

SPOTLIGHT

More gas, fewer brakes: Mitochondria withhold CoQ at the cost of ferroptosis defense

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Coenzyme Q (CoQ or ubiquinone) is an essential cofactor for mitochondrial energy production and a vital radical-trapping antioxidant that maintains membrane integrity. Additionally, CoQ shares an early biosynthetic pathway with cholesterol biosynthesis. In this issue, Ndoci et al. (<https://doi.org/10.1083/jcb.202507174>) reveal a regulatory system that preserves mitochondrial CoQ levels when the mevalonate pathway is impaired, though this prioritization leaves cells vulnerable to oxidative stress.

Coenzyme Q (CoQ) is a highly hydrophobic lipid molecule, consisting of a benzoquinone ring and an isoprenoid tail. The hydrocarbon chain ensures lipophilicity, whereas the quinone structure confers two major biological functions. It acts as an electron carrier in the mitochondrial respiratory chain and, in its reduced ubiquinol form, defends against cellular membrane oxidation by trapping phospholipid radicals. This antioxidant activity has drawn significant attention in the context of ferroptosis, a form of regulated cell death triggered by membrane lipid peroxidation (1). This lipid radical-trapping activity is powered by FSP1, a flavoprotein that promotes an FAD-dependent reduction of ubiquinone to ubiquinol using NAD(P)H as an electron donor (2, 3, 4). Alongside the canonical GPX4 pathway, the FSP1-CoQ axis constitutes the secondary line of defense against lethal membrane lipid peroxidation. Given that CoQ is predominantly synthesized within mitochondria, a robust regulatory machinery must exist to control the flux of CoQ from mitochondria to the cytoplasm, ensuring that its dual roles are fulfilled.

Previously, Deshwal et al. demonstrated that STARD7 regulates mitochondrial CoQ synthesis and its distribution to mitochondrial and non-mitochondrial membranes (5) (Fig. 1). STARD7 exists in two distinct forms, cytosolic (cyto-STARD7) and mitochondrial

(mito-STARD7). The cleavage activity of the mitochondrial rhomboid protease PARL is required to process and generate cyto-STARD7 (6). Cyto-STARD7 overexpression increases extramitochondrial CoQ levels, thereby conferring cellular resistance to ferroptosis induced by GPX4 inhibition. However, this accumulation occurs at the expense of the mitochondrial CoQ pool, which limits oxidative phosphorylation and restricts respiratory cell growth (5).

Notably, CoQ biosynthesis shares key upstream steps with cholesterol production. Isopentenyl pyrophosphate (IPP), a central metabolite of the mevalonate pathway, is utilized to build the isoprenoid tail of CoQ. As a result of this metabolic intersection, intracellular CoQ distribution may be regulated in response to fluctuations in cholesterol biosynthesis.

In this issue of the *Journal of Cell Biology*, Ndoci et al. performed a CRISPR-knockout (KO) screen in a cell model overexpressing cyto-STARD7 (7). Under these conditions, cells acquire resistance to ferroptosis induced by GPX4 inhibition, driven by an enhanced activity of the FSP1-CoQ axis (5). This screen identified genes whose loss resensitizes cyto-STARD7 cells to GPX4 inhibition; such genes are likely to regulate CoQ distribution alongside STARD7. To assess distinct

genetic dependencies for preventing ferroptosis, the authors modeled acute and chronic ferroptotic stress by varying the concentration and duration of treatment with the GPX4 inhibitor RSL3. The essentiality of FSP1 in both conditions underscores that the cellular defense mechanism relies heavily on the FSP1-CoQ axis in the absence of GPX4.

A top hit detected in both screens was SREBP cleavage-activating protein (SCAP). SCAP senses cholesterol depletion in the ER and, in response to low cholesterol levels, chaperones the transcription factor SREBP to the Golgi apparatus. There, SREBP is cleaved, subsequently translocating to the nucleus, and upregulates cholesterol synthesis genes to restore cellular cholesterol levels. Moreover, SREBP target genes are transcriptionally upregulated, and cholesterol ester levels are increased in cyto-STARD7 cells compared with their control cells, suggesting a metabolic dependency on cholesterol synthesis. Either genetic KO of SCAP or pharmacological inhibition of the SCAP-SREBP complex or the early-stage mevalonate pathway suppressed cholesterol synthesis, thereby enhancing sensitivity to GPX4-inhibition-triggered ferroptosis. Counterintuitively, total CoQ levels remained unaffected by this downregulation of cholesterol synthesis. Furthermore, GPX4 protein expression levels are unchanged by

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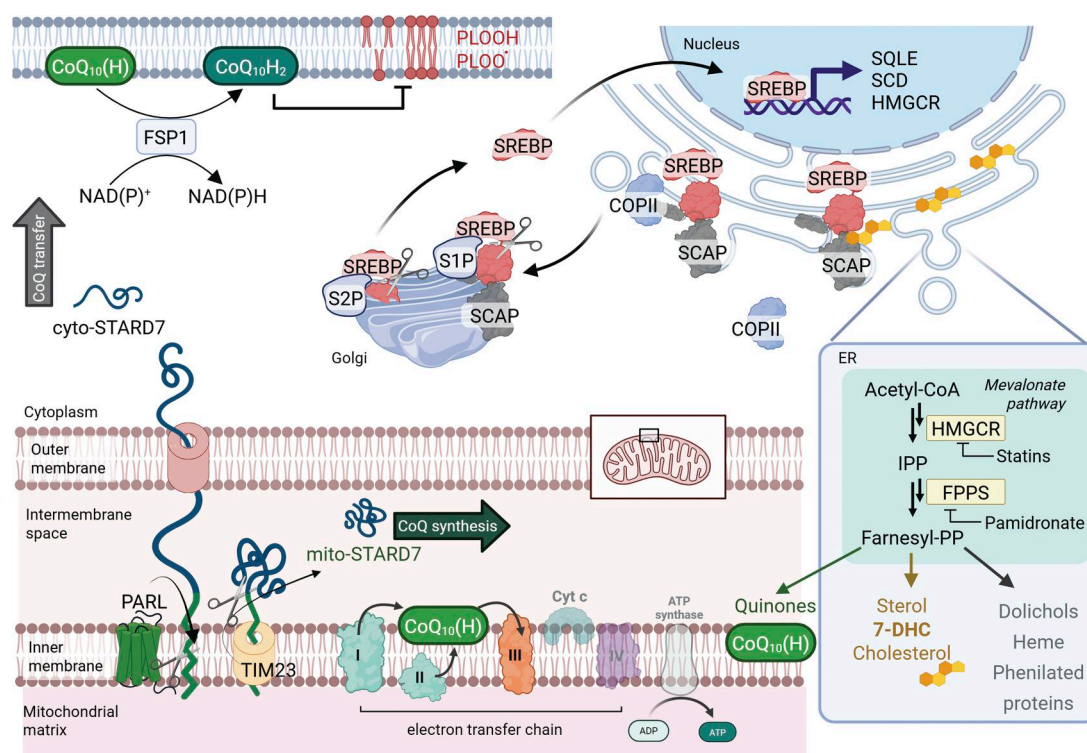


Figure 1. Dual roles of CoQ and the regulation of its biosynthesis and distribution. CoQ is produced within mitochondria, where it transfers electrons to support respiratory energy production in the inner mitochondrial membrane. Conversely, CoQ is moved to extramitochondrial membranes to scavenge lipid radicals in an FSP1- and NAD(P)H-dependent manner. The mevalonate pathway produces the isoprenoid precursors of CoQ, and the SREBP-SCAP axis functions as the main transcriptional regulator of this pathway. Mitochondrial and cytoplasmic STARD7 isoforms are responsible for CoQ trafficking, and these isoforms are regulated after translation by the mitochondrial proteases PARL and TIM23. CoQ10 is shown as the primary form of CoQ in humans. CoQ10(H), ubiquinone; CoQH2, ubiquinol; PLOO, phospholipid peroxy radical; COP II, coat protein complex II; S1P, site-1 protease; S2P, site-2 protease.

the metabolic stress caused by pharmacological SCAP inhibition.

Building on their previous work, the authors sought to explain this twist by measuring CoQ levels in isolated mitochondria and other cellular fractions (5). Their subcellular fractionation experiments revealed that the extramitochondrial fraction showed a significant decrease in CoQ levels upon SCAP inhibition, SCAP KO, or mevalonate pathway inhibition compared with controls, whereas mitochondrial CoQ levels remained unchanged under these conditions. These observations indicate that cells retain CoQ within mitochondria when cholesterol synthesis is compromised.

Since the final assembly and maturation steps of CoQ take place within mitochondria, the authors investigated how CoQ export from this organelle is regulated. As well established in the literature, the isoprenoid precursor IPP—generated in the ER by the mevalonate pathway—either enters mitochondria or is utilized for cholesterol synthesis. Therefore, IPP abundance might determine the extramitochondrial CoQ

availability. Because of the rapid turnover of IPP, they employed pamidronate, a pharmacological inhibitor of IPP downstream metabolism—an experimental approach to IPP detection/quantification, and further metabolic processes after IPP generation. As a result, IPP is significantly accumulated in cyto-STARD7 cells. This observation suggests that extramitochondrial CoQ availability depends on activation of the mevalonate pathway. This model is supported by two key findings: (1) SREBP target genes are highly upregulated in cyto-STARD7 cells, and (2) mitochondrial CoQ levels remain unchanged when the mevalonate pathway is suppressed. This indicates that mitochondria actively export excess CoQ to maintain steady-state mitochondrial levels when synthesis is elevated by abundant IPP. In summary, this study reveals that CoQ is prioritized for mitochondrial metabolism during cholesterol biosynthetic stress, such as SREBP transactivation inhibition or mevalonate pathway inhibition. Their elaborate techniques for measuring CoQ and related metabolites across

subcellular fractions, alongside their careful validation of ferroptosis, including the interplay between GPX4 and the FSP1-CoQ axis, provide strong warrants for these findings. While the authors clearly demonstrated altered CoQ distribution upon downregulation of the mevalonate pathway, future work will be needed to detail the precise mechanisms of CoQ export regulation when the pathway is upregulated—for instance, in an SREBP-overexpressing model, including IPP uptake and the specific roles of cytoplasmic and mitochondrial STARD7 isoforms. Given that cholesterol biosynthesis intermediates like squalene and 7-dehydrocholesterol also exhibit phospholipid radical-trapping activity (8, 9), this work opens an exciting new therapeutic window in cancer biology and ferroptosis, specifically by targeting the intersections of energy production, lipid synthesis, and antioxidant defense.

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