CELL BIOLOGY

Organelles share the load

Peroxisome–mitochondria contact sites manage mitochondrial oxidative stress

Marc Fransen

Eukaryotic cells contain organelles that carry out specialized functions essential for organismal health. In mammals, mitochondria primarily generate energy, while peroxisomes—named for their role in metabolizing the reactive oxygen species (ROS) hydrogen peroxide (H_2O_2)—help maintain redox balance (*1*). Both organelles also contribute to lipid metabolism and intracellular signaling through distinct yet complementary mechanisms (*2,3*). Their functions and stress responses depend on sustained interorganellar communication, which typically occurs at membrane contact sites (MCSs)—regions where organelle membranes are closely apposed and stabilized by molecular tethers (*4*). On page x of this issue, DiGiovanni *et al*. (*5*) report the discovery of a mammalian peroxisome–mitochondria tethering complex that dynamically responds to mitochondrial oxidative stress—an imbalance where ROS production exceeds antioxidant defenses—and enables the transfer of ROS from mitochondria to peroxisomes. These findings deepen understanding of the role of MCSs in cell biology and ROS regulation.

The term "ROS" refers to a diverse range of oxidant molecules with distinct properties and roles, ranging from cellular signaling to causing damage (*6*). Peroxisomes primarily metabolize H_2O_2 (*1*), whereas mitochondria generate both superoxide and H_2O_2, mainly through redox reactions in the electron transport chain, where molecular oxygen is reduced to superoxide and then converted to H_2O_2 by superoxide dismutases (*7*). Superoxide can disrupt mitochondrial iron-sulfur clusters, releasing ferrous ions that react with H_2O_2 to generate highly toxic hydroxyl radicals (*8*), so efficient H_2O_2 removal is essential to minimize downstream damage. If not properly controlled, this reaction can lead to oxidative damage to proteins, lipids, and DNA, contributing to a broad spectrum of oxidative stress-related conditions, including cancer, as well as neurodegenerative, cardiovascular, inflammatory diseases.

Accumulating evidence has revealed a close and complex relationship between peroxisomes and mitochondria (*1,2*). These organelles share key regulatory proteins involved in division, motility, antiviral signaling, and anti-apoptotic functions (*9*). Their abundance is controlled by overlapping transcriptional programs, highlighting their coordinated roles in essential metabolic and signaling networks (*1*). Peroxisomal dysfunction is frequently accompanied by mitochondrial impairment and oxidative stress, as observed in animal models of peroxisome biogenesis disorders (*10-12*). A prominent example is the group of Zellweger spectrum disorders, which are characterized by hypotonia, seizures, craniofacial abnormalities, developmental delays, and—in severe cases—early infant death (*2*). However, the underlying molecular mechanisms governing this crosstalk between peroxisome function and mitochondrial oxidative stress remain incompletely understood.

DiGiovanni *et al.* identified a previously unrecognized contact site between peroxisomes and mitochondria in cultured cell lines derived from humans and African green monkeys. This contact is mediated by acyl-CoA-binding domain-containing protein 5 (ACBD5), a peroxisomal membrane protein, and protein tyrosine phosphatase-interacting protein 51 (PTPIP51), an outer mitochondrial membrane protein also known as regulator of microtubule dynamics protein 3 (RMD3). The number of these interorganelle contacts increased significantly in response to mitochondrial ROS, induced by rotenone treatment or by culturing cells in media containing galactose or palmitic acid. Under these physiologically relevant conditions of mitochondrial oxidative stress, catalase—a potent H_2O_2 scavenging enzyme (*13*)—was more efficiently targeted to peroxisomes. Notably, catalase decomposes H_2O_2 without consuming nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), ensuring that this detoxification pathway remains efficient regardless of the availability of this key reducing agent. Augmented targeting of catalase to peroxisomes was accompanied by an increase in oxidation of peroxisomal glutathione, a key intracellular antioxidant. This is indicative of an increase in the amount of ROS within the peroxisome. Notably, the glutathione oxidation response was significantly diminished in cells lacking ACBD5 or expressing mitochondria-targeted catalase. These findings indicate that effective ROS transfer to the peroxisomal lumen is directly contingent on mitochondrial ROS production and requires intact ACBD5–PTPIP51 contact sites.

The findings by DiGiovanni *et al.* demonstrate that ACBD5–PTPIP51-mediated contacts between peroxisomes and mitochondria enable the transfer of mitochondrial ROS to peroxisomes, thereby helping mitochondria maintain a healthy balance between harmful oxidants and protective antioxidants (see the figure). This mechanism highlights the protective role of these contacts in mitigating oxidative stress and preserving mitochondrial function. The observed increase in peroxisomal redox capacity in response to elevated mitochondrial ROS further indicates that peroxisomes act as reducing sinks for mitochondrial ROS. Notably, the findings suggest that mitochondrial dysfunction in peroxisomal disorders may partly result from impaired ROS transfer due to disrupted organelle contact sites. Moreover, the increased number of these contacts in response to mitochondrial oxidative stress provides a mechanistic insight into how peroxisomes actively support mitochondrial health, expanding understanding of the physiological importance of MCSs and interorganelle communication.

Collectively, DiGiovanni *et al.* uncover a multi-organelle layer of mitochondrial antioxidant defense, thus positioning mitochondria–peroxisome contact sites as active participants in redox regulation. This discovery not only broadens the functional repertoire of MCSs but also introduces a conceptually compelling mechanism—ROS efflux from mitochondria to peroxisomes—that may help safeguard mitochondrial fitness. Given the central role of mitochondria in cellular and organismal health, the limited understanding of extrinsic mitochondrial antioxidant defenses, and the contribution of impaired organelle communication to age-related diseases—including neurodegenerative diseases like Alzheimer's and Parkinson's, as well as autoimmune and inflammatory disorders (*3*)—this work has far-reaching implications. However, it remains unclear to what extent the ROS-buffering function observed at peroxisome–mitochondria contacts applies to other peroxisome–organelle interfaces. Notably, ACBD5 also tethers peroxisomes to the endoplasmic reticulum via vesicle-associated membrane protein-associated protein B/C (VAPB) (*14,15*). Could similar ROS-regulating mechanisms be at play at these other contact sites? In parallel, the molecular mechanisms underlying the increase in peroxisomal localization of catalase and the number of ACBD5–PTPIP51 contacts in response to mitochondrial oxidative stress remain to be elucidated. It will also be important to establish whether these responses are influenced by cell type or physiological context, and to understand how redox regulation is coordinated amid peroxisomal oxidative stress. Ultimately, targeting ACBD5-PTPIP51 interactions could offer a therapeutic strategy to modulate mitochondrial ROS levels, with broad relevance for oxidative stress-related disorders.

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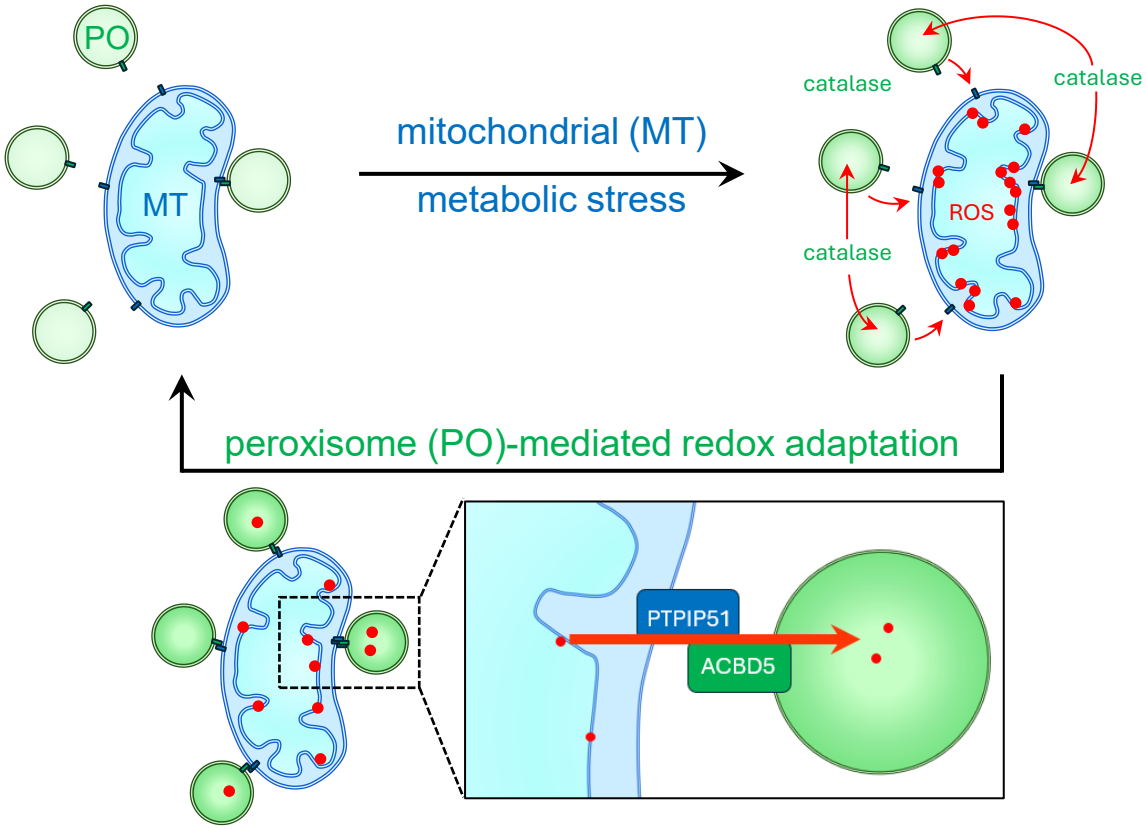
Department of Cellular and Molecular Medicine, Katholieke Universiteit Leuven, Leuven, Belgium. Email: marc.fransen@kuleuven.be

Peroxisome-mitochondria contact sites moonlight as oxidative stress managers – Organelles depend on dynamic membrane contacts to regulate a variety of cellular activities. A recently identified peroxisome (PO)-mitochondria (MT) tethering complex, composed of ACBD5 and PTPIP51, promotes these contacts under conditions that mimic physiological mitochondrial metabolic stress and ROS production. These conditions also enhance the import of catalase, a key antioxidant enzyme required for redox regulation, into peroxisomes. At the same time, the ACBD5-PTPIP51 tether facilitates the transfer of ROS from mitochondria to peroxisomes, helping to alleviate mitochondrial oxidative stress.


PO
MT
mitochondrial (MT)
metabolic stress
catalase
catalase
catalase
ROS
peroxisome (PO)-mediated redox adaptation
PTPIP51
ACBD5