ROMO1 links oxidative stress to mitochondrial integrity

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Abstract

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Oxidative stress is a state of redox imbalance in various diseases caused by increased reactive oxygen species (ROS) (Bansal et al. 2014). ROS are metabolic products which originate from different cells but are best associated with mitochondrial metabolism (Alfadda and Sallam 2012). In normal conditions, the final oxygen electron receptor reduces down to water in the mitochondria, however, under pathological conditions, the electrons leak out of the electron transport chain system and generates ROS (Turrens 2003). During times of environmental stress, these ROS levels can increase dramatically. While it is known that lower concentrations of ROS have effects through regulation of cell signaling cascades like redox signaling from the organelle to the rest of the cell, prolonged exposure of increased ROS concentrations may lead to injury to proteins, lipids, and nucleic acids (Brieger et al. 2012; Chung et al. 2006). This augmented ROS production then contributes to mitochondrial damage in a range of pathologies (Chung et al. 2006). Mitochondrial dysfunction results in oxidative stress and inflammatory response, underlying factors in a variety of diseases including acute lung injury, pulmonary fibrosis, neurodegenerative diseases, diabetes, cardiovascular diseases, and cancer (Bandyopadhyay et al. 2013; Bansal et al. 2014; Namsolleck and Unger 2014).

In addition to the well-established role of the mitochondria in energy metabolism, regulation of cell death has recently emerged as a second major function of these organelles. This seems to be intimately linked to the role of mitochondria as the major intracellular source of ROS, which are mainly generated at complex I and III of the respiratory chain (Cogliati et al. 2013). Excessive ROS production can lead to oxidation of macromolecules and has been implicated in mtDNA mutations, ageing, and cell death (Semenzato and Scorrano 2014). Although mitochondrial dysfunction can cause ATP depletion and necrosis, these organelles are also involved in the regulation of apoptotic cell death by mechanisms which have been conserved through evolution. Thus, many lethal agents target the mitochondria and cause release of cytochrome c and other pro-apoptotic proteins, which can trigger caspase activation and apoptosis (Semenzato and Scorrano 2014).

The dynamics of mitochondria undergoing fusion and fragmentation govern many mitochondrial functions, including the regulation of cell survival. Although the machinery that catalyzes fusion and fragmentation has been well described, less is known about the signaling components that regulate mitochondrial shape and fragmentation. Recently, mitochondrial-shaping proteins that catalyze the opposing processes of membrane fusion and fission have been identified. One noteworthy protein is ROMO1, a mitochondrial membrane protein which is known to be associated with cancer growth (Yu et al. 2014). ROMO1 also has been shown to affect cells through oxidative stress-induced proliferation, apoptosis, and senescence (Na et al. 2008; Shin et al. 2013; Chung et al. 2008). In the January 2014 issue of *Science Signaling*, Norton et al. (2014) discovered the impact of the novel protein ROMO1 (ROS modulator protein 1) on mitochondrial shape by using elegant study high-content screening technology and demonstrated that mitochondrial remodeling

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Fig. 1 The diagram is a representation of how ROMO1 suppression leads to cleavage of OPA1 due to an imbalance of OPA1 isoforms, thus preventing OPA1 oligomerization and augmenting cristae remodeling

that allows the release of cytochrome c (Cyt C). This reduced OPA1 oligomerization increases the cell sensitivity toward apoptotic insults

in the cristae and mitochondrial fusion is dependent on optic atrophy 1 (OPA1), a guanosine triphosphatase (GTPase) (Chung et al. 2006) (Fig. 1).

The study showed that oxidative stress promoted the formation of high-molecular weight ROMO1 complexes and that knockdown of ROMO1 promoted mitochondrial fission (Ratnaparkhi 2013). ROMO1 was essential for the oligomerization of the inner membrane GTPase OPA1, which is required to maintain the integrity of cristae junctions. Together, data identifies ROMO1 as a critical molecular switch that couples metabolic stress and mitochondrial morphology, linking mitochondrial fusion to cell survival (Ratnaparkhi 2013). Further Norton et al. revealed that ROMO1 is a redox-sensitive factor that forms inactive, high molecular weight complexes in response to oxidative stress and in its reduced, monomeric form drives mitochondrial fusion (Norton et al. 2014).

The study discovered that ROMO1 is required for the integrity of mitochondrial cristae junctions. From the analysis of the inner mitochondria, Norton et al. revealed that ROMO1 suppressed cells had mitochondria that displayed fewer or no cristae. Western blot analysis indicated that the abundance of mitochondrial sub compartment marker proteins was unchanged in ROMO1 suppressed cells, suggesting that

ROMO1 abundance does not affect mitochondrial mass or the abundance of outer membrane remodeling machinery (Norton et al. 2014).

Furthermore, to identify regulators of mitochondrial shape and morphology, Norton et al. (2014) performed genome-wide RNA interference image screening and revealed that ROMO1 as a novel regulator of mitochondrial fusion (Ratnaparkhi 2013). Their results show that cells expressing a ROMO1 construct at only the C-terminus which shows fragmentation, suggestive of a dominant negative effect of ROMO1 at the C-terminally tagged end. In addition, mitochondrial cells with suppressed ROMO1 had a fusion rate that was 50 % lower than the control cells. Thus Norton et al. revealed that ROMO1 is necessary for mitochondrial fusion. ROMO1 is also required for balance in OPA1 isoform abundance, and because ROMO1 localizes to the inner mitochondrial membrane and its silencing promotes fragmentation, authors explored the effect of loss of ROMO1 on OPA1, the inner membrane fusion guanosine triphosphatase (GTPase) that promotes cristae junction integrity and regulates mitochondrial fusion process (Scorrano 2013). Norton et al. revealed that long and short isoforms of OPA1 are required for mitochondrial fusion. However, the molecular explanation for this has been unclear. Authors show that loss of ROMO1

increases ROS and that ROMO1 itself forms disulfide bridges and incorporates into higher-molecular weight species in response to oxidative stress, which are counteracted by the glutathione system.

Mitochondrial ROS are a key element in the pathogenesis of a wide variety of cardiovascular diseases and disorders (Namsolleck and Unger 2014). These studies demonstrate, for the first time, that the protective effects of ROMO1 in the setting of oxidative stress are associated with integrity of mitochondrial cristae and shape (Grivennikova and Vinogradov 2013).

Norton et al. showed that ROMO1 regulates cristae junction integrity and the suppression of ROMO1 subdues oligomerization of OPA1, changes cristae morphology, and becomes more susceptible to cell death. Norton et al. data recognized this ROMO1 as a vital molecular key that connects metabolic stress and mitochondrial shape, linking mitochondrial fusion to cell survival. Their data also suggest that ROMO1 regulates cristae junction dynamics via enhancing OPA1 oligomerization. Since metabolic oxidative stress plays a critical role in the pathogenesis of many other diseases, the role of ROMO1 in this model will offer clues to its role in other oxidative stress-related diseases (Bansal et al. 2014).

Increased ROMO1 and OPA1 levels have been found in various types of human tumors (Lee et al. 2014). Hence, we agree with Norton et al. that it is fitting to focus on pursuing ROMO1 as this pathway could reveal potential treatments to eliminate the proliferation of cancer cells and consider the validation of the relationship between the protective effects of ROMO1 and OPA1 oligomerization which may open new avenues of clinical, anti-inflammatory therapeutic interventions in settings of oxidative stress (Semenzato and Scorrano 2014). However, the use of ROMO1 as a potential therapeutic target along with the existing therapies will require a better understanding of the mechanism of action of ROMO1. OPA1 cleavage inhibitors or ROMO1 inducers will provide novel candidates to ameliorate mitochondrial-mediated ROS diseases and offer new therapeutic strategies and drugs to resolve oxidative stress diseases in large scale (Bansal et al. 2014).

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