Cell death

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START smuggling CoQ to fight ferroptosis

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Extramitochondrial coenzyme Q (CoQ) can function as a potent anti-ferroptosis radical trapper. However, it is largely unknown how CoQ is transported from mitochondria to the plasma membrane. A study now suggests that PARL-mediated STARD7 processing is responsible for the cellular distribution of CoQ.

CoQ is mainly synthesized and stored in the mitochondria of eukaryotic cells. In mitochondria, CoQ plays important roles in processes such as the electron transport chain, uridine biosynthesis and fatty acid oxidation[1]. A recent unexpected advancement of CoQ biology is the discovery that, via its lipophilic radical trapping activity on the plasma membrane, the reduced form of CoQ can function as an endogenous inhibitor of ferroptosis – a cell death process that is driven by iron-dependent phospholipid peroxidation and is highly relevant to metabolism and various diseases[2]. The CoQ oxidoreductase FSP1 is involved in this novel function of CoQ by regenerating reduced CoQ from oxidized CoQ[3,4]. However, this anti-ferroptotic function of CoQ raises an obvious question: as CoQ biosynthesis occurs in mitochondria and as CoQ cannot freely penetrate membranes, what is the source of plasma membrane CoQ?

In this issue of *Nature Cell Biology*, Deshwal et al. report that StAR-related lipid transfer (START) domain containing 7 (STARD7) is responsible for the intracellular transport of CoQ from mitochondria to the plasma membrane[5].

As a lipid-binding protein, STARD7 localizes both to the cytosol and the mitochondria[6]. The cellular distribution of STARD7 is regulated by the inner membrane protease presenilin-associated rhomboid-like (PARL)[7]. PARL-mediated cleavage of STARD7 during its import into mitochondria promotes the release of a portion of mature STARD7 into the cytosol and of the remaining amounts into the mitochondrial intermembrane space[7]. Mitochondrial STARD7 functions as a lipid transfer protein for phosphatidylcholine (PC)[6] and shuttles PC between the outer and inner mitochondrial membranes[6,7] (Fig. 1). Cells that are deficient in STARD7 show a decreased mitochondrial PC content together with defective mitochondria morphology and activity[8].

Interestingly, *Parl*$^{-/-}$ mice show severe encephalomyelopathy that resembles Leigh Syndrome, which is a lethal mitochondrial disease that is characterized by neurological regression[9]. Mitochondrial proteins that are required for CoQ biosynthesis as well as CoQ (including CoQ9 and CoQ10) itself are dramatically decreased in *Parl*$^{-/-}$ brain cells, which causes severe respiratory chain defect[5,9].

To examine how PARL regulates CoQ synthesis, Deshwal et al. evaluated all known PARL substrates, and found that only knockout of STARD7 phenocopied the CoQ-deficient phenotype of PARL-knockout cells. This finding revealed an unexpected association between STARD7 and CoQ. They then reconstituted *STARD7*$^{-/-}$ cells with either STARD7 that was only localized in mitochondria (mSTARD7) or cytosolic STARD7 (cSTARD7). mSTARD7, but not cSTARD7, restored CoQ levels in *STARD7*$^{-/-}$ cells. Notably, PC binding-deficient mutant STARD7-R189Q did not restore CoQ levels. More importantly, mSTARD7 restored CoQ levels and mitochondria function in *PARL*$^{-/-}$ cells. Collectively, the researchers demonstrated that PARL-mediated STARD7 processing

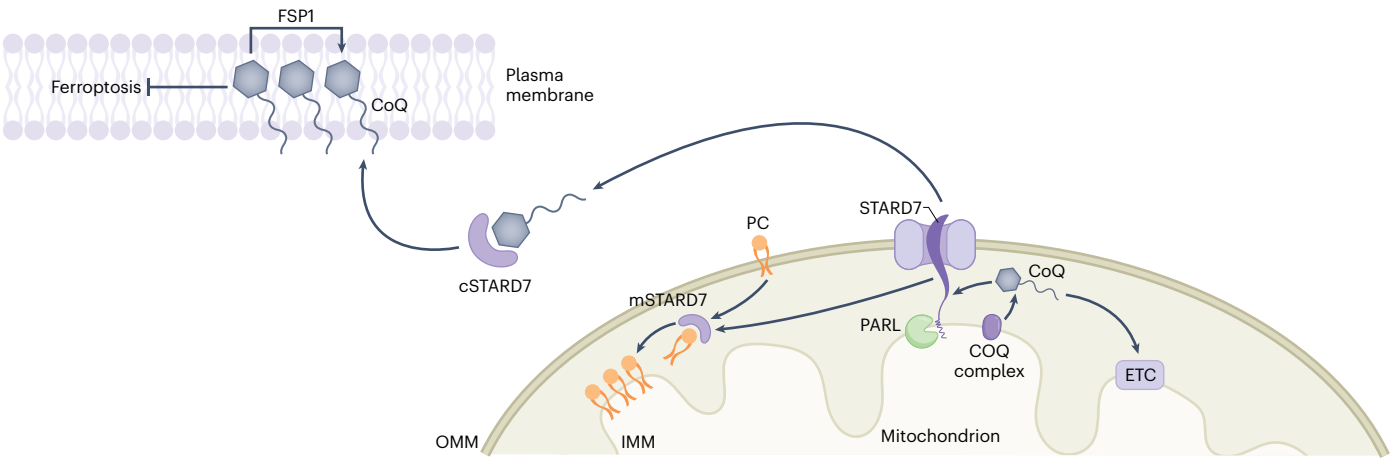

Fig. 1 | PARL-mediated STARD7 processing regulates CoQ synthesis and intracellular distribution. PARL-mediated cleavage of STARD7 during its import into mitochondria promotes the release of a portion of mature STARD7 into the cytosol, and the remaining amounts of STARD7 into the mitochondrial intermembrane space (IMS). cSTARD7 binds to CoQ and facilitates its transport from mitochondria to the plasma membrane, where CoQ suppresses ferroptosis. mSTARD7 shuttles PC between outer and inner mitochondrial membranes (OMM, IMM), and is responsible for the maintenance of CoQ synthesis and normal mitochondria function. COQ complex, CoQ biosynthetic enzyme complex; ETC, electron transport chain.

and mitochondria retention are required for the maintenance of CoQ synthesis.

As CoQ is a crucial suppressor of ferroptosis, Deshwal et al. reasoned that PARL and STARD7 may regulate ferroptosis through CoQ synthesis. They showed that the expression of PARL and STARD7, but not other PARL substrates, positively correlated with the resistance of cancer cells to the induction of ferroptosis. Moreover, both *PARL*$^{-/-}$ and *STARD7*$^{-/-}$ cells exhibited an increased susceptibility to ferroptosis. Surprisingly, re-expression of STARD7, but not mSTARD7 or cSTARD7, restored ferroptosis resistance in *STARD7*$^{-/-}$ cells, although mSTARD7 preserved total CoQ levels similarly to STARD7. They reasoned that both cSTARD7 and mSTARD7 are required for inhibition of ferroptosis.

Deshwal et al. further showed that ectopic cSTARD7 expression inhibited ferroptosis in wild-type cells, in which CoQ synthesis is normal. However, inhibition of CoQ synthesis by 4-carboxybenzaldehyde (4-CBA), or inhibition of FSP1 by iFSP1, blunted the protective effect of cSTARD7. Based on all these results, they hypothesized that cSTARD7 promotes the transport of CoQ from mitochondria to the plasma membrane, which, together with the enzymatic activity of FSP1, inhibits ferroptosis. Consistent with this hypothesis, overexpression of mSTARD7 in *STARD7*$^{-/-}$ cells only restored CoQ in mitochondria but not in the plasma membrane, whereas overexpression of cSTARD7 restored plasma membrane levels of CoQ only in wild-type cells but not in *STARD7*$^{-/-}$ cells. These data collectively showed that mSTARD7 is required for CoQ synthesis and that cSTARD7 is required for CoQ transport from mitochondria to the plasma membrane (Fig. 1). Direct in vitro binding of STARD7 to CoQ4 lent further support to this hypothesis.

Together, the findings by Deshwal et al. unveiled a function for PARL-mediated STARD7 processing in CoQ synthesis (which is regulated by mSTARD7) and transport from mitochondria to the plasma membrane (which is regulated by cSTARD7), which cohesively enables protection against ferroptosis. This study also raises a series of important questions for future investigation: how does mSTARD7 regulate CoQ synthesis? How does CoQ cross the mitochondrial membrane to reach its cytosolic side? Beyond random diffusion, is there a mechanism that ensures specific and effective transport of CoQ to the plasma membrane by cSTARD7? Is mitochondria to plasma membrane transport of CoQ regulated in response to specific biological cues? This last question is particularly interesting and might be highly relevant biologically. For example, Deshwal et al. noticed that cSTARD7 adversely affected cell growth in galactose-containing culture medium but not in glucose-containing medium, which suggests that CoQ distribution by cSTARD7 is important for balancing ferroptosis protection (which occurs at the plasma membrane) and oxidative phosphorylation (which occurs in mitochondria). More broadly, mitochondrial energetic metabolism has been demonstrated to be a driving force of ferroptosis[10] and correspondently, there is an anti-ferroptotic mechanism that functions inside of mitochondria and is mediated by mitochondrial CoQ and related enzyme DHODH[11]. These findings, together with that of Deshwal et al., are beginning to unveil a sophisticated and concerted role of mitochondria in the regulation of ferroptosis.

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Competing interests

D.L. is an inventor of a patent relevant to autophagy. X.J. is an inventor of patents relevant to cell death and autophagy. He is also a consultant and equity holder of Exarta Therapeutics and Lime Therapeutics.