Cardiac Mitochondria

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Mitochondria are organelles responsible for energy production and various other functions in eukaryotes. In the heart, mitochondria are of pivotal importance due to cardiomyocytes' intrinsic high energy needs.

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1. Origin and Morphology of Mitochondria

It is widely accepted that mitochondria are derived from bacteria that, billions of years ago, lived inside eukaryotic cells[1]. The *endosymbiotic theory* states that such bacteria gave early eukaryotes the capability to perform oxidative phosphorylation. Thus, they became pivotal to the very existence of eukaryotes and finally were embedded in the eukaryotic cellular structure. Of the >1000 genes constituting the human mitochondrial genome, only 37 are encoded in the mitochondrial DNA, the majority of genes being encoded in the nuclear DNA[2].

The outer membrane is very similar to other cell membranes, with a 1:1 protein-to-lipid ratio; the most represented protein in the outer membrane is porin, an integral membrane protein facilitating inflow and outflow of small molecules.

They have a double-membraned organization, consisting of an outer membrane and an inner membrane delimiting the intermembrane space; infoldings of the inner membrane constitute the cristae, while the space delimited by the inner membrane is termed the matrix[3].

The inner membrane is home to the enzymatic machinery that performs oxidative phosphorylation. This machinery is composed of four protein complexes and ATP synthase. Specific to the mitochondrial inner membrane is the negatively charged phospholipid cardiolipin, a key component for the functioning of enzyme complexes[4].

The mitochondrial matrix contains mitochondrial DNA, ribosomes, RNAs, and enzymes for the oxidation of pyruvate and fatty acids. Inside the matrix, the Krebs cycle takes place.

The morphology and functioning of cardiac mitochondria vary based on the physiological milieu, stage of development, and disease. Moreover, heterogeneity in mitochondrial morphology and position inside the cardiomyocyte likely reflects the existence of different patterns of mitochondrial response to physiological and pathological stimuli[5].

2. Mitochondrial Networks in the Heart: Biogenesis, Mitophagy, and Mitochondrial Dynamics

The proper functioning of cardiomyocytes requires continuous harmonization of mitochondrial function. This is obtained via the adaptation of mitochondria to current energy needs, which require dynamic expansion and contraction of mitochondrial pools, development of new mitochondria, and removal of “old” organelles; these processes, known as fusion, fission, biogenesis, and mitophagy[6], respectively, are key to the genesis and dynamics of mitochondrial networks.

Mitochondrial fusion and fission allow mitochondria to exchange components and ensure a proper myocellular distribution of these organelles, building a complex network of interactions commonly referred to as mitochondrial dynamics [7].

Mitochondrial fusion consists of the merging of, respectively, the outer and inner mitochondrial membranes of different mitochondria. This process is mediated by specific proteins, including mitofusins 1 and 2 (MFN1 and MFN2) on the outer membrane, and optic atrophy 1 (OPA1) on the inner mitochondrial membrane and intermembrane space[8].

Mitochondrial fission allows for redistribution of mitochondria inside the cardiomyocyte. It requires interaction of a cytosolic protein, namely dynamin-related protein 1 (DRP1), with an outer membrane protein called mitochondrial fission 1 protein (FIS1)[8], in forming the mitochondrial fission complex.

Mitochondrial dynamics is the result of continuous balancing between fusion and fission processes. For example, disrupting the fusion machinery determines mitochondrial fragmentation, inevitably leading to apoptosis[9]. Other proposed roles for fusion and fission have been hypothesized in various mitochondrial processes, including mitochondrial DNA (mtDNA) deletion and bioenergetics, and in different cardiac diseases, including cardiomyopathies and heart failure [7].

Mitochondrial biogenesis is the process by which mitochondria grow up and multiply[7]. In muscle cells, including cardiomyocytes, the division of pre-existing mitochondria is triggered by physical stress and various chemical signals. The expansion of the cardiac mitochondrial pool is needed in order to maintain a production of ATP sufficient for cardiac contractility. Biogenesis occurs via a transcriptional cascade involving, among others, the activation of PPARγ coactivator 1α (PGC-1α) and a subsequent increase in nuclear respiratory factors (NRFs), which cause the expression of mitochondrial DNA and proteins. Notably, the activation of PGC-1α also causes an increase in cell respiration and production of ATP.

Mitophagy is an autophagy process by which mitochondria are degraded by lysosomes for preserving mitochondrial homeostasis[7]. Mitophagy can be considered a “quality check” process that prevents accumulation of dysfunctional mitochondria, an event that would lead to activation of inflammatory pathways and cell death[7]. Triggers of mitophagy in the heart comprise hypoxia and excessive ROS production (i.e., during reperfusion).

The dysregulation of mitochondrial dynamics and mitophagy found is associated with defective removal of damaged mitochondria and subsequent activation of inflammatory responses, paving the way to cardiomyocyte aging [18] and heart failure (HF) [19]. In particular, disruption of quality control mechanisms may allow a malfunctioning mitochondrion to propagate its defect to the cell-level, ultimately leading to ROS overproduction and apoptosis[10].

Antioxidant systems (superoxide dismutase, glutathione peroxidase, glutathione reductase, etc.) represent the first level of quality control, preventing molecular damage from happening inside mitochondria [11]. When antioxidant systems fail, repair processes (molecular chaperones, mtDNA repair complexes, reductase systems) take over to recover the molecule if possible. If a molecule is irreparably damaged, an intramitochondrial proteolytic system performs its clearance[10]. Mitochondrial biogenesis, mitophagy, and mitochondrial dynamics play an active role in this context, so that an imbalance between fission and fusion events, as well as increased mitophagy and reduced biogenesis, potentially lead to diffuse cell damage and death, activation of proinflammatory pathways and, at the organism-level, aging and HF[11].

3. Mitochondrial Bioenergetics and Ion Handling in the Heart

Production of reduced equivalents, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), is of utmost importance for appropriate mitochondrial functioning. Such products are obtained by metabolization of different substrates—mainly free fatty acids within the myocardium—converging on the Krebs cycle to fuel the oxidative phosphorylation process[12]. ROS, previously considered by-products of oxidative phosphorylation, are now being seen as important signaling molecules[13].

Another emerging feature of cardiac mitochondrial function is calcium handling [24,25]. In physiological conditions, intracellular calcium is stored in the sarcoplasmic reticulum, and calcium transients to the cytosol are sensed by nearby mitochondria, triggering a burst in oxidative phosphorylation.

The outer mitochondrial membrane shows high permeability to calcium, so that cytosol and intermembrane space calcium concentrations are virtually equal. Calcium enters the matrix via the mitochondrial calcium uniporter (MCU) [14] complex on the inner mitochondrial membrane, which shows adaptive response patterns to low-versus-high calcium concentrations; during diastole, the MCU does not import calcium due to low cytosol concentrations and subsequent blockage by MCU regulatory proteins. Instead, during systole, rising calcium concentrations trigger a conformational change of said proteins, and calcium import is allowed.

Mitochondrial calcium export, on the other hand, requires the functioning of the Li^+-permeable Na^+–Ca^{2+} exchanger (NCLX), a member of the Na^+–Ca^{2+} exchanger family of antiporters. NCLX may maintain a steady state in mitochondrial calcium content by exporting the same quantity of calcium imported by the MCU. MCU and NCLX functioning is regulated by different means, including phosphorylation and variations in the mitochondrial membrane potential.

In conditions of calcium overload, NCLX exporting capacity is overcome, and calcium content rapidly increases in the mitochondrial matrix. This triggers the aggregation and opening of the mitochondrial permeability transition pore (MPTP) on the inner mitochondrial membrane, causing mitochondrial content to be released into the cytoplasm. This leads to a staggering loss in mitochondrial membrane potential, rapid ATP deprivation, and finally cell death.

In order to investigate the specific role of MCU in mitochondrial calcium handling, an MCU knockout mouse model was first developed and showed altered calcium loading capacity but no specific cardiac alterations. The same finding was confirmed in a follow-up study. Nevertheless, subsequent investigations demonstrated that acute—but not chronic—deletion of MCU confers protection against cell death in ischemia/reperfusion injury (IRI) mouse models by reducing MPTP activation. Interestingly, MCU was also found to be essential for the fight-or-flight adrenergic response [15].

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