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Chapter 5 – "Parkinson's disease – A role of non-enzymatic posttranslational modifications in disease onset and progression?"

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ABSTRACT

Parkinson's disease (PD) is a still incurable neurodegenerative disorder with a highly complex etiology. While about 10% of cases are associated with single-gene mutations, the majority of PD is thought to originate from a combination of factors such as environmental impact, lifestyle and aging. Even though investigations into the genetically caused cases have uncovered major pathomechanisms of the disease there still exists a wide gap concerning the molecular impact of the other risk factors. All of them are known to have a major impact on the oxidative burden of the cell and thus strongly influence the non-enzymatic posttranslational modifications (nePTMs) of proteins. These modifications are by now known to dramatically alter the stability of proteins, their interactomes, and also their functions. However, the knowledge of nePTMs and their possible causative role in the pathoetiology of PD is just starting to emerge again guided by research on PD-associated genes. In this short review, we will thus concentrate on known nePTMs of two PD-associated genes, SCNA and DJ-1, and discuss their role in the pathoetiology of PD. In the future, it will, however, be essential to unravel the complete "environmental proteome" to understand the impact of nePTMs on PD etiology. This might open up new pathways urgently needed to develop new diagnostic and therapeutic tools for this still incurable disease.

1. Introduction

Neurodegenerative diseases are mostly multifactorial diseases whose etiology is determined by a genetic component but also by the organismal environment and the aging process. So far, however, the exploration of pathological processes has mostly focused on transcript abundance, even though the genetic outfit of a patient is essentially stable over time and hardly accessible by a direct influence of environmental factors. In contrast, the proteome is highly susceptible to environmental changes such as tobacco smoke, pollution, alcohol, certain drugs, and diet. Protein activities, stability, and degradation of many proteins are regulated by posttranslational modifications (PTMs) induced by the environment and/or disease states. In bacteria, yeast, and plants it has already been shown that post-translational modifications of individual proteins represent a powerful strategy for an adaptation to physiological changes, (extreme) environmental challenges, or even aging in animals (Baldensperger et al., 2020; Eichler, 2020). Even though the connection between proteome alterations and subsequent metabolic and phenotypic changes remains a tough task to be addressed - specifically in higher organisms -, recent advances in proteomics and mass spectrometry start to unravel how the environment affects the biology of proteins. At the cellular level, it turns out that common targets of the "environmental proteome" are energy metabolism, cytoskeleton, protein turnover, and oxidative stress, all of which are known molecular culprits of the etiology of neurodegenerative disorders such as Parkinson's Disease (PD).

2. Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease with an incidence rate of 1–2% of the population (Poewe et al., 2017). In advanced stages, PD is characterized by motor disabilities caused by the degeneration of dopaminergic neurons (DAns) specifically in the substantia nigra pars compacta (SNpc) (Fahn, 2003). Another pathological hallmark of PD found in the majority of cases is the development of intracellular

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inclusions termed Lewy bodies (LB) (Poewe et al., 2017). The most characteristic motor disabilities used for clinical diagnosis include resting tremors, bradykinesia, rigidity, and postural instability. Interestingly, motor symptoms are often preceded by olfactory dysfunctions or neuropsychiatric alterations such as depression or REM-sleep-behavior-disorder (RBD) (Chaudhuri et al., 2006; Doty, 2012; Fahn, 2003). Although the exact cause of PD remains still elusive, both genetic as well as acquired factors are known to contribute to PD etiology which makes PD a multifactorial disease (Obeso et al., 2017). Accordingly, PD can be subdivided into familial inherited, toxin/drug-induced, and sporadic PD. With a prevalence of about 85–90%, sporadic PD which cannot be attributed to specific genetic mutations is the most common form (Ball et al., 2019).

2.1. Risk factors

Recent studies suggested that environmental factors like rural residences, toxins/pesticides as well as certain occupations (farming, mining, or welding) are associated with an increased risk of developing PD (Ball et al., 2019). Another risk factor is gender, as men are twice as often affected by PD (van den Eeden et al., 2003). However, the greatest risk factor is age (Reeve et al., 2014). Before the age of 50, the prevalence of PD is quite low, while after the age of 85 the incidence rate increases up to 3–5% of the population. In our aging society, the amount of PD patients is predicted to double between 2005 and 2030 (Dorsey et al., 2007). Thus, molecular mechanisms, such as changes in post-translational modifications, e.g. involved in the process of cellular aging are highly likely to be instrumental in the pathoetiology of PD.

2.2. Genetic mutations

Most pathological hallmarks of PD have been identified by studying PD-associated monogenetic mutations. These mutations affect a group of genes referred to as PARK1-23 (Deng et al., 2018; Lola Cook Shukla et al., 2019; Poewe et al., 2017). Posttranslational modifications changing the function/activity of these genes have been described mostly for two of them: α-synuclein (official symbol: SNCA) and DJ-1 (official symbol: PARK7).

α-synuclein is an example of those genes inherited in an autosomal dominant manner. α-synuclein was the first PD-associated gene discovered (Nussbaum, 2017; Polymeropoulos et al., 1997) and is probably also the most intensively studied PD-associated gene so far. Mutations in α-synuclein typically affect its folding ability which makes α-synuclein insoluble and promotes aggregation, introducing intracellular inclusions termed Lewy bodies (Kim et al., 2014). It has also been associated with regulating mitochondrial structure and function as the majority of PD-associated genetic mutations (Park et al., 2018). α-synuclein is one of the PD-associated genes for which several post-transcriptional modifications have already been described. It is e.g. phosphorylated, ubiquitinated, nitrated, and O-GlcNAcylated. Many of these PTMs are known to affect α-synuclein aggregation potential and toxicity (Zhang et al., 2019).

A prominent example of a gene causing autosomal recessive fPD is DJ-1. DJ-1 is thought to be involved - amongst others - in the antioxidant system protecting cells against oxidative stress. Although it is ubiquitously expressed, it is enriched in cells with a high energetic burden (Repici and Giorgini, 2019). It was recently suggested to be a moonlighting protein (Panicker et al., 2021), thus its function varies between different tissues and cell types. Besides oxidation (discussed below), DJ-1 is also known to be modified by sumoylation, *S*-nitrosylation, and phosphorylation (Ariga et al., 2013) and seems to play a distinct role in the cellular defense against glycation (discussed below). Nevertheless, the exact contribution of DJ-1 mutations and specifically the respective roles of its PTMs to PD pathogenesis remains largely elusive.

2.3. Major pathomechanism in PD-etiology

Several quite distinct cellular and molecular mechanisms have been implicated in PD pathogenesis (Fig. 1). A central role plays the aggregation of α-synuclein. However, abnormal protein clearance, neuroinflammation, and specifically mitochondrial dysfunction play a major role in the onset and progression of PD, too (Picca et al., 2021). The first link between mitochondrial dysfunction and PD became evident around 40 years ago when several people were exposed to the mitochondrial complex I inhibitor 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) and suffered from parkinsonian-like symptoms afterward (Langston et al., 1983). Since then varying degrees of complex I and II deficiency have been described in postmortem brain tissue (substantia nigra and cortex) of sporadic PD patients (Banerjee et al., 2009; Exner et al., 2012; Fløngs et al., 2018). The cause for this deficiency is mostly unknown, however, dysfunctional complex I is a major source of reactive oxygen species (ROS), which are thought to be substantial contributors to DAn degeneration (Dias et al., 2013). Additionally, most PD-associated genes including DJ-1, PINK1, Parkin (official symbol: PRKN), SNCA, and LRRK2 are involved in, amongst others, mitochondrial homeostasis and quality control (Franco-Iborra et al., 2018; Pickrell and Youle, 2015; Strobbe et al., 2018). Mutations in these genes may reduce the cells' ability to adapt to cellular requirements and to remove damaged mitochondria. This may also result in elevated ROS generation and susceptibility to oxidative stress. Recent reports also indicated that many mitochondrial proteins are modified via various PTMs and become primarily inactivated as a consequence of this process (Stram and Payne, 2016).

3. Non-enzymatic PTMs in Parkinson's disease

PTMs are coming more and more into the focus of research in neurodegenerative diseases since they are increasingly recognized as being important for the control and modulation of protein function (Harmel and Fiedler, 2018). Thus, these modifications are in the position to influence many aspects of cell biology in health and disease. PTMs can be simply oxidation, the addition of a small methyl group but also the addition of a large polyprotein chain to a protein. Thus it is not surprising that alone in the Uniprot database more than 680 different PTMs are listed (uniprot.org/docs/ptmlist, 2021). Besides the post-translational modifications of proteins mediated by enzymes (i.e. phosphorylation catalyzed by protein kinases.) PTMs are often induced by spontaneous chemical reactions. PTMs change the structure, stability, and functions of proteins in the cells, adding another hitherto underestimated layer to the complexity of molecular interactions within the cell (Prabakaran et al., 2012; Walsh et al., 2005). The vast number of possible non-enzymatic PTMs allows covering only a few selected ones in this review article. Thus, we will concentrate on some outstanding examples in the context of PD, such as oxidation, nitration, and glycation, all of which are known to affect proteins associated with the pathoetiology of PD, specifically SCNA and DJ-1.

3.1. Oxidation

The non-enzymatic PTMs mostly occur when a redox-sensitive amino acid side (i.e. Lys, Arg, Pro, His, Tyr, and Cys) is exposed to a reactive metabolite. The most common reactive metabolites are reactive oxygen species (ROS) and reactive nitrogen species (RNS), both (RONS) of which are essential signaling molecules produced by aerobic metabolism. The reaction of ROS with some side chains of proteins leads to an oxidative post-translational modification of the proteins. Very often these modifications – if stable – change the stability and the function of the modified proteins. Post-translational modifications - if reversible - are part of the normal cellular physiology, specifically of the anti-oxidative defense system. This is specifically needed in the brain since the mammalian brain is metabolically very active and is a major

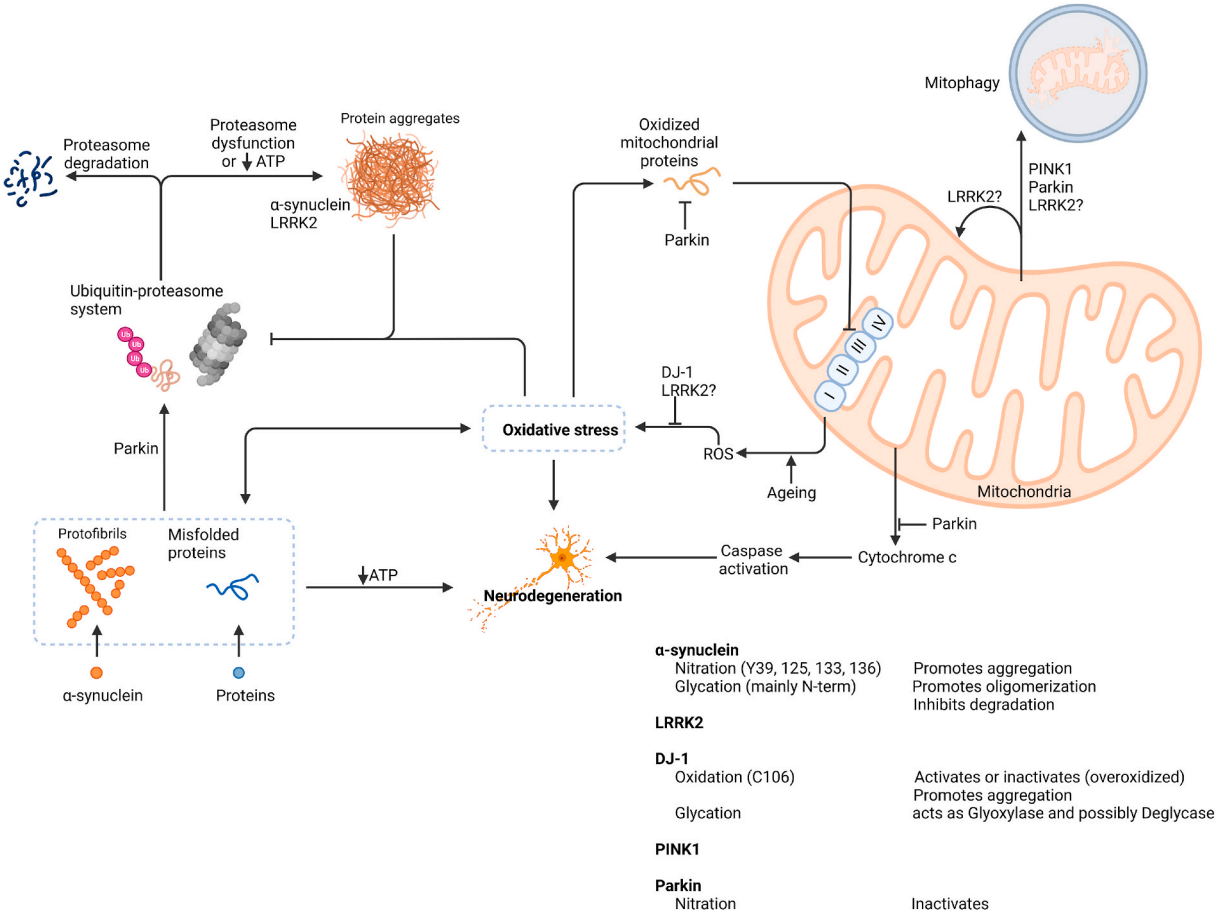

Fig. 1. Pathological events contributing to Parkinson's disease etiology. The main pathways of cell toxicity and thus DAn degeneration are thought to be deficiencies in mitochondria, α-synuclein/protein misfolding and aggregation (Abou-Sleiman et al., 2006) mediated by genetic mutations as well as post translational modifications.

producer of RONS (Colton and Gilbert, 2002; Friedman, 2011a, 2011b). Therefore, RONS-dependent redox signaling is particularly important in the normal physiology of the brain (Beckhauser et al., 2016; Colton and Gilbert, 2002). However, under pathological conditions, RONS can reach excessive levels, generating oxidative and nitrosative (O/N) stresses, which often lead to irreversible changes and thus damage of DNA, lipid, and proteins which is detrimental to cell function (Jones, 2006; Ray et al., 2012).

A prime example in PD, of how PTM can change the functionality of a protein, is the oxidative post-translational modification (Ox-PTM) of DJ-1. DJ-1 is characterized by the presence of a highly oxidation-sensitive cysteine (C106), which easily undergoes oxidation. Upon oxidative stress, the reduced C106 becomes oxidized to C106–SO_2H or to C106–SO_3H via the unstable and reversible C106–SOH. Thus, this stepwise ROS-dependent oxidative PTM of C106 allows DJ-1 to function as a dosage-sensitive oxidative stress sensor (Cookson, 2012). The oxidative state of C106 is not only an indicator for cellular oxidative stress, but it is also determining the functionality of the protein. The stable C106–SO_2H form is postulated to represent the functionally active DJ-1 and exerts its neuroprotective function. In contrast, the reduced state of DJ-1 and its overoxidized state - C106–SO_3H – are associated with its loss of function (Ariga et al., 2013; Blackinton et al., 2009; Canet-Avilés et al., 2004). More specifically, under reducing conditions DJ-1′s chaperone activity and the ability to inhibit α-synuclein aggregation is abolished as is the case under a high oxidative burden. In addition, C106–SO_3H is also prone to aggregation (Ariga et al., 2013; Kumar et al., 2019; Repici and Giorgini, 2019; Wilson, 2011). The presence of oxidatively damaged DJ-1 in the brains of PD patients also hints towards a prominent role of the Ox-PTM of DJ-1 in the disease (Choi et al., 2006).

Still, the precise role of these non-enzymatic modifications of DJ-1 are still far from being understood. This might be due to the fact, that DJ-1 is highly likely a so called moonlighting protein, thus a highly evolutionarily conserved protein with multiple distinct biochemical activities and functions (Jeffery, 2003; Panicker et al., 2021). A characteristic of these proteins is that they undergo oxidative modifications essential for their functions and in addition - depending on the oxidative status - present with distinct interactomes. Thus, it might well be that DJ-1′s dose-dependent oxidative modification is co-opted by different species and cell-type-specific stress response systems as an activation signal. This renders the detection of its precise role in the pathoetiology of human PD a highly challenging task.

Since oxidative stress is regarded as one of the major contributors to the pathoetiology of PD for a long time, it is not surprising, that there exists a long list of literature reporting pre-clinical and clinical trials that evaluate the therapeutic potential of antioxidants. Antioxidants are enzymes, molecules, ions, or even very stable radicals capable of delaying or preventing another molecule's oxidation, thus, protecting from the damage induced by ROS and RNOS. In the context of PD molecules such as Coenzyme Q10, inosine, N-Acetylcysteine, Vitamin C, and E as well as glutathione received special attention (Duarte-Jurado et al., 2021). Intriguingly, while in the majority of preclinical studies a beneficial neuroprotective effect of antioxidants - e.g. Coenzyme Q10 - could be demonstrated (Horvath et al., 2003; Spindler et al., 2009), the effect was hard to reproduce in clinical trials, if at all (Zhu et al., 2017). Still, a recent meta-analysis of clinical trials evaluating the therapeutic

efficacy of glutathione indicated that the treatment might slightly improve motor functions in patients with PD (Wang et al., 2021). These at a first glance unsatisfactory results of treating PD with antioxidants in humans might be due to two main factors. First, clinical trials normally include patients with clear symptoms of PD. However, PD is characterized by a long prodromal phase (up to decades) (Schaeffer et al., 2020) in which oxidative damage is already accumulating. This implies that reducing oxidative stress in the advanced stages of PD might exert only limited effects on disease progression. Second, it also has to be considered that - in contrast to the preclinical models - the human population is very heterogeneous with respect to disease etiology and progression (Berg et al., 2021). Thus, clinical trials on stratified patient cohorts are needed in order to reliably judge the effect of antioxidant treatments. However, such clinical trials are now beginning to be initiated. For example, since 2018 there is a clinical trial registered in which genetically stratified subgroups of PD patients with a distinct enrichment of risk variants in mitochondrial genes are treated with Coenzyme Q10 (Prasuhn et al., 2019). In sum, since these two major confounders have been disregarded in the design of the clinical trials up to now, the treatment with antioxidants at early stages of PD – best in the prodromal phase – is still a highly attractive therapeutic option. Additionally, to fully elucidate the potential of antioxidants for treating PD, the delivery and bioavailability of most antioxidants need to be improved. Commonly antioxidants were administered e.g. oral, intranasal, or intravenous so far (Duarte-Jurado et al., 2021). To reach critical brain regions such as the SNpc and to be taken up by cells within these regions antioxidants need to pass several hurdles like their poor absorption, limited membrane permeability, and short half-life. Thus, increasing the antioxidant dosage not necessarily increases cellular concentrations which, however, would be necessary for antioxidants to fulfill their protective effects. However, improved delivery and transportation systems such as encapsulation into or linkage to liposomes and other nanovesicles might help to increase antioxidant stability and bioavailability in the future (Khalil et al., 2019).

3.2. Nitration

Like oxidation, nitration is an undesired modification that is the consequence of nitroxidative stress that disrupts nitric oxide ($^{\bullet}NO$) signaling (Radi, 2004, 2013). High levels of ROS in the presence of $^{\bullet}NO$ lead to an enhanced formation of nitrating species such as nitrogen dioxide ($^{\bullet}NO_2$) or peroxynitrite (NO_3^-). These species cause a nitration of amino acids, most notably, tyrosine by free radical reactions (Radi, 2004). Thereby the hydrogen atom in the 3' position of the tyrosine phenolic ring is replaced by a hydrophilic nitro group (NO2) to form 3-nitrotyrosine. The consequences of this modification are steric hindrances, conformational changes and it may also prevent tyrosine phosphorylation (Radi, 2013). Additionally, it can affect intramolecular electron transfer processes in tyrosine nitrated proteins (Yokoyama et al., 2010).

Interestingly, protein tyrosine nitration is preferentially directed to specific cellular locations and thus a specific subset of proteins. Due to the short biological half-time of nitrating species (Ferrer-Sueta and Radi, 2009), proteins close to the source of nitrating species e.g. mitochondria are more severely affected (Heijnen et al., 2006; Radi et al., 2002). This is especially hazardous for PD, as mitochondrial dysfunction is a prominent pathological culprit and also the majority of genes linked to PD are involved in mitochondrial function making these proteins prone to nitration.

One of the best examples for tyrosine nitration in PD is α-synuclein (SNCA) which was found in large quantities in the brains of patients suffering from PD (Giasson et al., 2000; He et al., 2019). α-synuclein has four tyrosine residues (Y39, Y125, Y133, Y136) located in the N-terminal and the C-terminal region, the latter has been proposed to be essential for the stability and solubility of α-synuclein (Barrett and Timothy Greenamyre, 2015; Chavarría and Souza, 2013). Nitration is thought to force α-synuclein into a misfolded state facilitating its aggregation. This was found to be further enhanced by pathogenic α-synuclein mutations (Paxinou et al., 2001). Also, α-synuclein degradation was found to be affected by nitration. Tyrosine nitration resulted in a lower rate of α-synuclein degradation mediated by the protease calpain I (Mishizen-Eberz et al., 2005) and hampered the autophagic clearance of α-synuclein aggregates as non-nitrated Y133 is required for the phosphorylation of S129 which modules the autophagic process (Kleinknecht et al., 2016). As nitration crucially affects α-synuclein solubility and clearance, it could be assumed that it is a major contributor to DAn degeneration. And indeed, the injection of nitrated α-synuclein into the rat SN caused severe DAn degeneration and PD-associated phenotypes like bradykinesia and postural instability (Yu et al., 2010).

Besides α-synuclein, also Parkin has been reported to be affected by nitration in PD. Elevated levels of cysteine nitrated Parkin were found in the brains of patients suffering from PD (Chung et al., 2004; Sunico et al., 2013). Excessive and persistent nitration of Parkin was shown to impact its E3 ubiquitin ligase activity which resulted in an accumulation of damaged proteins and mitochondria (Chung et al., 2004; Sunico et al., 2013; Yao et al., 2004). Similar alterations are known to be introduced by pathogenic Parkin mutations in fPD (Arkinson and Walden, 2018; Ge et al., 2020). Thus, non-enzymatic PTMs are in the position to mimic the pathogenic effect of genetic mutations known to be linked to the disease.

3.3. Glycation

Another non-enzymatic PTM important for neurodegenerative disorders is the glycation of proteins, nucleic acids, or lipids. Glycation is responsible for the formation of advanced glycation end-products (AGEs), which are a heterogeneous group of compounds. They are formed by a chemical reaction - called the Maillard reaction - between the carbonyl group of reducing sugars, dicarbonyls, or oxidized lipids and the free amino groups of nucleic acids, phospholipids, and proteins. This reaction reversibly generates a Schiff's base which is then transformed into a stable ketoamine, the Amadori product. After further complex, partly incompletely understood and pH-dependent reactions, the chemically stable AGEs are finally formed which may also lead to the formation of bonds with adjacent proteins, (Castellani et al., 1996; Takeuchi et al., 2021; Videira and Castro-Caldas, 2018). Thus, glycation - similar to oxidation and nitration - potentially alters the function of proteins by disrupting molecular conformation and altering enzyme activity. Furthermore, even though glycated proteins are still degraded by the ubiquitin-proteasome system, their degradation is significantly slower and strongly dependent on the level of glycation (Patil et al., 2020; Raupbach et al., 2020), which puts further stress on the cell.

The formation of AGEs under physiological conditions takes weeks to years. Therefore, AGEs are also regarded as culprits of the aging processes formed by a slow and steady modification of long-lived substrates/proteins (Monnier et al., 1999). However, the same process can take place within hours when substrate availability (e.g. hyperglycemia) or oxidative stress is increased (Akhter et al., 2021). Thereby AGE-formation can also affect short-lived substrates and impair their function (Schiekofer et al., 2003). Thus, diseases prone to produce a hyperglycaemic state (such as Diabetes mellitus (DM)) and/or diseases in which increased oxidative stress is regarded as a pathological event (such as many neurodegenerative diseases like PD) are highly likely to be strongly affected by AGE formation. Indeed, the presence of AGEs close to one of the histopathological hallmarks of PD, the Lewy bodies, has already been demonstrated about 25 years ago in the substantia nigra and locus coeruleus (Castellani et al., 1996). Furthermore, a recent systematic review and meta-analysis has reported that patients with DM have a higher risk of developing PD, even though the prevalence of DM in PD patients is unaltered (Komici et al., 2021). The latter causes the still controversial discussion concerning whether diabetes is a risk factor for PD or not. Undisputed is that the presence of DM is associated with greater PD severity and faster progression, which suggests that DM may

be a facilitating factor of neurodegeneration. The molecular underpinnings of this association are still unexplored but highly likely also include the glycation of proteins. In this context, however, it has to be kept in mind that PD-associated alterations in glucose metabolism in the brain are associated with reduced cellular glucose uptake rather than with a respective increase (Zilberter and Zilberter, 2017). Thus, alternative molecular mechanisms like impaired insulin signaling alterations might also be relevant (Ansari and Emerald, 2019) in the context of the interdependency of diabetes and PD. Furthermore, glucose presents itself with a low reactivity as a glycating agent. In contrast, some dicarbonyls that are byproducts of glucose metabolism exhibit a very high reactivity and are regarded to be the major glycation agents in cells. Among these is the toxic dicarbonyl methylglyoxal (MGO).

MGO is one of the most relevant and reactive glycation agent in vivo being about 20,000-fold more reactive than glucose (Thornalley, 2005). It reacts with lysine residues on proteins forming carboxyethylysine (CEL). Moreover, other agents such as glyoxal and 3-deoxy-glucosone are also potent glycation agents, leading to the formation of several AGEs amongst which are carboxymethylysine (CML) and 3-deoxyglucosone lysine dimer (DOLD). Unfortunately, often overlooked is the fact that MGO is formed mostly as a byproduct of glycolysis and that it glycates one of the major enzymes in this pathway, the moonlighting enzyme GAPDH. Glycated GAPDH presents with a reduction in its activity, thus, a vicious cycle is initiated with the production of even more toxic MGO (Muronetz et al., 2017) increasing thereby the dicarbonyl stress. Intriguingly, α-synuclein, one of the PD-associated genes, is binding to one of the central enzymes of the glycolysis: Glycerinaldehyd-3-phosphat-Dehydrogenase (GAPDH). Enhanced binding of α-synuclein results in GAPDH inactivation. Interestingly, if α-synuclein - as a long-lived protein - is glycated itself, GAPDH inactivation is further increased (Semenyuk et al., 2019), thus exacerbating the production of MGO even more. In addition, further modulation of α-synuclein biology by its glycation - mostly at its N-terminal region - extends to an induction of its oligomerization and promotion of α-synuclein inclusion formation. The glycation of α-synuclein is also associated with a decrease of its clearance via the autophagy-lysosome pathway, the ubiquitin-proteasome system, and its release from the cell (Vicente Miranda et al., 2017). In sum, glycation of α-synuclein promotes the production of toxic MGO and its own aggregation resulting in increased oxidative stress and the formation of Lewy bodies.

Interestingly, DJ-1 has also been linked to the metabolism of MGO. DJ-1 confers protection against toxic effects of glyoxal treatment in different cellular systems and worms (Lee et al., 2012). Experimental evidence hints towards the ability of DJ-1 to deglycate α-synuclein which results in a reduction of intracellular α-synuclein aggregates (Sharma et al., 2019). Furthermore, it has been shown that DJ-1 attenuates the glycation of specifically complexes I and III of the electron transport chain within mitochondria (Pantner et al., 2021). Thus, it also counteracts MGO induced glycation damage of mitochondrial proteins, which seem to be the main targets of MGO action. Indeed, already small increases in MGO induce a two-to threefold increase in mitochondrial oxidative stress (Rosca et al., 2005) (e.g. increase in ROS and NOS (Akhter et al., 2021)). It also impairs the electron transport chain (Wang et al., 2009) and decreases mitochondrial membrane potential and intracellular ATP levels (Arriba et al., 2007; Prestes et al., 2021).

In PD this effect of glycation is important since mitochondrial dysfunction and concomitant ROS production - as indicated above - is one of the major pathophysiological mechanisms implicated in PD etiology. Also, it becomes evident that a vicious circle between oxidative stress - inducing the formation of AGE products - and AGE products inducing ROS - might be initiated (Fig. 2). Thus, cellular defense mechanisms against glycation are essential for the health of a cell.

The cellular defense against dicarbonyl stress does not solely rely on the ubiquitin-proteasome system (UPS). There exist additional two primary cellular defense systems against glycation. One line of defense is mediated by glyoxalases I and II that convert reactive aldehydes - of which MGO is a prominent candidate - into less reactive products (e.g. in the case of MGO into lactate). This reaction is glutathione - (GSH)

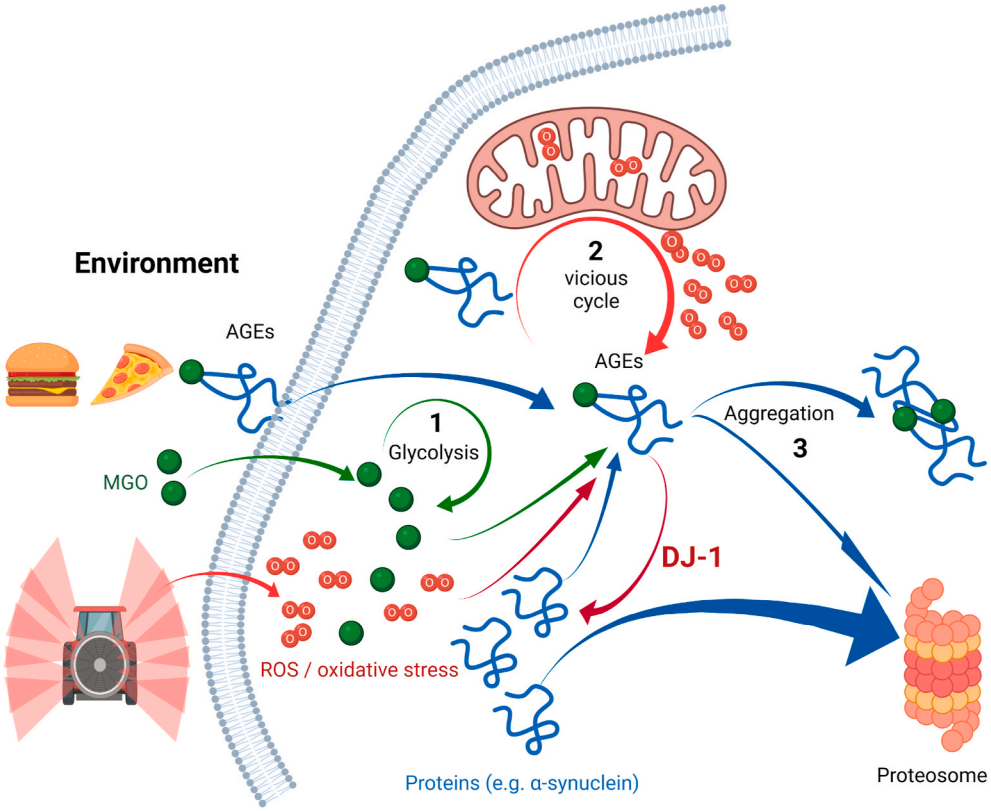

Fig. 2. Contribution of reactive oxygen species (ROS) and advanced glycation end-products (AGEs) with the main glycation agent dicarbonyl methylglyoxal (MGO) to pathological events in Parkinson's disease. Glycation can be triggered by environmental challenges such as diet (AGEs produced by high temperatures in food), MGO exposure (mostly experimental) and increased oxidative stress produced by environmental toxins (such as pesticides). Within cells (1) glycation can increase the production of further toxic MGO as byproduct of glycolysis, (2) the ROS induced AGE formation is followed by an AGE induced ROS formation and creates a vicious cycle of toxicity with the mitochondria, and (3) AGEs are less well degraded by the UPS-system, and can form aggregates. A-synuclein, when glycated, increases the formation of MGO within the glycolysis and is proned to aggregate. Active DJ-1 is acting as a deglycosylase and potentially as a deglycase, thereby reducing the glycation burden of the cell.

dependent. Interestingly, a GSH-independent glyoxylase activity - glyoxylase III - was attributed to Hsp31, a member of the DJ-1 superfamily in bacteria and yeast (Bankapalli et al., 2015) and subsequently - albeit with much lower activity - to human DJ-1 (Lee et al., 2012; Matsuda et al., 2017). Thus, DJ-1 might decrease glycation levels in the cell via "metabolizing" MGO. The second front-line against glycation is mediated by deglycases that directly remove glycation adducts from proteins. Again, members of the DJ-1 superfamily including DJ-1 itself have been described as acting as a protein deglycase (Richarme et al., 2015; Richarme and Dairou, 2017). This deglycase activity of DJ-1 is, however, still under active debate (Jun and Kool, 2020). Thus, it remains to be clarified whether deglycation by DJ-1 is solely a result of its glyoxylase III activity or also of an active deglycase function.

Last but not least in the context of PD, it also has to be mentioned that glycated proteins (AGEs) are ligands of the receptors of AGE (RAGEs) (Akhter et al., 2021; Jeong and Lee, 2021). Activated RAGEs initiate pro-inflammatory pathways within the cells which are also thought to contribute to PD pathology (Gąsiorowski et al., 2018). It has been shown that RAGEs are elevated in PD brains and inflammatory processes in the brain are also thought to be a culprit of PD etiology. Indeed elimination of RAGEs protected dopaminergic neurons from cell death in PD animal models (Teismann et al., 2012; Wang et al., 2020b).

Altogether, there exists evidence that the non-enzymatic PTM of glycation of proteins may play an important role in the molecular pathoetiology of age-related PD.

In this context it is worthwhile to mention that non-diabetic PD patients with altered HbA1c (glycated hemoglobin) levels - as a measure for changes in glycation – developed balance impairments and a faster progression of motor symptoms than non-diabetic patients with euglycemia (Markaki et al., 2021). Thus, glycation might be an attractive target for therapeutic interventions in PD. In this context, the anti-diabetic drug metformin has gathered special attention (Agostini et al., 2021). It - besides other possible neuroprotective mechanisms - reduces levels of glucose, scavenges MGO (Kinsky et al., 2016), and increases Glo-1 activity (Kender et al., 2014). It also ameliorates PD symptoms in pre-clinical mouse models of PD (Wang et al., 2020a). However, the translation of preclinical findings into the human setting is hampered by conflicting results (Qin et al., 2021). But again, it must be stated that these yet inconclusive results may be due to a high degree of heterogeneity among patients with respect to their genetics and life circumstances. Furthermore, the still short time intervals between the enrollment and the follow-ups in these studies might lead to an underestimation of the correlation between metformin intake and PD, specifically considering the long duration of the symptomless prodromal phase of PD. Another attractive therapeutic target for interfering with the detrimental effect of glycation would be to disrupt the signaling between AGEs and their receptors the RAGEs. Indeed, there exist already several small molecules developed to inhibit RAGEs (Kim et al., 2021). However, the existence of many RAGE variants, the vast amount of ligands, and the multitude of intracellular processes evoked by the AGE-RAGE interaction are critical issues that still need to be addressed before the transition of RAGE inhibitors into clinical trials (Rojas et al., 2019).

4. Concluding remarks

It is becoming increasingly clear that non-enzymatic PTMs of proteins play a hitherto underestimated role in the molecular reaction of the organism towards environmental stimuli but also in the molecular pathoetiology of neurodegenerative diseases such as PD. While undoubtedly these non-enzymatic PTMs are crucial for the physiological functions of proteins in the healthy brain (i.e. controlling synapse function etc.) excessive or pathogenic non-enzymatic PTMs start to emerge as being essential for the onset and progression of diseases. Thus, based on the fundamental insight that post-translational modifications are key to the diversity of the proteome, and in turn, to the diversity of an organism in health and disease, it is now time to have a closer look into the molecular pathological effects of these modifications. Furthermore, the wealth of reactive metabolites, capable of undergoing spontaneous chemical reactions with proteins, strongly implicates that so far we have only had a glimpse on the entirety of the non-enzymatic PTMs designed by nature. Therefore, whilst MS-based proteomics over the past years has greatly advanced our knowledge of post-translational modifications of proteins and their role in biological processes, we still have a long way to go. Besides improving existing and designing novel analytical approaches it also will be necessary for investing in generating new tools and reagents and - highly important - in systems-level approaches to unravel the impact of PTMs on cellular and organismal behavior - both in health and disease. In the future, the knowledge about the impact of aberrant PTMs - induced by disease state or environment - on PD pathoetiology might open up new paths in managing and potentially in identifying urgently needed new diagnostic and therapeutic pathways for this still incurable disease.

Declaration of competing interest

The authors declare no competing interests.

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