011; Kamata *et al.*, 2005). It was found that patients with an autoinflammatory syndrome (TRAPS, TNF receptor-associated periodic syndrome) possessed increased basal levels of mtROS in cells that are responsible for production of IL-6 and TNF-α, independent of the NLRP3 inflammasome activation. Indeed, increased levels of IL-6 and TNF-α were observed after inflammation induction in the absence of NLRP3, caspase-1 or IL-1R. All of these findings underscore a common pathway identifying mitochondria as a crucial source of ROS, driving inflammation through mechanisms either inflammasome-dependent or inflammasome-independent. MtROS in particular, but also other key factors in inflammation induction such as NLRP3 and IL-1β, might be therapeutically targeted for treating inflammatory diseases. It has already been demonstrated that blocking excessive ROS with antioxidants reduces inflammation. Treatments with mitochondria-targeted antioxidants such as Mito-TEMPO (Trnka *et al.*, 2009) or MitoQ (Murphy , Smith, 2007; Villalba *et al.*, 2010), scavengers specific for mtROS, have been shown to reduce the secretion of IL-1β or IL-6 *in vitro* (Bulua et al., 2011; Nakahira et al., 2011). Such findings are promising and warrant further study in controlled clinical trials to confirm the *in vivo* efficacy of antioxidants.

Chronic inflammation is associated with physiological and pathological aging (Franceschi *et al.*, 2007). Jurk *et al.* demonstrated that *nfkb1* -/- mice show premature aging. In particular, their data suggest that chronic low-grade inflammation can accelerate aging via ROS-mediated exacerbation of telomere dysfunction and cell senescence (Jurk *et al.*, 2014). Recently, the NLRP3 inflammasome has been shown to be implicated in several aging-related diseases like gout, T2D, obesity and cancer. AMP-activated protein kinase (AMPK) plays a pivotal role in the control of metabolic events involved in the pathophysiology of aging. Nevertheless, it has emerged as an important integrator of inflammation signaling (Cordero *et al.*, 2018). In fact, many of the various AMPK-dependent pathways regulate NLRP3 inflammasome activation during aging. Aging has a negative effect on the quality of immune responses, which increases the frequency and severity of infectious diseases. Recent results demonstrate the role of inflammation and oxidative stress in age-

related changes of immune cell survival factors in the bone marrow with an accumulation of IFN-y, TNF, and ROS which induce IL-15 and IL-6 expression. The treatment with the ROS scavengers NAC and Vit-C reduces cytokine levels, suggesting that antioxidants may be beneficial in counteracting immunosenescence by improving immunological memory in old age (Pangrazzi *et al.*, 2017). Furthermore, osteoarthritis, a whole-joint degenerative multifactorial disorder, is influenced by oxidative stress and aging. Cartilage of osteoarthritis patients has significantly more ROS-induced DNA damage than normal cartilage and this damage is mediated by IL-1β. The overproduction of reactive oxygen species in osteoarthritis regulate intracellular signaling processes, such as chondrocyte senescence and apoptosis, extracellular matrix synthesis and degradation along with synovial inflammation and dysfunction of the subchondral bone (Lepetsos , Papavassiliou, 2016).

All these findings identify the ROS-mediated inflammation as a possible target in the treatment of a wide range of aging-related diseases, suggesting the use of antioxidants, both natural and synthetic.

Mitochondria, ROS, cell death and aging

Apoptosis, the process that allows multicellular organisms to eliminate unnecessary, dangerous, or damaged cells without evoking inflammation or tissue damage, takes place in a wide number of physiological and pathological events (Green , Kroemer, 2004). Its efficacy for removing hazardous cells is circumvented in viral diseases and neoplasia by specific molecular routes. On the other hand, the progressive occurrence of apoptosis in non-proliferating cells has been proposed as the basis for a number of degenerative disorders, as well as in progressive loss of organ function during aging (Green *et al.*, 2011). Thus, understanding the control mechanisms of apoptosis is a major goal for the development of new therapeutic approaches. Mitochondria, traditionally considered the powerhouses that supply energy to the cells, are also considered vessels filled with an array of weaponry that can be unleashed to promote the apoptotic signaling cascade, resulting in the demise of the cell. Apoptotic stimuli cause the release of pro-apoptotic mitochondrial mediators into the cytoplasm (cytochrome c, AIF, Smac/DIABLO). Their assembly with cytosolic proteins forms a complex (apoptosome) that recruits and activates caspases leading the cell into apoptotic death (Adams , Cory, 2002). The molecular mechanism of this release is unclear, but most likely requires the activity of a large-conductance channel, known as the permeability transition pore, PTP, that remains again an elusive molecular entity (Lepetsos , Papavassiliou, 2016). Main regulators of the PTP include voltage-dependent anion channel (VDAC) in the outer mitochondrial membrane (OMM), adenine nucleotide translocase (ANT) in the inner mitochondrial membrane

(IMM), Cyclophilin D in the mitochondrial matrix and more recently the mitochondrial phosphate carrier (PiC) (Leung *et al.*, 2008). Whereas, hexokinase II (HKII), mitochondrial creatine kinase (CK), benzodiazepine receptor (PBR), and Bcl-2-family members (Bcl-2, Bcl-x_L, and Bax) are currently included as putative regulatory components. However, despite the use of multiple methodologies, the identity and the number of PTP's components are still elusive, and it remains to be clarified whether ANT and VDAC are the main components of pore or accessory. As showed using isolated mitochondria from mice knock-out for ANT or VDAC and CypD, where a permeability transition response to the classical inducer calcium (Ca^{2+}) was monitored, suggested a limited role for these proteins (Baines *et al.*, 2007; Basso *et al.*, 2005; Kokoszka *et al.*, 2004; Nakagawa *et al.*, 2005). Could be, seen its variable composition, that the structure of pore depends on the tissue as well as the pathophysiological state (Halestrap, 2009): in fact, four homologous genes, whose expression is not only tissue specific, but also vary according to the pathophysiological state of the cell, encode ANT. Or VDAC, where the different isoforms appear to rely on their ability to engage protein-protein interactions with different partners complicating VDAC's contribution to cell death, strictly dependent from isoform and stimulus (Cheng *et al.*, 2003; Rapizzi *et al.*, 2002). These and other PTP proteins are targets of ROS, and oxidative modifications of those proteins containing thiol groups will significantly impact PTP activation and thus mitochondrial ions fluxes, as mentioned later (Zoratti , Szabo, 1995), (Costantini *et al.*, 1996; Kowaltowski *et al.*, 2001).

In response to pro-apoptotic stimuli, including ROS and Ca^{2+} overload, the PTP assumes a high-conductance state that allows the deregulated entry of small solutes into the mitochondrial matrix along their electrochemical gradient (Morciano *et al.*, 2015). The opening of the PTP induces mitochondrial swelling, and these large-scale alterations of organelle morphology may allow the release of the caspase cofactors into the cytosol (Yang , Cortopassi, 1998). Evidences by which PTP opening may accelerate aging can represent the link between PTP-driven apoptosis, ROS and senescence. It is reported that PTP may be the culprit of the progressive age-dependent NAD^+ depletion inside mitochondrial matrix (Schriewer *et al.*, 2013) affecting DNA repair mechanisms and the protective sirtuin pathway (Merksamer *et al.*, 2013) prompting the cell to senescence and death. This relationship is not univocal; indeed also aging could favor PTP opening (Rottenberg , Hoek, 2017) giving rise to an intricate loop. Interestingly, an extracellular agonist-stimulated Ca^{2+} uptake by mitochondria in mouse embryonic fibroblasts (MEFs) is gradually decreased with culture time (**Figure 8**). Moreover, many reports described dysregulations in Ca^{2+} homeostasis and mitochondrial membrane potential in aged cells in terms of calcium buffering thresholds, that significantly decrease (Gant *et al.*, 2015; Pandya *et al.*, 2015) and a lowered MMP

(Sugrue , Tatton, 2001). These changes intensify PTP opening events in senescent cells (Paradies *et al.*, 2013) and the liaison with age-dependent mitochondrial ROS accumulation is very strong as the oxidation of channels and transporters like MCU (Dong *et al.*, 2017) in which the oxidation of the reactive thiol represented by Cys-97 showed constitutive channel activity and a consequent mitochondrial calcium overload), the mitochondrial calcium uptake 1 (MICU1) and phospholipids contributes to the progressive damage and dysregulation of proteins and to the exchange of radical species between mitochondria and cytosol, where during aging, it could become the main exchange route.

Recently, it has been proposed a multistep nature of the PTP complex opening involving first, a disassembly of ATP synthase dimers and second, a correct rearrangement of the C-ring in the IMM (Bonora *et al.*, 2017; Morciano *et al.*, 2017). This is coherent with previous findings in which a reduced dimerization status of ATP synthase was detected in aging cells, thus prompting them to cell death (Daum *et al.*, 2013). Indeed, it is reported that aging is intimately related to a decline of mitochondrial functions (Sun *et al.*, 2016) and young, middle-aged and senescent cells own important mitochondrial differences in terms of IMM integrity and organization, as well as the oxidative state of proteins, mtDNA and phospholipids; for instances, it has to be remarked that ATP synthase in young cells is mainly detected in dimeric and oligomeric structures (Daum et al., 2013) to fully support the energetic requirement of the cell and the correct curvature of the IMM. Recent findings award the synthasome assembly to PTP modulators, such as CypD and generally, to conditions preventing mitochondrial permeability transition (MPT) (Beutner *et al.*, 2017); on the other hand, in senescent mitochondria, a highly dynamic transition from dimers to monomers occur (Daum et al., 2013).

Investigation of the molecular routes of apoptosis has revealed the important role of mitochondria in decoding oxidative insults **(Figure 2)**. In fact, oxidative stress and altered mitochondrial function have consistently been proposed to be major determinants of lifespan, as shown by several studies with transgenic overexpression-antioxidants systems (Parkes *et al.*, 1998; Sun *et al.*, 2008), or as shown by experiments with fundamental genes for mitochondrial redox regulation thioredoxins and glutaredoxins (Chen *et al.*, 2002; Choksi *et al.*, 2011; Diotte *et al.*, 2009; Enoksson *et al.*, 2005; Kim *et al.*, 2010; Nagy *et al.*, 2008; Stanley *et al.*, 2011). Indeed, Mouse Embryonic Fibroblast cells (MEFs) from which p66shc has been completely depleted, are resistant to oxidative stress induced apoptotic death (Migliaccio et al., 1999). This death is p53-dependent, and knockout of either p53 or p66shc causes resistance, suggesting that p66shc is downstream of p53 in the pathway (Trinei *et al.*, 2002). In agreement with this finding, mice with p66shc completely knocked out are resistant to paraquat, and live about 30% longer than controls.

The relationship between mitochondria and p66shc emerged by the effective localization of the protein to the organelle: part of the cytosolic pool translocates to mitochondria (Orsini et al., 2004). In the intermembrane space (IMS), p66shc binds cytochrome *c* and acts as a redox-enzyme, generating H_2O_2, in turn inducing the opening of the PTP and cellular apoptosis. ROS production by p66shc appears to be a specialized function whereby electrons are subtracted from the ETC to catalyze the partial reduction of molecular oxygen (Giorgio *et al.*, 2005). The redox activity of p66shc explains the decrease in ROS levels observed in p66shc knockout cells (Migliaccio *et al.*, 2006), and is also responsible for an altered mitochondrial metabolism under basal conditions, characterized by lower oxygen consumption (Nemoto *et al.*, 2006). Clear and specific references about p66shc and its aging activity will be addressed in detail in a next section, emphasizing pivotal molecular proteins involved in p66shc's signal transduction as new targets of pharmacological therapy.

The tumor suppressor Fhit protein characterizes another pivotal mitochondrial pro-apoptotic route (Rimessi *et al.*, 2009) associated with oxidative-stress induction. It is absent or reduced in many types of human tumors including lung, oesophagus, stomach, kidney and cervical carcinomas (Croce *et al.*, 1999). Fhit is encoded by the FHIT gene, located within a fragile region of chromosome 3 of the human genome and is frequently altered in cancers and inactivated in cancer-derived cell lines (Inoue *et al.*, 1997). Direct evidence from Fhit-deficient cancer cells shows that chemotherapy-induced cell death is accompanied by a mild response to production of ROS, suggesting that Fhit-deficiency could negatively influence treatment outcome. In addition, Fhit loss has been considered as a mechanism to delay cell aging due to its ability to overcome oncogene-induced senescence (Waters *et al.*, 2014); indeed, it is known that oncogene activation generates, most of the time, irreversible DNA damage allowing senescence or apoptosis pathways in pre-neoplastic cells. In this key passage, observations made in $Fhit^{+/+}$ and $Fhit^{-/-}$ MEF cells, Fhit function is highly dependent on its DNA "caretaker" role prompting p53 deregulation and avoiding senescence once lost (Miuma *et al.*, 2013). Although Fhit is identified as a cytosolic protein, it may sort to mitochondria where it interacts with ferredoxinreductase (fdxr), a flavoprotein transactivated by p53 (Trapasso *et al.*, 2008). Through interaction with chaperones Hsp60 and Hsp10, mitochondrial Fhit modulates electron-transfer from NADPH via the activity of fdxr. The Fhit/fdxr complex generates ROS and increases Ca^{2+} uptake into mitochondria, potentiating the effects of apoptotic agents (Rimessi et al., 2009). The sorting of Fhit to mitochondria is now recognized as essential to its tumor suppressor actions in apoptosis induction. Together, these results identify a mitochondrial signaling step at the center of the mechanisms of the anticancer action of Fhit, and draw attention to the importance of pharmacologically regulating its intracellular sorting and

organelle activity, as confirmed by the overexpression of mitochondrial-targeted Fhit-chimera in tumor cells (Rimessi et al., 2009).

In recent years, an interesting role in regulating cell destiny has been identified for autophagy (the catabolic pathway for degradation of intracellular proteins and organelles via the lysosome) (Klionsky *et al.*, 2016; Scherz-Shouval , Elazar, 2007). Autophagy is mainly activated by nutrient starvation and it plays a dual role: it is primarily a survival mechanism, but it also leads to cell death, thus possibly acting as an alternative to apoptosis (Levine , Kroemer, 2008). In contrast to the well-documented pro-survival function of autophagy, some examples of ROS-induced autophagy linked to cell death have been described in tumor cells. Treatments with rotenone and TTFA (inhibitors of complex I and II, respectively) in cancer cell lines induced autophagy-dependent cell death, displaying increased mitochondrial ROS production. Use of siRNA against autophagy genes or the autophagy inhibitor 3-MA produces reversal of the effects of autophagic cell death (Chen *et al.*, 2007b). Today, the precise role of autophagy in cancer is strongly debated, but it remains a potentially important area of development for new therapeutic interventions. Scientific evidence supports both tumor promoting and suppressive functions for autophagy. The exact role of it during cancer progression depends on tumor type, context and stage. Although genetic evidences confirm a role for autophagy as a tumor suppressor mechanism, it can also promote the maintenance of models of ovarian cancer and gastrointestinal stromal tumor (Guo *et al.*, 2011; Gupta *et al.*, 2010; Lu *et al.*, 2008). The requirement for autophagy becomes more apparent in later stages as tumor cells cope with micro-environmental stresses encountered during progression and metastasis (Roy , Debnath, 2010). The tumor suppressive functions are most apparent during tumor initiation, where H-ras^{12v} induces different autophagic responses depending on the duration of oncogene overexpression. After 48 hours of Ras overexpression, autophagy inhibits cell proliferation, whereas a longer time of oncogene-overexpression, cell proliferation was enhanced by autophagy (Wu *et al.*, 2011). Growing evidence suggests that in different pathological contexts, cross-talk between apoptosis and autophagy takes place; this is intimately interconnected during stress responses, and anti- or pro-survival effects have been shown in cancer or neurodegenerative diseases, respectively (Codogno , Meijer, 2005; Kroemer *et al.*, 2007). For this reason, researchers have a marked interest in developing pharmacological regulators of autophagy as alternative therapeutic approaches to counter the dysfunctional apoptotic response during pathological conditions. On the other hand, in healthy conditions, growing (but not yet direct) evidences link autophagy to aging revealing this pathway as cure-all for longevity and thus, a landmark for therapeutic manipulations. These observations were made in many systems such as yeast, *S. Cerevisiae*, *Drosophila* and ultimately in mammals with concordant findings that describe

a reduced age-dependent activation of autophagy in mammals (Kaushik *et al.*, 2012; Vittorini *et al.*, 1999), in *in vitro* senescent cultures and isolated organs from old rodents (Cuervo , Dice, 2000). In addition, the disruption of a type of autophagy, classified as chaperone-mediated autophagy, promoted cell sensitivity to stress, a condition dramatically associated to decreased longevity (Massey *et al.*, 2006). Another proof by which autophagy could be deeply involved in an extended lifespan derive from protein overexpression studies in which increased levels of ATG5, ATG7, ATG8 and SIRT1 autophagy proteins prevented ER stress and oxidative insult-induced cell death, improved glucose tolerance and clearance, and preserved motor function (Lee *et al.*, 2008; Pyo *et al.*, 2013; Yang *et al.*, 2010). Although all these observations support the hypothesis that some forms of basal autophagy could ameliorate aging-associated dysregulated pathways, further efforts are required to get direct and final evidences.

Redox regulation by moderate levels of ROS is also observed in autophagy. It is generally accepted that mitochondria play a fundamental role in ROS-mediated autophagy regulation (Azad *et al.*, 2009; Kim *et al.*, 2007a; Kirkland *et al.*, 2002; Kissova *et al.*, 2006; Xu *et al.*, 2006). A specialized form of the autophagy process, called mitophagy, degrades defective mitochondria. Mitophagy helps to maintain a healthy population of mitochondria in the cell (Rimessi *et al.*, 2013), and thus reduces oxidative damage (Scherz-Shouval , Elazar, 2007). Increases in cellular ROS lead to loss of MMP, which is considered a trigger for mitophagy (Kim *et al.*, 2007b). Under serum deprivation, a typical decrease in MMP is observed in hepatocytes prior to engulfment by autophagosomes, while cyclosporin A (a typical PTP inhibitor) prevents this depolarization and the autophagosomal proliferation (Elmore *et al.*, 2001; Rodriguez-Enriquez *et al.*, 2009). Indeed, a recent study showed that mitochondria provide the membrane source for autophagosome biogenesis during the autophagy process (Hailey *et al.*, 2010). Tracking photolabelled mitochondria showed that fusion and fission events permitted the segregation of abnormal mitochondria, which were then degraded by mitophagy (Twig *et al.*, 2008), and that the pro-fission protein Fis1 triggered mitophagy only when associated with mitochondrial dysfunction (Gomes , Scorrano, 2008).

Mitochondrial dysfunction and oxidative stress in age related neurodegenerative diseases

Links between mitochondria and neurodegeneration have been reported for several years, with the first hints stemming from studies of classical mitochondrial disorders. Interestingly, the incidence of neurodegenerative diseases increases with aging, which means that some of the mitochondrial phenotypes found in aged individuals are similar to some mitochondrial hallmarks found in neurodegeneration. In this type of disease, mtDNA mutations lead to impairment of mitochondrial respiration, ATP synthesis, reduction in MMP, and increased ROS production

(DiMauro , Hirano, 2009). These defects usually cause a bioenergetic deficit in tissues with the highest energy demand, particularly the central nervous system and muscular tissue, causing neurological disorders, ataxia, muscle weakness, stroke-like episodes, epilepsy, and other disease types. Similarly, deregulation of mitochondrial physiology and increased oxidative stress, often at an early stage, have been correlated with the most common neurodegenerative diseases including AD, PD, Huntington's disease (HD) or Amyotrophic Lateral Sclerosis (ALS), among others (Lin , Beal, 2006). In all of these pathologies, mitochondria appear to be central hubs of the pathophysiological process, due to their impaired ability for ATP synthesis and for an increased production of ROS (Szeto, 2006). In fact, alterations of mitochondrial function as well as increased oxidative stress were found in patients affected by these pathologies.

Loss of neurons in the hippocampus and neocortex combines with two brain alterations in AD: the accumulation of senile plaques (composed of amyloid-β, Aβ) and neurofibrillary tangles (made of the hyperphosphorylated protein tau). The principal risk factor for AD is age, but there are also cases of autosomal dominant familial forms caused by mutations in amyloid precursor protein (APP), presenilin-1 (PS1) or -2 (PS2). Mitochondrial abnormalities such as alterations of tricarboxylic acid cycle enzymes, and reduced activity of respiratory complexes I, III and IV were found in *post mortem* brains of patients with AD (Bosetti *et al.*, 2002; Gibson *et al.*, 1998; Lin , Beal, 2006; Reddy, 2006; Reddy , Beal, 2008). Direct evidence of oxidative stress was obtained in the brains of early-stage AD animal models by using in vivo electron paramagnetic resonance (EPR) imaging with methoxycarbamyl-proxyl (MCP) as a redox-sensitive probe (Fang *et al.*, 2016), with these defects being associated not only with cognitive defects but also with mitochondrial dysfunction. It has been demonstrated that Aβ25-35 and Aβ1-40 induce apoptotic cell death in cerebral endothelial cells, and Aβ-neurotoxicity is associated with mitochondrial dysfunction (increased generation of ROS, excitotoxicity, apoptosis and inflammation) (Mattson, 2000). Moreover, AD-associated metabolic alterations have been described to alter mitochondrial dynamics in the neurons, causing interference with local ATP and calcium gradients (Correia *et al.*, 2016), as well as alterations in cardiolipin species, which may explain alterations in mitochondrial respiratory chain activities and increased ROS generation (Monteiro-Cardoso *et al.*, 2015). SIRT3, a sirtuin protein has recently been shown to be decreased in the context of AD, leading to p53-mediated negative effects on mtDNA transcription and resulting in inhibition of respiration and increased oxidative stress (Lee *et al.*, 2017). As referred above, SIRT 3 is involved in the regulation of mitochondrial respiration and oxidative stress through regulation of protein acetylation and SOD2 expression/activity (Pereira et al., 2012).

Rhein and colleagues showed that convergence of Aβ and tau on mitochondria with associated defects in mitochondrial complexes I and IV cause disturbances in the respiratory and energy system of ^{triple}AD mice. The same work describes that age-related oxidative stress leads to dysfunctional energy metabolism and consequently to neuronal death (David *et al.*, 2005; Rhein *et al.*, 2009). Other *in vitro* and *in vivo* studies by Keil et al demonstrated that Aβ induces mitochondrial adaptation and failure in a vulnerable and dose-dependent pattern, with NO being involved in these processes (Keil *et al.*, 2004).

APP has an unidentified mitochondrial-signal sequence that targets it to mitochondria. Aβ interacts with Aβ-binding alcohol dehydrogenase (ABAD), and this interaction leads to release of cytochrome *c* and an increase of ROS generation (Lustbader *et al.*, 2004). Yet, it has not been revealed if APP could be processed to Aβ directly within mitochondria or if processing precedes Aβ translocation. The finding that AD patients display impaired mitochondrial APP translocation and accumulation between OMM and IMM as well as evidences showing the presence of γ secretase in the mitochondrial matrix suggest that mitochondria could be a processing site for APP and that this event is fundamental for the onset of pathology and increased oxidative stress (Devi *et al.*, 2006; Pavlov *et al.*, 2011). Recently, it was proposed that overexpression of Aβ modifies the activity mitochondrial fusion and fission proteins. In particular, an increase of Fis1, a decrease of DLP1 (fission proteins), and a decrease of the fusion protein OPA1 were measured. All these alterations lead to mitochondrial fragmentation, reduction of MMP and increase in ROS generation, most likely resulting from deficient quality control mechanisms (de Moura *et al.*, 2010; Wang *et al.*, 2008b).

It was proposed that the “mitochondrial cascade” might provoke AD development due to accumulation of mutations in mitochondrial genes which causes insufficient respiratory chain accompanied with increased ROS production, and results in more and more severe mtDNA damage that leads to severe oxidative stress, stimulating AB toxicity (Swerdlow *et al.*, 2014). Although it was not possible to identify any mitochondrial mutations causing AD, an increased number of point mutations in mtDNA isolated from brains of AD patients, relative to controls, has been reported (Lin *et al.*, 2002). However, recent studies indicated such mutations appear to be effects of errors during the mtDNA replication process rather than be caused by ROS (Hoekstra *et al.*, 2016). In contrast to AD, PD is characterized by tremor, rigidity, postural instability and bradykinesia. PD is caused by degeneration of the dopaminergic neurons of the substantia nigra, combined with accumulation of α-synuclein- and ubiquitin-containing inclusions, called Lewy bodies, in the surviving neurons (de Moura et al., 2010). Disordered protein handling/degradation, mitochondrial

dysfunction and increased oxidative stress have been shown to be correlated with sporadic and familial PD as well as Parkinsonism due to exposure to toxins or pesticides (Dagda *et al.*, 2009).

Several neurotoxins that affect dopaminergic neurons act at the mitochondrial level and induce oxidative stress in that organelle. One toxin is the heroin contaminant 1-methyl-4-phenyl-1,2,3,6-tetrahydroxypyridine (MPTP), which produces a Parkinsonian phenotype (Przedborski , Jackson-Lewis, 1998). MPTP is converted to $MPDP^+$, and then to the active metabolite MPP+ by astrocytes and acts as an inhibitor of complex I of the mitochondrial ETC (Langston *et al.*, 1983), promoting cytochrome *c* release from the IMM (Banerjee *et al.*, 2009). Interestingly, both MPTP and its metabolites, $MPDP^+$ and MPP^+, reveal also mutagenic properties (Ulanowska , Wegrzyn, 2006) (Ulanowska *et al.*, 2007). Thus, one can speculate that they might potentially cause also mutations in mtDNA, accelerating the disease development. Other compounds that inhibit complex I and contribute to PD development include the pesticides rotenone and paraquat, commonly used in farming. The latter acts by causing degeneration of dopaminergic neurons and increased oxidative stress (Cicchetti *et al.*, 2005). Chronic exposure to rotenone leads to dopaminergic degeneration and formation and aggregation of α-synuclein and ubiquitin, as well as oxidative damage and caspase-dependent cell death (Rego , Oliveira, 2003). Moreover, rotenone itself is widely used as a tool for the generation of PD models in *Drosophila*, mice and rats. The appearance of cytoplasmic inclusions containing alpha synuclein and ubiquitin is reported in the different biological models, as well as dopaminergic neuron degeneration and impairment of locomotor activity in animal models, resembling the human pathology (Blandini , Armentero, 2012; Coulom , Birman, 2004; Inden *et al.*, 2011). It was reported how rotenone administration induces ATP depletion, increased oxidative stress and death in a neuroblastoma model. Interestingly, ATP depletion in that model, induced by exposure to 2-deoxyglucose did not induce cell death, suggesting that ROS production is the critical event in rotenone-induced toxicity. Moreover, these effects were abolished by overexpression of the rotenone insensitive Respiratory Complex I subunit ND1 derived from yeast (Sherer *et al.*, 2007). Nonetheless it has been shown that NDUFS4 KO mice were completely insensitive to rotenone-induced neurodegeneration (Choi *et al.*, 2008). The results obtained appear to suggest that there are more than one binding site for rotenone in mitochondrial Complex I (Fendel *et al.*, 2008), with the most relevant appearing to be ND1 (Murai *et al.*, 2007). Moreover, a redox-active dopamine analogue, 6-hydroxy-dopamine (6-OHDA), induces the death of dopaminergic neurons and leads to an increase of free radicals, abolishing α-synuclein's role.

A new player which has been described to have an important role in an early stage of PD is the mitochondrial LON protease. It was recently determined that Lon protease expression increased

in the ventral mesencephalon of MPTP-treated animals, in the same time-frame as the appearance of oxidized proteins and dopaminergic cell loss. The authors also observed a loss of Lon activity by ROS and carbonylation in α-ketoglutarate dehydrogenase (KGDH), aconitase or subunits of respiratory chain complexes (Bulteau *et al.*, 2017). Interestingly, not only Lon operates as a mtDNA and protein quality control protein (Pinti *et al.*, 2016; Sepuri *et al.*, 2017), but it was recently shown to relocate to mitochondrial-associated membranes upon different stimuli (Polo *et al.*, 2017), suggesting that ROS may affect mitochondrial-ER interactions in PD through inactivation of Lon, besides avoid its quality control activity.

Recent studies demonstrated that mutations of different genes involved in mitochondrial function or with antioxidant activities cause familial PD. The leucine-rich repeat kinase 2 (LRRK2) is the most commonly mutated gene in the familial and sporadic type of PD (Kachergus *et al.*, 2005), while DJ-1, parkin and PINK-1 are involved in autosomal recessive Parkinsonism (Dagda et al., 2009; Kitada *et al.*, 1999).

Relatively high levels of mutant mtDNA, particularly with deletions, were reported in dopaminergic neurons of elderly people as well as in PD patients (Bender *et al.*, 2006) (Kraytsberg *et al.*, 2006; Lin *et al.*, 2012). Studies on animals gave quite similar results, i.e. accumulation of deletions in mtDNA in brains, particularly in substantia nigra, of PD models (Dolle *et al.*, 2016; Parkinson *et al.*, 2014; Tzoulis *et al.*, 2016). Moreover, depletion of mtDNA was also reported in this disease (Grunewald *et al.*, 2016). Thus, it is possible that mtDNA dysfunctions might contribute to development of PD.

In HD, the abnormal expansion of polyglutamine repeats in the Huntingtin (HTT) protein (above 40 repeats) cause aggregation of the unfolded protein that lead to neuronal degeneration in the cortex and striatum. Similarly to PD, alterations of mitochondrial respiratory complexes (especially II and III) were found in *post-mortem* brain samples (Damiano *et al.*, 2010). Furthermore, altered MMP in lymphoblasts from patients and augmented lactate production in brain suggest a connection between mitochondrial dysfunction and HD. In addition, inhibitors of respiratory complex II, such as 3-nitropropionic acid and malonate, induce a HD pathological phenotype in animals (Beal, 1994). Mutated HTT is sufficient to decrease ATP synthesis and impair respiratory chain activity, while overexpression of respiratory complex II subunits is enough to recover mitochondrial function and sensitivity to apoptosis in neurons expressing a 82 glutamine HTT (Benchoua *et al.*, 2006). The physiological role of HTT is still under debate, although it has been shown to co-locate with the OMM, and to regulate mitochondrial trafficking along axons (Chang *et al.*, 2006). Interestingly, HTT facilitates PTP opening during Ca^{2+} stimulation in neurons and promote ROS production upon 3-NP exposure in cybrids (Ferreira *et al.*, 2010), suggesting that

mutated HTT could have a role in the regulation of ROS metabolism. In fact, the PTP has been proposed as a major factor for mitochondrial damage in HD (Quintanilla *et al.*, 2017).

Increased levels of DNA lesions and mutations, both base pair substitutions and deletions of larger DNA fragments, were reported in nuclear and mitochondrial genomes of HD patients and in animal models of this disease (summarized in (Ayala-Pena, 2013)). This suggests that mutations in DNA, including those in mtDNA, might be important factors in development of HD. The problem of mtDNA depletion is more complicated, as different groups reported either decreased (Liu *et al.*, 2008; Petersen *et al.*, 2014) or increased (Chen *et al.*, 2007a) levels of mtDNA in HD patients relative to controls. Recent studies, based on testing biological material from a relatively large population, indicated higher levels of mtDNA in leukocytes, but depletion of mtDNA in fibroblasts of HD patients relative to healthy controls (Jędrak *et al.*, 2017). Therefore, it was suggested that both size of the study group, and particularly the kind of investigated tissue, as well as some methodological and technical details important for adequate measurement of mtDNA levels, might be responsible for differences in results published by various groups (Jedrak *et al.*, 2017). Nevertheless, it appears that levels of mtDNA might be changed in HD patients, while either decreased or increased, depending on the tissue. Since mtDNA depletion has been suggested to occur in the brain of HD patients due to ROS-generated DNA damage, and due to evident accumulation of mutations in mtDNA and nDNA, a model of progression of HD, driven by accumulation of mtDNA lesions caused by toxicity of mutant HTT, and resultant enhanced production of ROS which cause mtDNA depletion, has been proposed (Ayala-Pena, 2013). According to this model, mtDNA dysfunction leads to deficiency in mitochondrial functions and subsequent neurodegeneration.

Similar connections between mitochondria and neurodegeneration are present in ALS. Alterations of mitochondrial structures and number, as well as defects in respiratory chain complexes have been observed in post-mortem samples of spinal cord. Genetic causes of ALS are still poorly understood. Approximately 90% of ALS cases are sporadic, and of the remaining 10% (familial ALS) only 20% are attributed to genetic disorders. These cases are linked to mutations that alter SOD1 activity. SOD1 is considered one of the most important cellular scavengers of the cytoplasmic superoxide anion. Recently, SOD1 presence has been confirmed in mitochondria, particularly in the OMM and the IMS, where it may exert a scavenging activity. Apparently, its localization to the IMS is fundamental for its correct maturation (Reddehase *et al.*, 2009) and this observation gains special relevance in the context of ALS. It is well known that mutant SOD1 found in patients generates toxic aggregates (Bruijn *et al.*, 1998). Recently, mutant SOD1 was discovered to specifically aggregate in mitochondria and induce mitochondrial impairment and induction of

apoptosis (Cozzolino *et al.*, 2009). Although SOD1 mutations affect only a small fraction of ALS patients, it is plausible that similar mechanisms involving mitochondria and oxidative stress are responsible for the induction of pathogenesis in most of the patients.

Is preventing mitochondrial oxidative stress with antioxidants effective? – The example of neurodegenerative diseases

As a natural consequence of the multiple connections between mitochondria, oxidative stress and neurodegeneration, several strategies have been developed directed at reducing oxidative stress and recovering from the pathological phenotype. Several compounds with antioxidant properties have been shown to reduce oxidative stress and increase cell survival in *in vitro* systems **(Figure 9)**.

Lipoic acid (LA), a cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase, and N-acetyl-cysteine decrease mitochondrial oxidative stress in fibroblasts derived from AD patients. LA used in a combination with acetyl-l-carnitine (ALCAR, a membrane permeable form of the mitochondrial acetyl carrier carnitine) protected primary cortical neurons against apoptosis induced by 4-hydroxy-2 nonenal (Abdul , Butterfield, 2007).

Coenzyme Q 10 (CoQ10), a fundamental cofactor in the respiratory chain with elevated antioxidant properties, was able to protect human neuroblastoma cells from paraquat- and rotenone-induced mitochondrial dysfunction and cell death. Similarly, the mitochondria-targeted form, MitoQ, prevented cell death in fibroblasts from patients affected by Friedreich's Ataxia (FA). This molecule possesses elevated antioxidant properties, preserves mitochondrial functions and reduces ROS formation even in Rho zero cells (lacking mitochondrial DNA).

Other mitochondria-targeted antioxidants are potentially interesting. MitoE, an analogue of Vit-E, shows elevated scavenging activity in fibroblasts from FA patients. MitoQ and LPBNAH, a derivative of PBN, protected neuroblastoma cells from H_2O_2-induced oxidative stress and Aβ1-42 toxicity.

Antioxidant-based strategies also appear widely effective in animal models of neurodegenerative disease. Natural antioxidant-like CoQ, Vit-E, creatine, and green tea polyphenols showed protective effects in mouse models of both PD and AD (Beal, 2003). LA significantly increased survival in HD mice models N171-82Q and R6/2 (Andreassen *et al.*, 2001), and also reduces oxidative stress in aged rats and reduces memory impairment in aged mice (Quinn *et al.*, 2007). The combination of LA and ALCAR reduced aging-related mitochondrial damage in rats and promotes neuron survival during glutamate-induced toxicity (Nagesh Babu *et al.*, 2011).

Ginkgo biloba extract seems to be of therapeutic benefit in the treatment of mild dementia of different etiology, especially as regards AD (Janssen *et al.*, 2010). Leuner and colleagues suggest that mitochondrial protection and reduction of oxidative stress are important components of the neuroprotective activity of Ginkgo biloba extract (Leuner *et al.*, 2007).

A novel class of cell-permeable small peptides that selectively partition into the inner mitochondrial membrane and possess intrinsic mito-protective activities have been developed and proposed as a novel class of mitochondria-targeted antioxidants. These novel peptides were originally designed by Szeto and Schiller, and have been designated SS peptides. This class of molecules is characterized by a structural motif that alternates aromatic residues and basic amino acids. Contrary to MitoQ and MitoE, these aromatic-cationic peptides are taken up by mitochondria but are not delivered into the matrix. Furthermore, uptake is not dependent on MMP (the extent of uptake was only reduced by ~10–15% in mitochondria that were depolarized with FCCP), and is not limited to mitochondria with normal MMP. This is a major advantage when dealing with diseased mitochondria with a reduced MMP (Zhao *et al.*, 2004). Animal studies indicated that these novel mitochondria-targeted peptides have excellent pharmacokinetic properties and are relatively free of toxicity, suggesting that they may have enormous therapeutic potential. Several different compounds have been tested and most of them display antioxidant properties (SS-02, SS-19, SS-31) and have been demonstrated to inhibit mitochondrial ROS production, prevent mitochondrial swelling, and neuronal cell loss in animal models of ALS (Petri *et al.*, 2006) and PD (Yang *et al.*, 2009). Interestingly, the SS-20 peptide that does not show antioxidant properties appears to be potent in protecting neuronal loss in a mouse model for Parkinson's disease.

Despite the collective success of antioxidant strategies in recovering the pathological phenotype in cells and animal systems, convincing clinical results are still lacking. In 1997, Sano *et al.* published one of the first clinical studies testing compounds that protect against mitochondria-mediated oxidative stress (Sano et al., 1997). This study was a double blind, placebo-controlled, randomized, multicenter trial in patients with moderate severity AD. This study tested both selegiline (an inhibitor of monoamine oxidase) and α-tocopherol (Vit-E) for two years in a total of 341 patients. Unfortunately, no significant benefits where observed.

More recently, MitoQ, considered one of the most promising mitochondria-targeted antioxidants, was tested in a Phase 2 trial on PD patients. The double blind, placebo-controlled study was conducted for 12 months in 128 patients, but failed to provide evidence that MitoQ could ameliorate the pathological condition (Snow *et al.*, 2010).

Clinical failure for the tested antioxidant therapies could be explained by many reasons. First, the inability to measure mitochondrial damage and contributors to oxidative damage may be

due to low bioavailability of the compound within the brain because of difficulties in crossing the blood brain barrier. Second, the therapy is usually administered to patients in advanced stages of the pathology, in a condition under which the scavenging activity of the compound might not be sufficient to reverse the phenotype (as this may be due to a different, specific mechanism, at this stage already independent of oxidative stress).

Together with mitochondrial dysfunction and oxidative stress, another characteristic common in most neurodegenerative diseases is the presence of aggregated proteins. Examples include: Aβ in AD, α-synuclein and ubiquitin in PD, mutant SOD1 in some forms of ALS, and mutant HTT in HD. As already cited, in most of the cases, protein aggregates accumulate also in mitochondria, promoting the increase of oxidative stress and impairment of mitochondrial functions.

Interestingly, in rats, administration of epoxomicin or PSI, two proteasomal inhibitors, leads to generation of an animal model of Parkinson's disease (McNaught *et al.*, 2004). It is well known that proteasomal degradation requires ATP, while elevated levels of oxidative stress impair correct protein folding and, in the case of AD, promote BACE overexpression and accumulation of Aβ (Tamagno *et al.*, 2005). A model could be envisioned in which the presence of protein aggregates can promote mitochondrial dysfunction and ROS generation. This would promote protein misfolding and impairment of proteasomal activity, initiating a cycle leading to neuronal death and progression of the pathology.

It should be considered that even if altered oxidative stress is a common feature of neurodegeneration, ROS might not be generalized as toxic components, but rather act as proper signalling molecules. The pathways of MAPK (mitogen-activated kinase), PI3K (phosphoinositide 3-kinase) and PKCs are ROS-sensitive and could promote cell proliferation in the presence of some oxidants (Giorgi *et al.*, 2010; Hole *et al.*, 2010). In the presence of ROS, the PI3K pathway can induce the nuclear respiratory factor 2, while PKCs can sustain brain remodelling and synaptogenesis after stroke (Sun et al., 2008). Moreover, ROS also mediate cell survival through the activation of HIF1a and NF-κB. HIF1a results in glycolytic switch and reduction of respiratory protection during stroke or hypoxia conditions (Siddiq *et al.*, 2005) or in HD neurodegeneration animal models, while NF-κB maintains the expression of antiapoptotic factors such as GADD45B and XIAP (Pahl, 1999).

Thus, it should be considered that in an oxidative environment, such as found in brain cells from patients with neurodegenerative disease, systems are likely adapting in an attempt to survive. Administration of antioxidants could help cells to recover their equilibrium, but could also be helpful for stimulating pathways that manage ROS metabolism. From this point of view, the

stimulation of Nrf2 is a promising target. This protein is normally present at low levels in the cytosol, bound to the Cul3-based E3 ligase adaptor KEAP1. Under oxidative stress, KEAP1 undergoes conformational changes, leaving Nrf2 free to move within the nucleus. In the nucleus, it binds to ARE and exerts its transcriptional activity to promote the expression of antioxidant genes such as NQO1, SOD1 and GST (Nguyen *et al.*, 2009).

To date, sulforaphane is considered one of the most potent compounds for promoting Nrf2 activation. Sulforaphane is usually obtained from cruciferous vegetables, converted from glucosinolate or glucoraphanin. Sulforaphane is able to oxidize cysteine residues on KEAP1, leading to Nrf2 activation. In an animal model of stroke, administration of sulforaphane or carnosic acid (another Nrf2 activator) led to neuroprotection and improvement of neurological functions (Satoh *et al.*, 2008). Furthermore, modulation of Nrf2 improved neurological impairment in animal models of AD, HD, or after administration of the pro-Parkinsonian drug MPTP (Calkins *et al.*, 2005; Kanninen *et al.*, 2009).

Investigating antioxidant strategies as therapeutic interventions in neurodegenerative disease is a promising area of inquiry, but convincing clinical results remain elusive. The development of such strategies should involve compounds that act on pathways controlling intracellular ROS metabolism, including adjuvants of antioxidant compounds, as well as compounds modulating proteasomal activity **(Figure 10)**.

CONCLUSIONS

In addition to the well-characterized energy-producing functions, mitochondria are an important intracellular source of ROS. Multiple mitochondrial functions and interconnections exist between aerobic energy metabolism, generation of ROS, activation of the apoptotic pathways and other fundamental homeostatic and signalling pathways (*e.g.*, Ca^{2+} homeostasis, lipid and nucleotide synthesis). Thus, mitochondrial impairment determines various degrees of energy failure and deregulation of ROS production. An in-depth investigation of all these effects will be the prerequisite to identify effective strategies to counteract the deleterious and multiple consequences of mitochondrial malfunctioning. The comprehension of the mechanisms regulating mitochondrial physiology and homeostasis, and in particular the control of mitochondrial ROS production, may have a significant impact for the development of novel therapies for the treatment of a wide variety of human diseases.

However, it should be noted that many clinical trials using antioxidants (in conditions such as cardiovascular diseases, cancer, diabetes, and neurological degenerative diseases, as well as to slow the aging process) have provided contradictory results. Thus, although the experimental

evidence for an antioxidant therapy is quite promising, further validation work is required. Despite the unresolved questions about the parallel role of ROS in oxidative damage or as signaling molecules, the causal link of mitochondria impairment in aging and associated diseases is unequivocal.

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ABBREVIATIONS

3MA, 3-methyladenine; 4-HNE1, 4-hydroxy-2-noneal; 6-OHDA, 6-hydroxy-dopamine; 8-oxodG, 8-oxo-7,8-dihydro-2'-deoxyguanosine; Aβ, amyloid-beta; ABAD, Ab-binding alcohol dehydrogenase; AD, Alzheimer's disease; adenine nucleotide translocase, ANT; AIF, apoptosis-inducing factor; ALS, Amyotrophic Lateral Sclerosis; AHL, age-related hearing loss; ALCAR, acetyl-1-carnitine; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; APDC, 4-amino-2,4-pyrrolidinedicarboxylic acid; APP, amyloid precursor protein; ARE, Nrf2/antioxidant response element; Ca^{2+}, calcium ion; $[Ca^{2+}]c$, cytosolic calcium concentration; $[Ca^{2+}]m$, mitochondrial calcium concentration; CoQ10, Coenzyme Q 10; CPT1mt, malonyl-CoA-insensitive CPT1A; CR, caloric restriction; CRTC 1 - CREB-regulated transcription coactivator 1; CsA, cyclosporine A; CT, computed tomography; CVDs, cardiovascular diseases; DA, dopamine; DAG, intrahepatic diacylglycerol; Dnm1p, dynamin-related protein 1; Drp1, dynamin-related protein 1; DTT, dithiothreitol; EC, endothelial cell; EDRF, endothelium-derived relaxing factor; EGF, epidermal growth factor; EPR, electron paramagnetic resonance imaging; ER, endoplasmic reticulum; *(Ercc 1)*$^{-/\Delta}$, hhe excision repair cross-complementation group 1; ETC, electron transport chain; fdxr, ferredoxinreductase; FA, Friedreich's Ataxia; FAs, fatty acids; FFA, free fatty acids; Fis1, fission protein 1; FRTA, Free Radical Theory of Aging; GFP, green-fluorescence protein; GPx, glutathione peroxidase; GSH, glutathione; GST, gluthatione S-transferase; HCC, hepatocellular carcinoma; HD, Huntington's disease; HUVECs, Human umbilical vein endothelial cells; HG, high glucose; HK, hexokinase; HO-1, heme oxygenase-1; H_2O_2, hydrogen peroxide; HSPs, heat shock proteins; HTT, huntingtin; IDH2, $NADP^+$-dependent isocitrate dehydrogenase 2; IIS, insulin signaling; IMM, inner mitochondrial membrane; IMS, intermembrane space; IPC, ischemic preconditioning; iPSC, induced pluripotent stem cells; I/R, ischemia/reperfusion; ITPR2, inositol 1,4,5-trisphosphate receptor type 2; JNK, c-Jun NH2-terminal kinase; KO, Knockout; LA, lipoic acid; LC3, MAP1 light chain 3; LCFA, long-chain fatty acids; LRRK2, leucine-rich repeat kinase 2; MAMs, mitochondria associated membranes; MAPK, mitogen-activated protein kinase; mitochondrial assembly regulatory factor (Marf); MDA, malondialdehyde; MEFs, mouse embryonic fibroblast cells; Mff, mitochondrial fission factor; Mfn1, mitofusin 1; Mfn2, mitofusin 2; MFRTA, Mitochondrial Free Radical Theory of Ageing; MGM1, dynamin-like GTPas; Mid49, mitochondrial dynamics protein of 49 kDa; Mid51, mitochondrial dynamics protein of 51 kDa;

MMP, mitochondrial membrane potential; MnSOD, manganese- dependent superoxide dismutase; mitochondrial phosphate carrier, PiC; MPC, mitochondrial pyruvate carrier; MPP^+, 1-metyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; mtDNA, mitochondrial DNA; Mtfp1, mitochondrial fission process 1; mTOR, mammalian target of rapamycin kinase; NAC, N-acetylcysteine; non-alcoholic fatty liver (NAFL); NAFLD, non-alcoholic fatty liver disease; NASH, steatohepatitis; NF-κB, nuclear factor-kappa B; NO, nitric oxide; Nox, NADPH oxidases; $O_2^{\bullet-}$, superoxide; •OH, hydroxyl radical; OMM, outer mitochondrial membrane; $ONOO^-$, peroxynitrite; Opa1, optic atrophy 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PD, Parkinson's disease; PBR, peripheral benzodiazepine receptor; Pin1, peptidyl-prolyl isomerase; PINK1, PTEN-induced putative kinase protein 1; PKC, protein kinase C; POLG, DNA polymerase γ; PPARs, peroxisome proliferator-activated receptors; Prx, peroxiredoxins; PS, presenilin; PSSG, protein mixed disulfide; PTP, permeability transition pore; PUFAs, polyunsaturated fatty acids; RNS, reactive nitrogen species; ROS, reactive oxygen species; SIRT, mitochondrial NAD^+-dependent deacetylase sirtuin; SOD1, Zn-Cu superoxide dismutase; SOD2, manganese superoxide dismutase; SOD3, superoxide dismutase 3; SREBP-1c, sterol regulatory element-binding protein-1c; SS peptides, Szeto-Schiller peptides; STOML2, Stomatin-like protein 2; T2D, type 2 diabetes; TCA, tricarboxylic acid; TFAM, transcriptor factor A; TMEM135, transmembrane protein 135; TPP^+, triphenyl phosphonium cation; Trx2, thioredoxin; UCP, uncoupling proteins; Vit-C, Vitamin C; Vit-E, Vitamin E; VLDL, very low-density lipoproteins; voltage-dependent anion channel, VDAC; WD, Wilson disease

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Table 1. Effect of aging on changes of liver mass and function.

Finding(s)	Change(s)	Reference
Liver mass	Decrease by 20-40%	(Schmucker, 2005; Wynne et al., 1989)
Perfusion and blood flow	Decrease by up to 50% after age 30	(McLean and Le Couteur, 2004)
Accumulation of hepatic dense body compartment (lipofuscin)	Increase	(Gregg et al., 2012; Schmucker, 1998) (Cogger et al., 2014; Schmucker, 2005)
Hepatocyte size (macrohepatocytes)	Increase	(Schmucker, 1998) (Watanabe et al., 1978)
Polyploidy	Increase	(Schmucker, 1998; Watanabe et al., 1978)
Pseudocapillarization	Increase	(Cogger et al., 2014; McLean et al., 2003)
Functional liver function tests	Decrease	(Hall et al., 2005; Rahmioglu et al., 2009)
Albumin synthesis	Decreased (animal studies) Unchanged (human studies)	(Anantharaju et al., 2002) (Fu and Nair, 1998)
Serum albumin	Minor decrease	(Tietz, N. W. et al., 1992)
Hepatic uptake of HDL1-cholesterol	Decrease	(Bravo et al., 1994)
LDL receptor	Decrease	(Miller, 1984; Schmucker, 2005)
serum LDL-cholesterol levels	Increase	(Anantharaju et al., 2002) (Miller, 1984)
Liver steatosis, inflammation, fibrosis, anisokaryosis, cellular senescence	Increase	(Gregg et al., 2012)
Accumulation of oxidation products	Increase	(Gregg et al., 2012)
Cytochrome P450	Decrease by 30%	(Sotaniemi et al., 1997)
Drug metabolic clearance	Slower by 20-40%	(Turnheim, 2003)
Synthesis of vitamin-K-dependent clotting factors	Decrease	(Froom et al., 2003)
Gallbladder bile	Increased cholesterol saturation index	(Valdivieso et al., 1978; Wang, 2002)
Mitogen-activated protein kinase activity	Decrease	(Schmucker, 2005)
Number of binucleated hepatocytes	Increase	(Gan et al., 2011; Premoli et al., 2009)

Table 2. Damaging effects of aging on mitochondria of the hepatocytes.

Finding(s)	Change(s)	Reference
mtDNA damage	Oxidative lesions	(Ames et al., 1993; Lopez-Torres et al., 2002)
mtDNA mutations	Increased apoptosis Unchanged oxidative stress	(Kujoth et al., 2005)
Mitochondrial lipid oxidation	Decreased membrane phospholipid peroxidability. Decreased Δ9-desaturase activity coefficient. Decreased levels of 16:1 and 18:1 fatty acids. Decreased membrane stability Increased amount of polyunsaturated fatty acids (in cardiolipin) Increased inner mitochondrial phospholipase A_2 activity	(Laganiere and Byung, 1993) (Pappu et al., 1978)
Content of cytochrome oxidase	Loss of enzymatic activity	(Wilson and Franks, 1975)
Malondehaldeide accumulation	Increase	(Von Zglinicki et al., 1991)
Mitochondrial number	Decrease	(Cogger et al., 2014; Gan et al., 2011; Premoli et al., 2009)
Intracellular oxidant production (dichlorofuorescin)	Increased (whole tissue, mitochondria) Mediated by electron transport chain and NADPH oxidase	(Bejma, J et al., 2000; Bejma, J. et al., 2000)

Figure 1. Potential role of mitochondrial ROS increase in aging

During aging, mitochondrial ROS production steadily increases, leading to mitochondrial damage and decreased lifespan. Here we report the major events contributing to aging (upper panel), or most important chemicals and experimental interventions, which may promote longevity (bottom panel).

Figure 2 Schematic representations of two pivotal apoptotic molecular routes, involved during oxidative stress and oncogenic stress, respectively

A) Oxidative stress-induced activation of PKCβ leads to phosphorylation of p66shc at Serine 36 residue, allowing translocation of protein to mitochondria by PIN1-dependent mechanism. The mitochondrial pool of p66shc oxidizes cytochrome c and catalyzes the reduction of O_2 to H_2O_2, inducing ROS production and successively apoptotic induction. B) Oncogenic stress promotes the binding between FHIT and mitochondrial-import complex Hsp60/Hsp10. In mitochondria FHIT interacts with FDXR promoting ROS production and cytochrome c release, respectively, leading to apoptotic response.

Figure 3. Mitochondrial network displays huge heterogeneity and shape rearrangements

Examples of mitochondrial network are shown in both immortalized (A: HEK, B: Cos7, C: IB3) and primary cultured cell lines (D: Human Fibroblast, E: Rat Myotube, F: Rat Adipocyte, G: Rat Oligodendrocyte Progenitor). Rearrangement of mitochondrial network is also a typical adaptation to stress stimulus such as oxidative stress as shown for Mouse Embryonic Fibroblast before (Hi) and after (Hii) exposure to H_2O_2.

Figure 4. The number of contact sites between mitochondria and the ER in young and senescent human fibroblasts

(**A**) Image of the endoplasmic reticulum (ER) (green) and mitochondria (red) in young and senescent human fibroblasts. Maximum intensity projections of confocal micrograhs from young and old fibroblasts expressing mitochondria-targeted Cherry (magenta) and ER-targeted GFP (green) contacts sites are represented by colocalization areas (white). Colocalization extents were quantified using Pearson's and Mander's coefficients. (**B**) Activity of senescence-associated β-galactosidase in young and senescent human fibroblasts. Cells referred as "young" fibroblasts were at 4^{th} passage, and the "old" ones (senescent) at 16^{th} passage.

Figure 5. Fenton and Haber-Weiss reaction

In the presence of catalytic amounts of trace metals (like iron and copper), highly reactive hydroxyl radicals ($^{\bullet}OH$) are generated from hydrogen peroxide via the Fenton and Haber-Weiss reaction.

Figure 6. Putative pathways linking oxidative stress, mitochondrial dysfunction and hyperglycemia

GSH, glutathione; ROS, reactive oxygen species; UCP2, uncoupling protein-2.

Figure 7. ROS as causative agents in cardiovascular diseases (CVDs) and therapeutic approaches targeting mitochondrial oxidative damage

(A) Principal mechanisms of ROS production and subsequent mitochondrial dysfunction leading to CVDs. Mitochondria participate in the pathogenesis of hypertension: increased blood pressure has been associated with an excessive endothelial cells (EC) production of superoxide ($O_2^{\bullet-}$) and H_2O_2; UCP1 expression also increases $O_2^{\bullet-}$ production and decreases the availability of NO. ROS production by endothelial mitochondria contribute to heart disease: angiotensin-II, hyperglycemia, or hypoxia increase mitochondrial ROS production in EC, which then stimulate the NADPH oxidase; moreover ROS produced by the NADPH oxidase, activate mitochondrial KATP channels, suggesting a possible feedback amplification system. Exposure of endothelial cells to oxidized lipids (oxLDL) induces ROS formation, which has a pivotal role in atherogenesis. During ischemia O_2 is lacking and mitochondria hydrolyze ATP in order to maintain the mitochondrial membrane potential ($\Delta\Psi$); the cardiac cell strives to maintain ATP production, this eventually results in mitochondrial Ca^{2+} overload, mitochondrial depolarization, and increases the generation of ROS. Restoration of blood flow will help to restore ATP levels, but the damaged mitochondria generate enormous amounts of ROS during reperfusion and promote mitochondrial permeability transition pore (mPTP) opening and activation of apoptosis, triggering ischemia/reperfusion (I/R) injury. **(B)** Approaches to deliver drugs to the mitochondria and prevent ROS-induced mitochondrial oxidative damage. Compounds conjugated to the lipophilic triphenylphosphonium cation (TPP^+) can be delivered selectively into the mitochondrial matrix in a potential-driven manner; a series of mitochondria-targeted antioxidants have been designed to decrease superoxide (MitoSOD), hydrogen peroxide (MitoPeroxidase), ferrous iron (MitoTEMPOL), lipid peroxidation (MitoQ, MitoE) and preventing mPTP opening (TPP^+-CsA). Recently, Szeto and Schiller (SS) peptides targeting the inner mitochondrial membrane have been developed; they concentrate in a potential independent manner and possess intrinsic mitoprotective activities.

Figure 8. Mitochondrial calcium uptake as a function of cell culture passage number

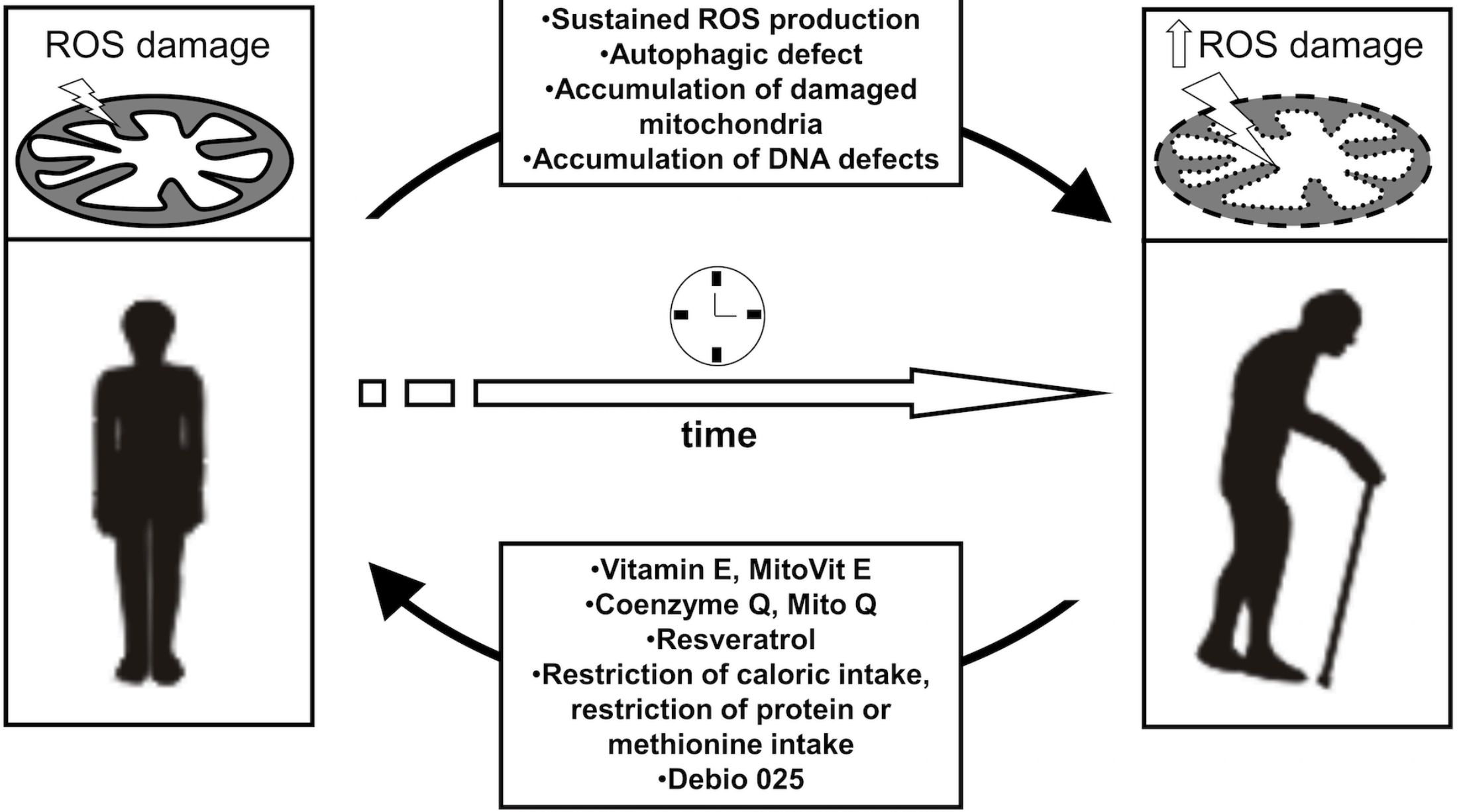
Representative quantitation of mitochondrial Ca^{2+} uptake elicited by ATP 100 μM in mouse embryonic fibroblasts (MEFs) from low and high passage rates. Mitochondrial calcium concentration ($[Ca^{2+}]_m$).

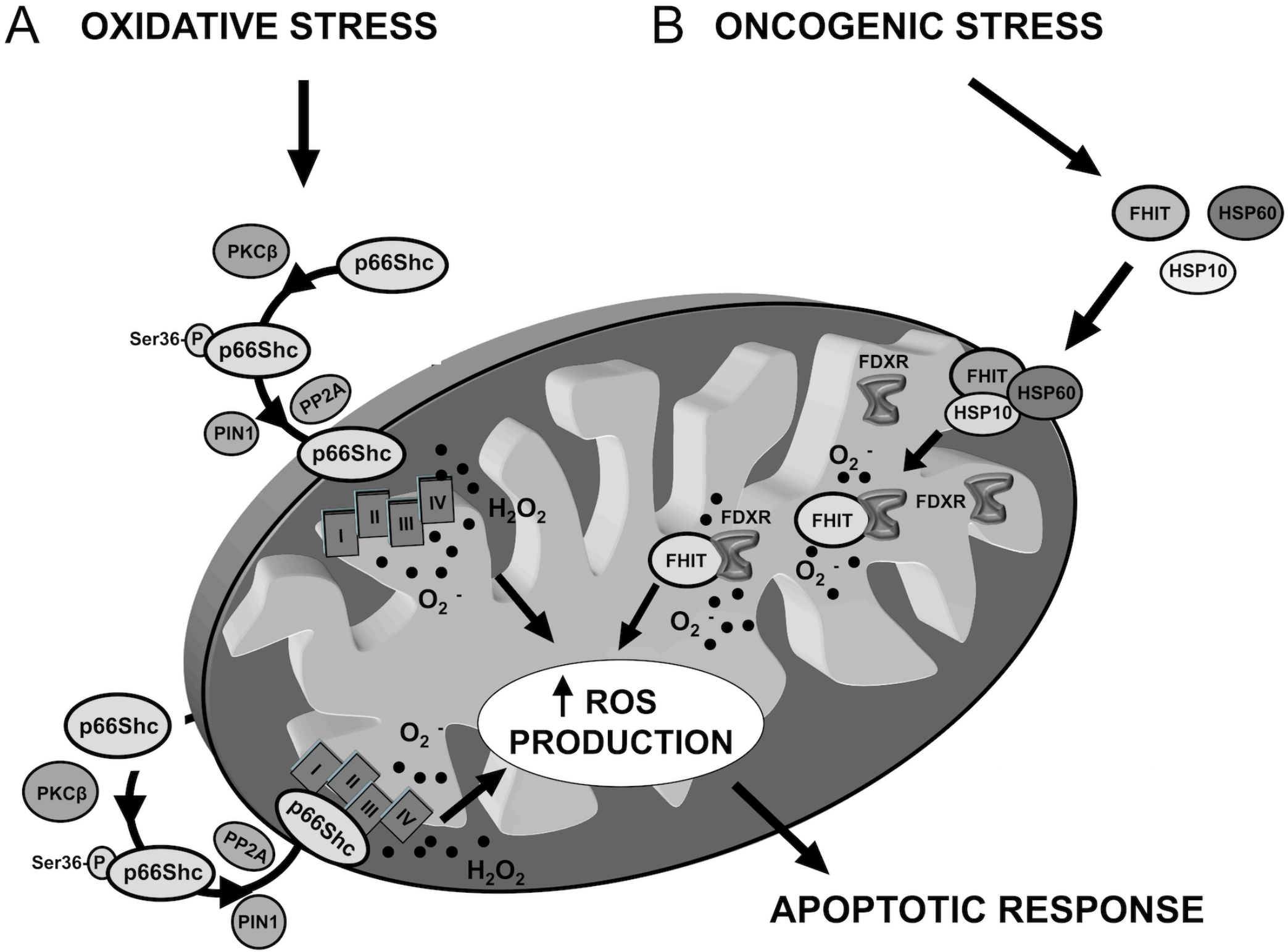
Figure 9. Mitochondrial Related Alterations in principal Neurodegenerative disorders

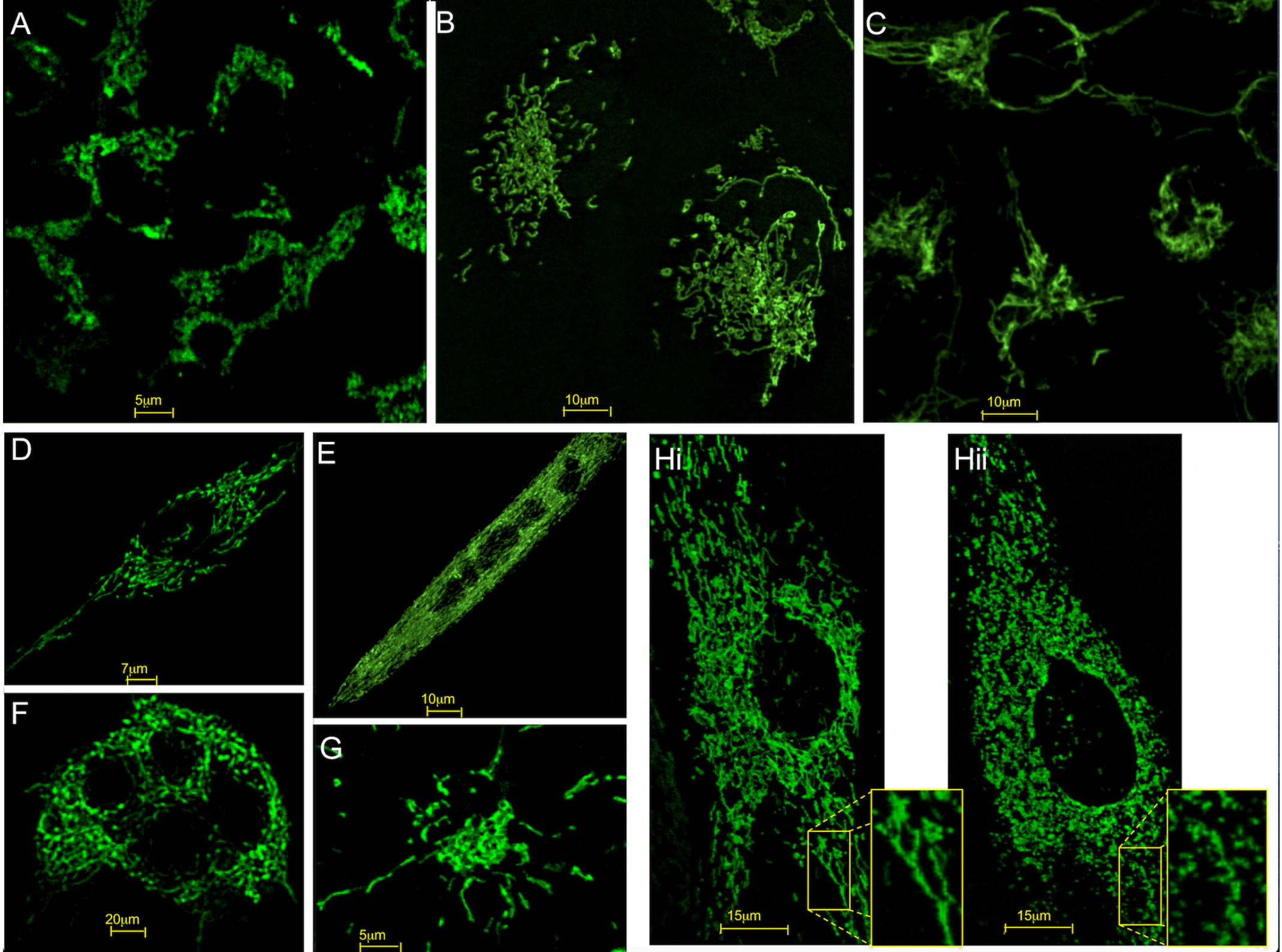
In Alzheimer's Disease Amyloid peptides (Ab) can aggregate to mitochondria and interact with Ab alcohol dehydrogenase (ABAD) to induce Cytochrome C release and ROS production. Contemporary altered activity of Krebs Cycle enzymes (KC), complexes of respiratory chain and proteins involved in mitochondria fusion and fission leads to impaired mitochondrial remodeling and ROS production. Similar readouts on mitochondrial physiology are observed in Parkinson's disease. Aggregation of mutant synuclein (syn) impair activity of respiratory complex I similarly as many pro-parkinsonian compounds. In this scenario should be added the activity of mutant proteins like PINK1, DJ-1, Parkin, LRRK2 that impair mitochondrial modeling and recycling as promoting induction of Cytochrome C release. In Huntington disease mutant huntingtin (carrying poliQ expansion) can impair activity of II respiratory complex (with consequent ROS production) and mitochondria transport along filaments in axons. Also superoxide dismutase 1 (SOD1) mutations causing ALS can induce appearance of toxic mitochondrial aggregates that lead to improved toxic ROS production. Altered protein or OXPHOS complexes activities are shown with a plus or minus symbol in a circle, mutant proteins instead are marked by an M in a circle.

Figure 10. Schematic view of various compounds that reduce oxidative stress in diseases mentioned in the text and their correlation with neurodegenerative disorders

Mitochondrial selective compounds can act in directly buffering ROS production, like Szeto-Shiller peptides (SS), Vitamine E or Coenzyme Q (CoQ) and derivatives. Buffering of ROS production could by obtained by inhibiting interaction between Keap1 and the nuclear respiratory factor 2 (NRF2). Restoration of mitochondrial functions has been also obtained by the use of drugs targeting Kreb's cycle, like Lipoic Acid, acetyl-l-carnitine (ALCAR) or Creatine.


ROS damage
•Sustained ROS production
•Autophagic defect
•Accumulation of damaged mitochondria
•Accumulation of DNA defects
ROS damage
time
•Vitamin E, MitoVit E
•Coenzyme Q, Mito Q
•Resveratrol
•Restriction of caloric intake, restriction of protein or methionine intake
•Debio 025


A OXIDATIVE STRESS
B ONCOGENIC STRESS
PKCβ
p66Shc
Ser36-P
p66Shc
PP2A
PIN1
p66Shc
I
II
III
IV
H_2O_2
O_2^-
FDXR
FHIT
HSP60
HSP10
FHIT
HSP60
HSP10
FDXR
O_2^-
FDXR
FHIT
FHIT
O_2^-
O_2^-
ROS PRODUCTION
O_2^-
p66Shc
PKCβ
Ser36-P
p66Shc
PP2A
PIN1
p66Shc
I
II
III
IV
H_2O_2
APOPTOTIC RESPONSE


A
5µm
B
10µm
C
10µm
D
7µm
E
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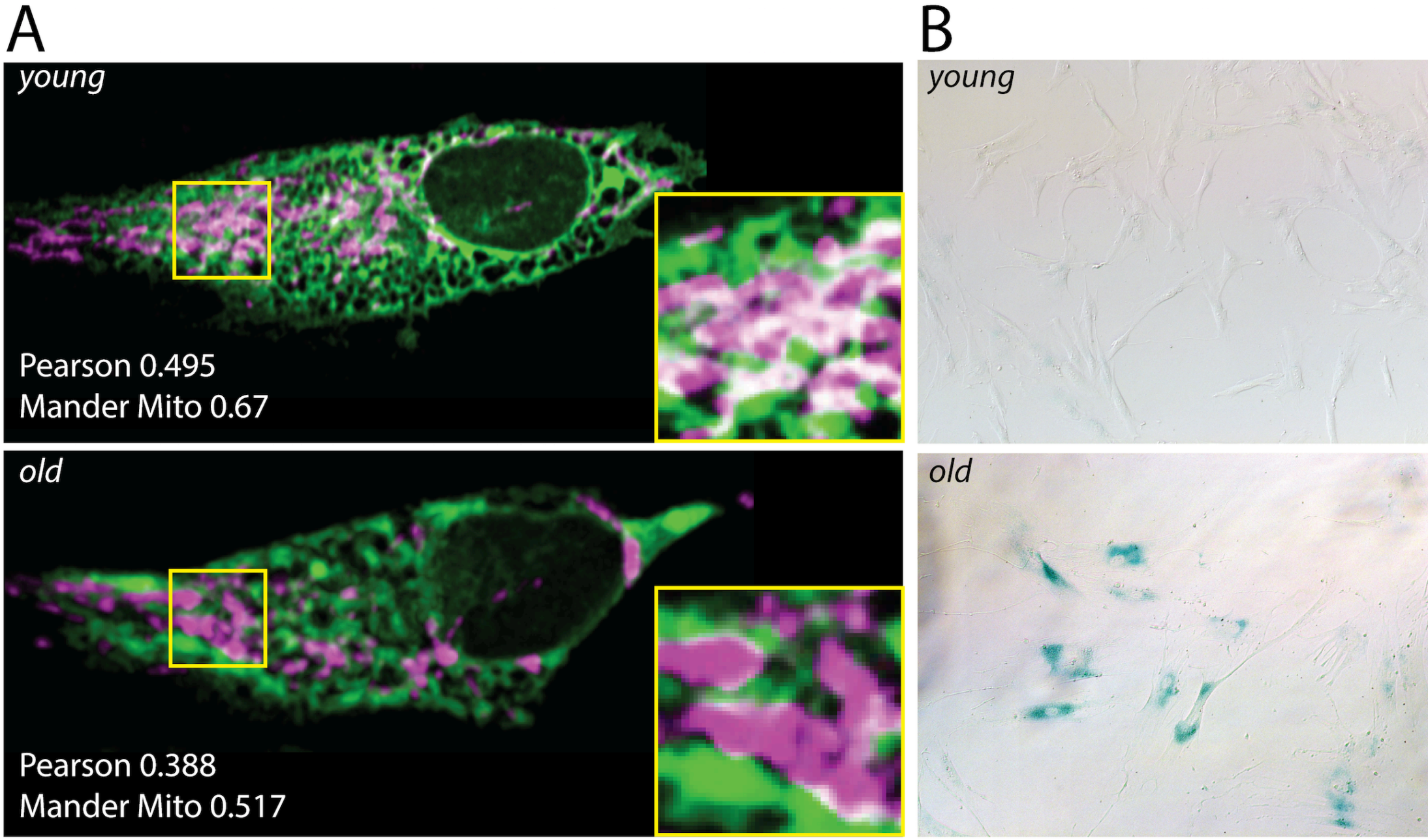
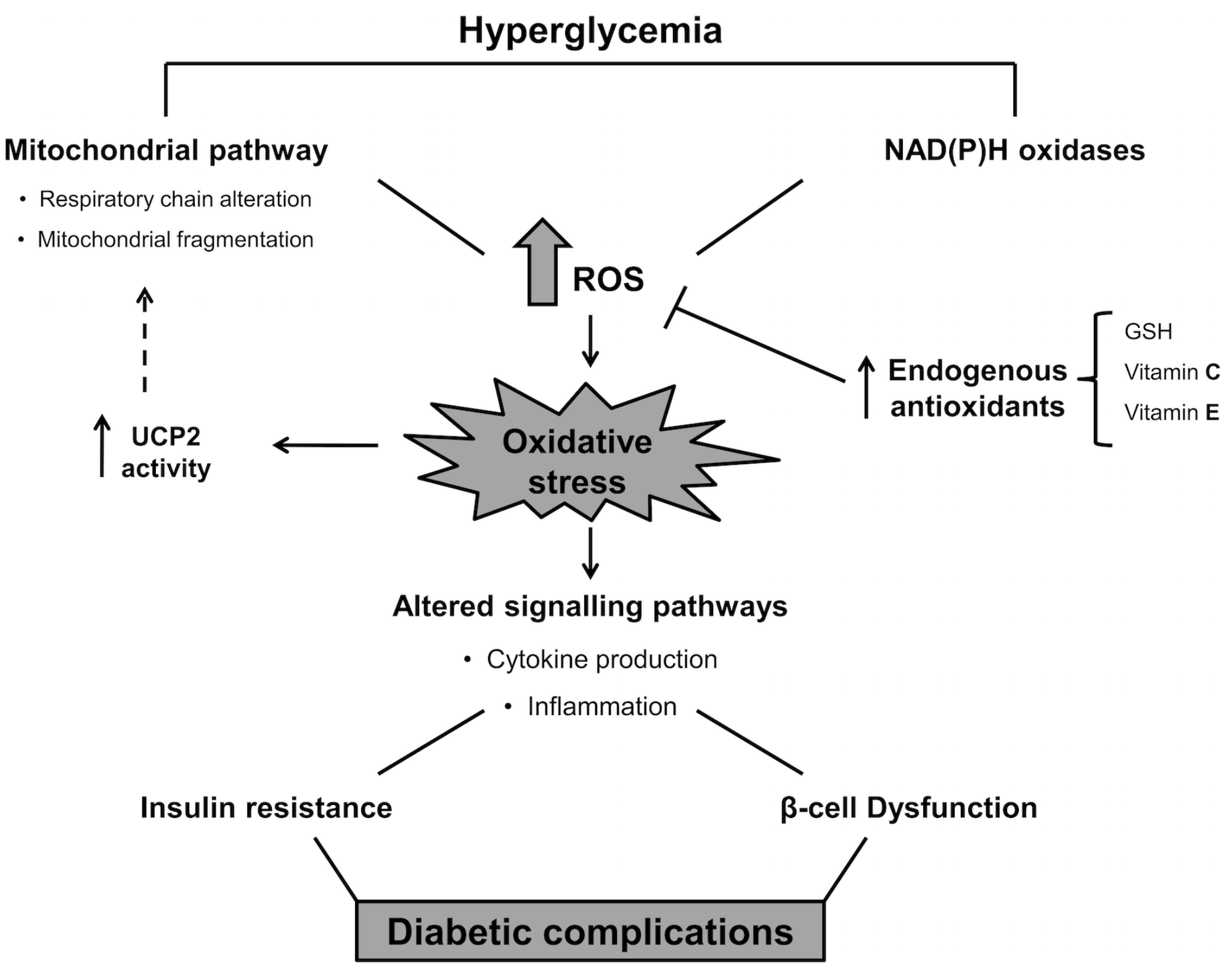
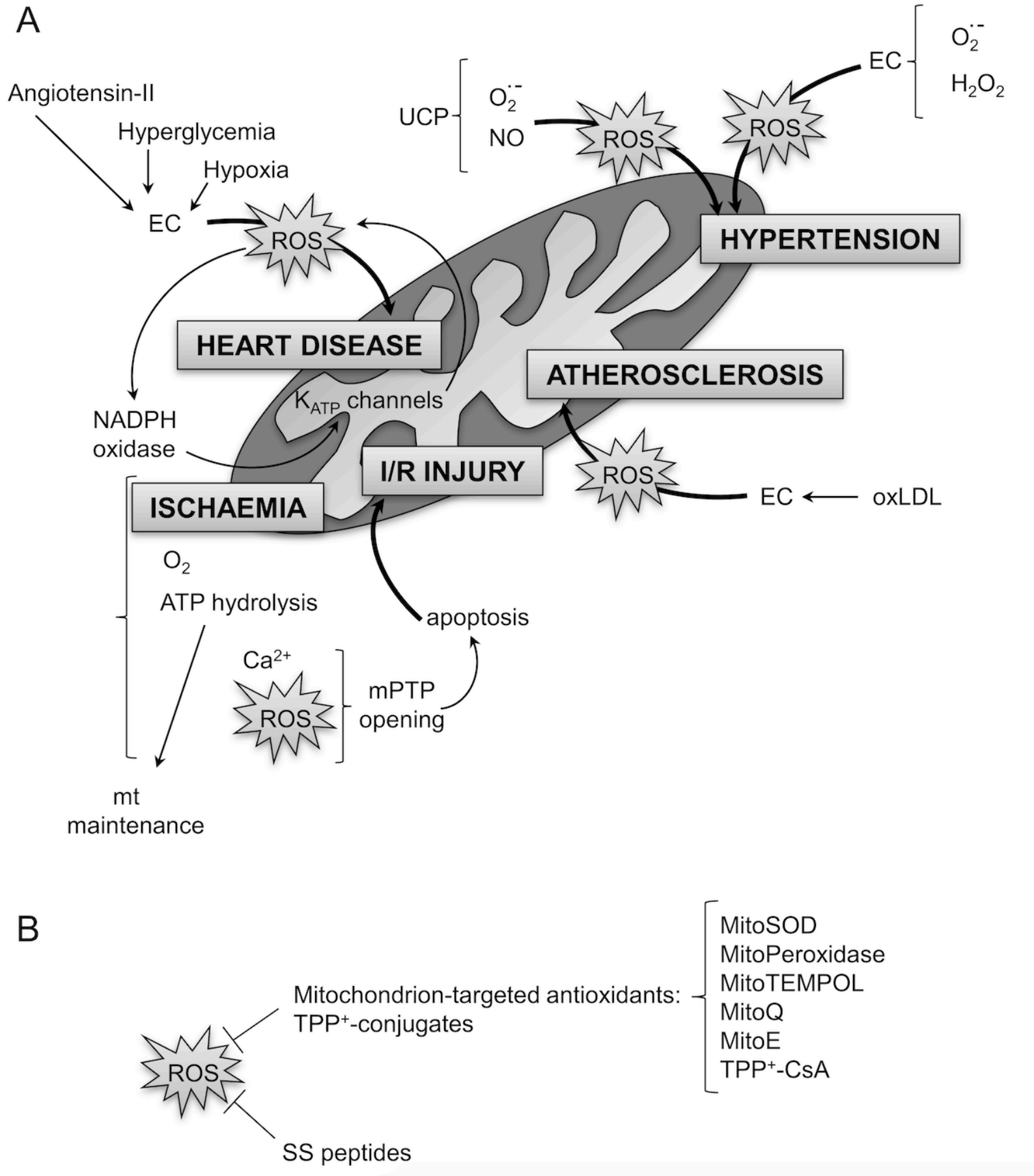
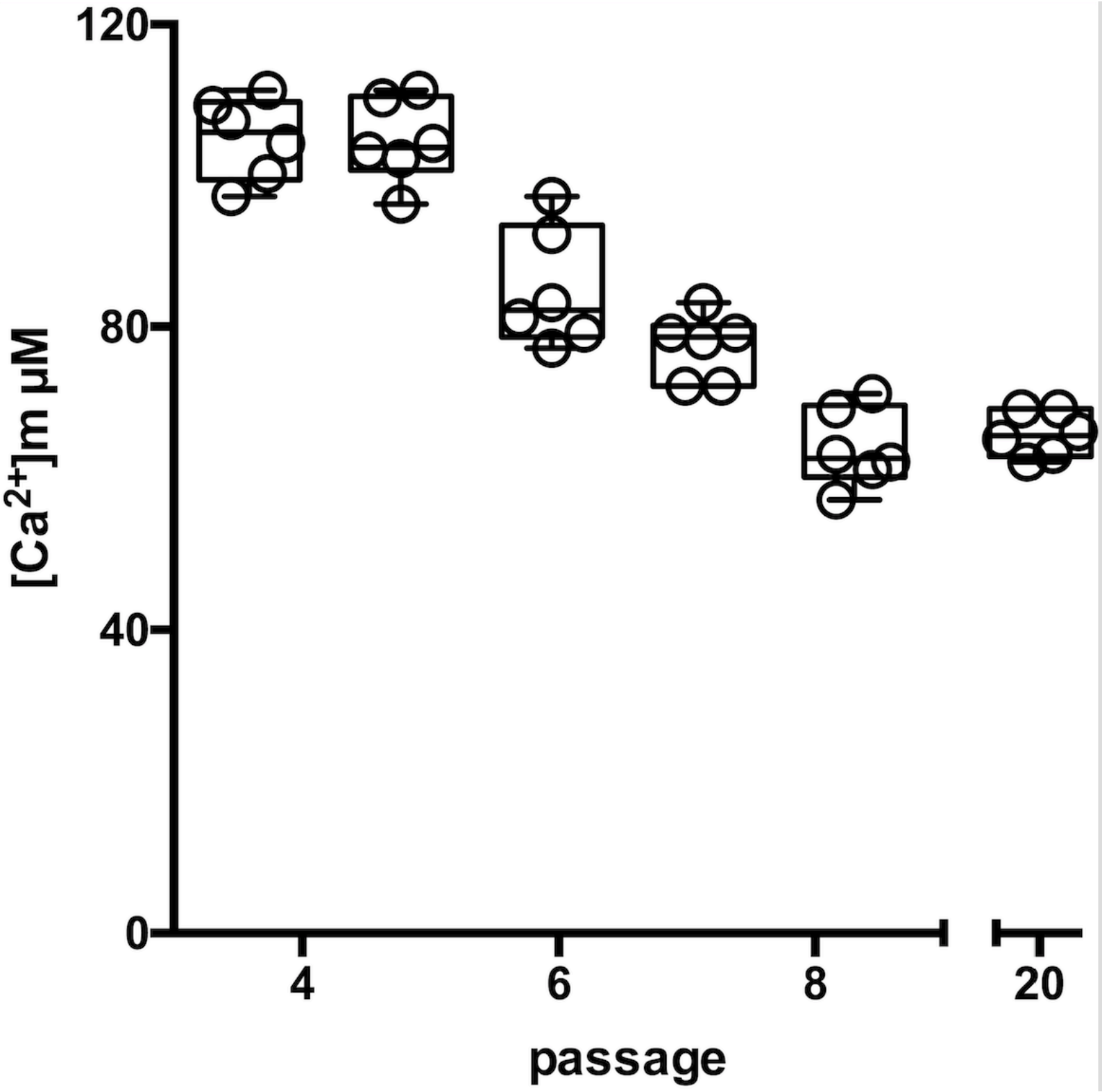
F
20µm
G
5µm
Hi
15µm
Hii
15µm

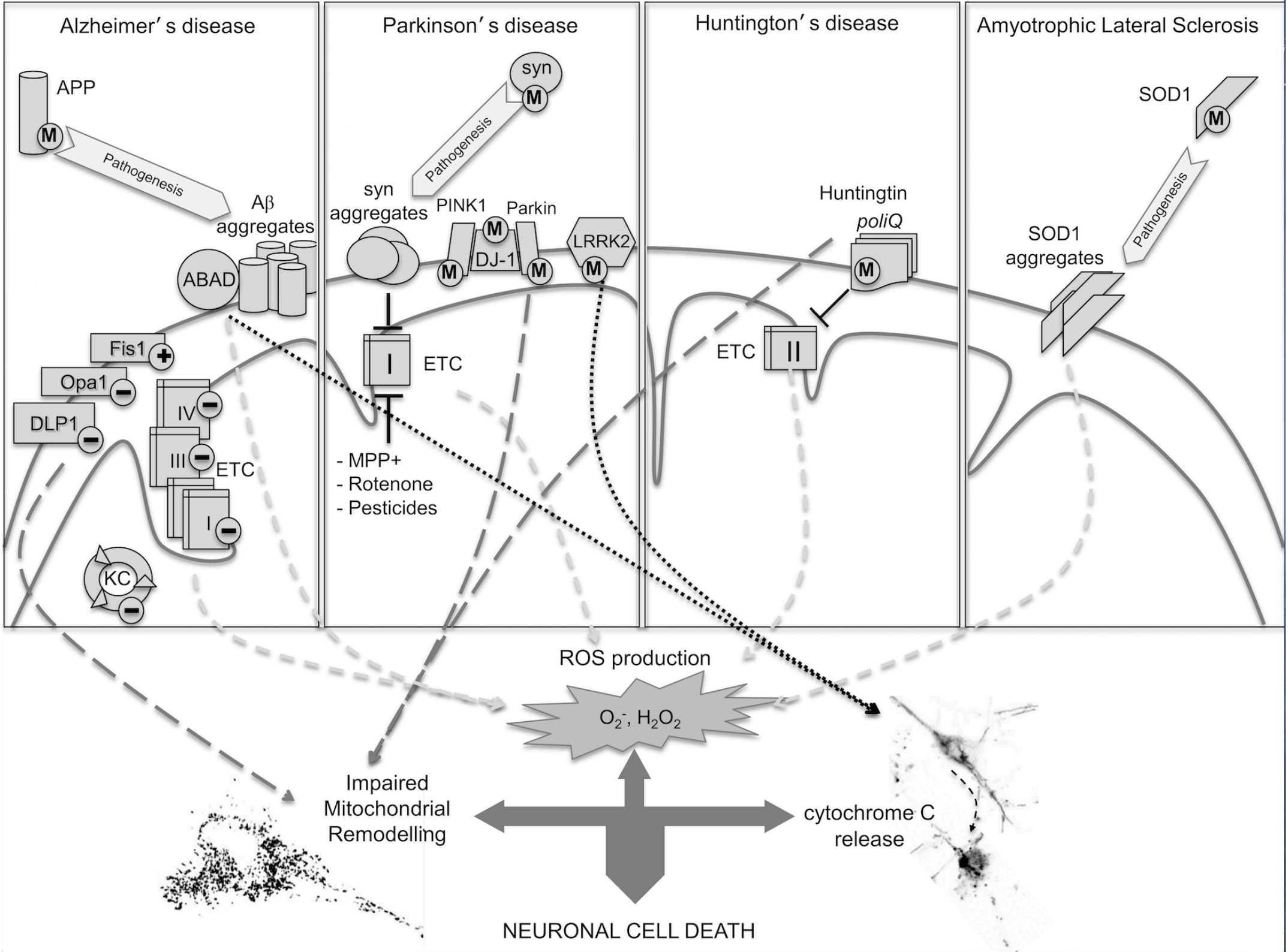

A
young
Pearson 0.495
Mander Mito 0.67
old
Pearson 0.388
Mander Mito 0.517
B
young
old

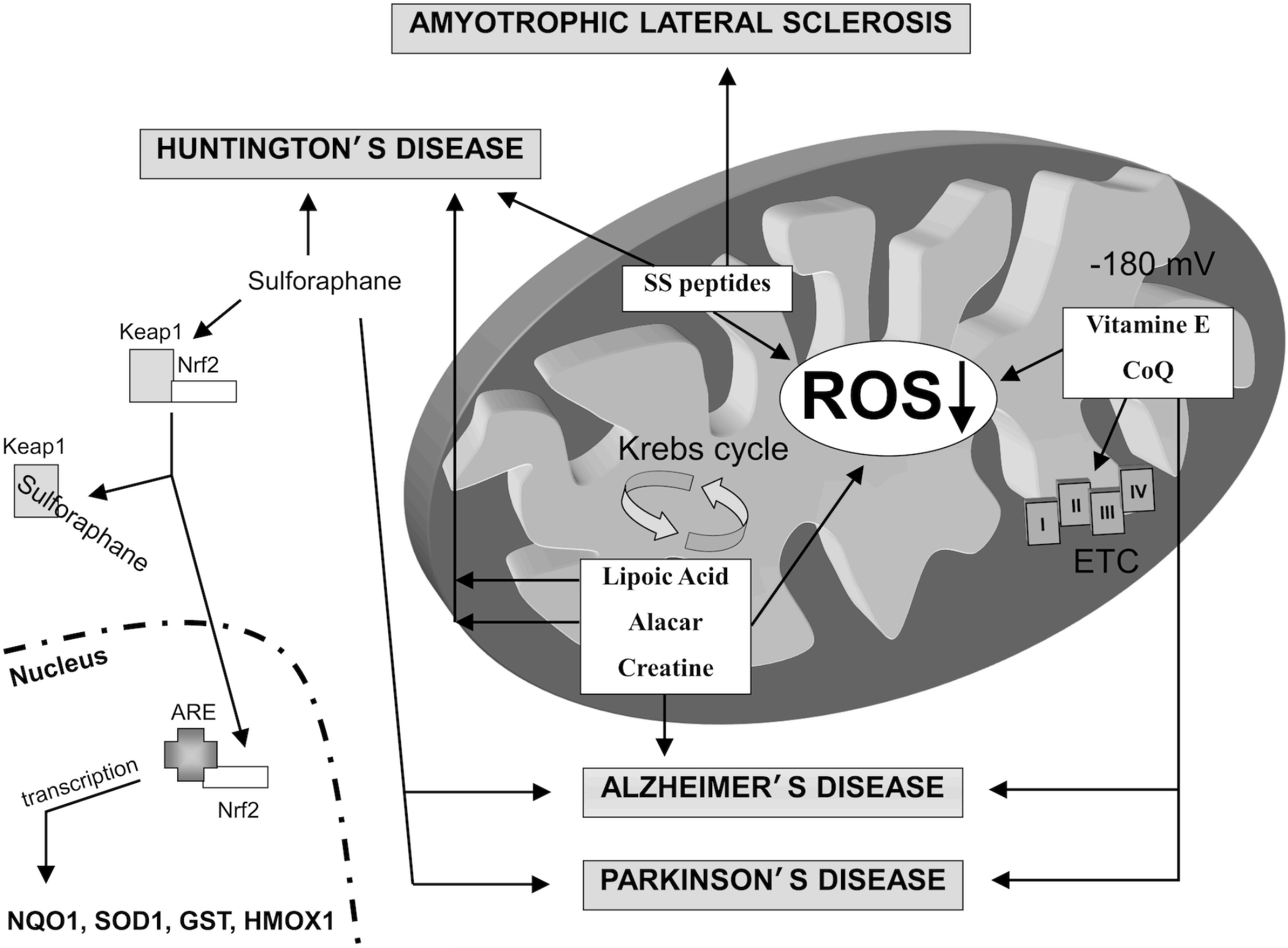
	$Fe^{3+}/\mathbf{Cu^{2+}} + O_2$	$Fe^{2+}/\mathbf{Cu^{1+}} + O_2$
Fenton reaction	$Fe^{2+}/\mathbf{Cu^{1+}} + H_2O_2$	$Fe^{3+}/\mathbf{Cu^{2+}} + OH + OH$
Haber-Weiss reaction	$O_2 + H_2O_2$	$O_2 + OH + OH$


Hyperglycemia
Mitochondrial pathway
• Respiratory chain alteration
• Mitochondrial fragmentation
NAD(P)H oxidases
ROS
UCP2 activity
Oxidative stress
Endogenous antioxidants
GSH
Vitamin C
Vitamin E
Altered signalling pathways
• Cytokine production
• Inflammation
Insulin resistance
β-cell Dysfunction
Diabetic complications


A
Angiotensin-II
Hyperglycemia
Hypoxia
EC
ROS
UCP
$O_2^{\cdot-}$
NO
ROS
ROS
EC
$O_2^{\cdot-}$
H_2O_2
HYPERTENSION
HEART DISEASE
ATHEROSCLEROSIS
K_{ATP} channels
NADPH
oxidase
I/R INJURY
ROS
EC
oxLDL
ISCHAEMIA
O_2
ATP hydrolysis
apoptosis
Ca^{2+}
ROS
mPTP
opening
mt
maintenance
B
Mitochondrion-targeted antioxidants:
TPP+-conjugates
MitoSOD
MitoPeroxidase
MitoTEMPOL
MitoQ
MitoE
TPP+-CsA
ROS
SS peptides


120
80
40
0
[Ca2+]m µM
4
6
8
20
passage


Alzheimer′ s disease
Parkinson′ s disease
Huntington′ s disease
Amyotrophic Lateral Sclerosis
APP
M
Pathogenesis
Aβ
aggregates
ABAD
Fis1
Opa1
DLP1
IV
III
ETC
I
KC
syn
M
Pathogenesis
syn
aggregates
PINK1
Parkin
M
DJ-1
M
M
LRRK2
M
I
ETC
- MPP+
- Rotenone
- Pesticides
Huntingtin
poliQ
M
ETC
II
SOD1
M
Pathogenesis
SOD1
aggregates
ROS production
O_2^-, H_2O_2
Impaired
Mitochondrial
Remodelling
cytochrome C
release
NEURONAL CELL DEATH


AMYOTROPHIC LATERAL SCLEROSIS
HUNTINGTON' S DISEASE
Sulforaphane
Keap1
Nrf2
Keap1
Sulforaphane
Nucleus
ARE
transcription
Nrf2
NQO1, SOD1, GST, HMOX1
SS peptides
-180 mV
Vitamine E
CoQ
ROS
Krebs cycle
I
II
III
IV
ETC
Lipoic Acid
Alacar
Creatine
ALZHEIMER' S DISEASE
PARKINSON' S DISEASE