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Review article

Mitochondrial quality control in the myocardium: Cooperation between protein degradation and mitophagy

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ABSTRACT

Mitochondria are critical for cardiomyocyte survival and maintenance of normal cardiac function. However, changes in the extra- or intracellular environments during stress can cause excessive damage to mitochondria and lead to activation of cell death. In fact, there is evidence that mitochondrial dysfunction is an important contributor to both development of heart failure and the aging process. To counteract the adverse effects resulting from mitochondrial damage, cells have evolved mitochondrial quality control pathways that act at both the protein and organelle levels. Quality control of proteins in the outer mitochondrial membrane is monitored by the ubiquitin–protease system, whereas chaperones and proteases act in the various compartments of the mitochondria. When the damage is too excessive and the degradation machinery is overwhelmed, the entire mitochondrion is eliminated by an autophagosome. Together, these pathways ensure that myocytes maintain a functional network of mitochondria which provides ATP for contraction. Unfortunately, chronic stress and aging can negatively affect proteins that are involved in the mitochondrial quality control pathways which leads to accumulation of dysfunctional mitochondria and loss of myocytes. In this review, we provide an overview of the proteins and pathways that regulate mitochondrial quality control in the cell with an emphasis on pathways involved in maintaining protein and organelle homeostasis. We also delve into the effects of reduced mitochondrial quality control on aging and cardiovascular disease.

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1. Introduction

Mitochondria are critical for myocyte function. The contracting cardiac myocyte requires a lot of energy in the form of ATP which is provided by mitochondria via oxidative phosphorylation. To ensure a continuous supply of ATP, the myocytes are densely packed with mitochondria. Unfortunately, reactive oxygen species (ROS) are byproducts of this process and are generated primarily by Complexes I and III of the electron transport chain during oxidative phosphorylation. The myocytes have developed a strong ROS-neutralizing defense which can deactivate the excess ROS that is produced. However, when the levels of ROS overwhelm the detoxifying systems, these species, such as hydrogen peroxide and superoxide anion, can damage cellular components as well as produce misfolded mitochondrial proteins [1]. Accumulation of damaged proteins can impair mitochondrial function and lead to activation of cell death. Consequently, the removal of damaged mitochondria is important for cell survival, particularly in high-energy post-mitotic tissues such as the heart. Therefore, it is not surprising that cells have developed mitochondrial quality control pathways that act at both the protein and organelle levels to counteract the adverse effects resulting from protein/organelle damage. These pathways ensure that the cells can maintain a functional network of mitochondria to prevent unnecessary cell death. There is evidence that mitochondrial dysfunction is an important contributor to both development of heart failure and the aging process, and studies indicate that this is due in part to reduced mitochondrial quality control.

Mitochondria are composed of four different compartments (the outer mitochondrial membrane, intermembrane space, inner mitochondrial membrane, and mitochondrial matrix) and therefore contain a number of different proteins that are involved in mitochondrial protein quality control (Fig. 1 and Table 1). Quality control (QC) is monitored by chaperones and proteases in the various compartments of this organelle. For instance, mitochondrial chaperones, such as HSP60 and HSP70, contribute to mitochondrial QC by mediating the refolding of misfolded proteins back to their native structures [2,3]. The methionine sulfide reductase system, consisting of MsrA and MsrB, reduces oxidized methionine back to methionine [4]. However, accumulation of unfolded or damaged mitochondrial proteins above a certain threshold overwhelms the mitochondrial refolding and repair capacity and thus requires activation of mitochondrial protein degradation machinery to remove damaged proteins [5]. Furthermore, when the degradation machinery is unable to remove damaged components, it leads to mitochondrial dysfunction and subsequent activation of autophagy [6]. This pathway is responsible for eliminating the entire organelle where the dysfunctional mitochondrion is sequestered inside an autophagosome and subsequently delivered to a lysosome for degradation.

Studies indicate that the accumulation of dysfunctional mitochondria in diseased or aged tissues might, in part, be due to reduced mitochondrial quality control. Chronic stress and aging affect proteins that are involved in the mitochondrial quality control pathways. In this review, we provide an overview of the proteins and pathways that are involved in mitochondrial QC with an emphasis on pathways involved in maintaining protein and organelle homeostasis in cells. We also delve into the effects of reduced mitochondrial quality control on aging and cardiovascular disease.

2. Mitochondrial protein quality control

2.1. Outer mitochondrial membrane (OMM)

The ubiquitin protease degradation system (UPS), known for its role in the breakdown of cytosolic proteins, also contributes to degradation of mitochondrial proteins. These proteins are post-translationally modified by ubiquitination, extracted from the membrane, and delivered to the 26S proteasome, where they are finally degraded [5] (Fig. 1). A proteomics study analyzing ubiquitinated proteins in the mouse heart found that mitochondrial proteins were the majority of substrates for ubiquitination in the heart [7]. Remarkably, these proteins were from all four different mitochondrial compartments. In this case, these proteins are most likely retro-translocated from their compartment of

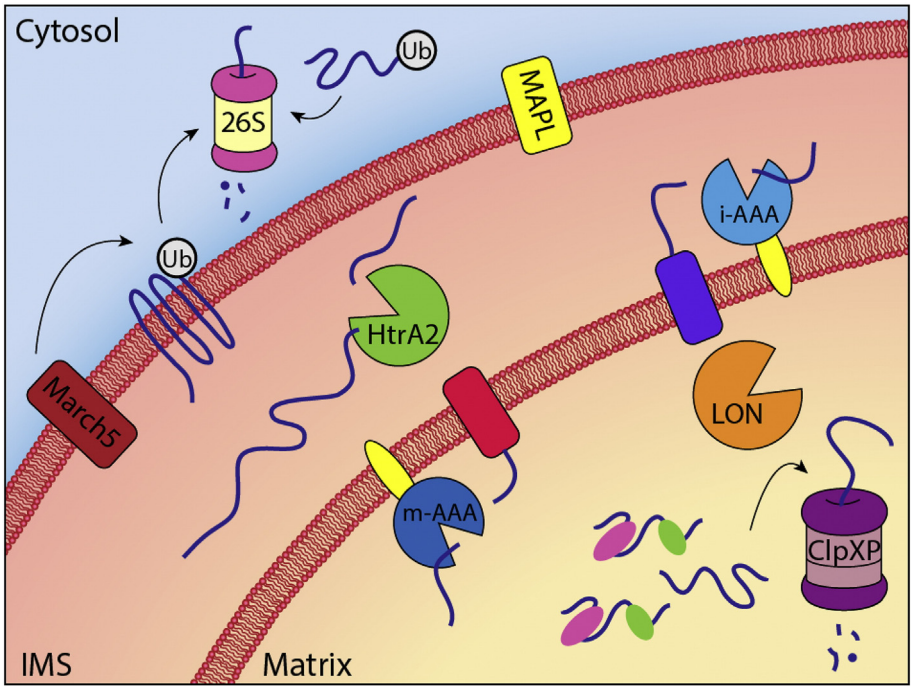

Fig. 1. Protein quality control in the mitochondrion. Outer mitochondrial membrane (OMM) E3 ubiquitin ligases such as March5 and MAPL tag proteins for degradation by the 26S proteasome, which is also responsible for the breakdown of the majority of ubiquitinated cytosolic proteins. Within the intermembrane space (IMS), HtrA2 is the chief protease in charge of protein degradation. Two ATPases Associated with diverse cellular Activity proteases, the matrix (m-) and the intermembrane (i-) AAA, identify misfolded polypeptides on their respective side of the IMM for degradation. Lon and ClpXP are the two most important QC proteases in the mitochondrial matrix. Lon is primarily responsible for the removal of oxidized proteins. ClpXP, composed of two ClpP subunits flanked by ClpX, plays a role in the unfolded protein response, degrading proteins unbound by chaperones (pink and green).