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Global Spotlights

Mitochondria and the heart

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Cardiac work demands a substantial amount of energy, stored in adenosine triphosphate (ATP), necessary for both contraction and relaxation. To meet these energy requirements, the heart is equipped with an efficient metabolic machinery. Mitochondria, the central organelle in maintaining cardiac function, primarily generate ATP through oxidative phosphorylation, involving redox reactions coupled with a chemiosmotic process across their membranes. Additionally, mitochondria play a role in regulating cell death and survival and modulating second messenger levels, such as calcium ions (Ca^{2+}) and reactive oxygen species (ROS).

Mitochondrial function

In the adult heart, 60%–90% of ATP production occurs through fatty acid oxidation in mitochondria, while 10%–40% is derived from pyruvate oxidation. Other substrates like amino acids and ketone bodies represent minor sources of energy. However, the contribution of different substrates can vary depending on substrate availability, energy demand, and hormonal action. This metabolic flexibility is influenced by the capacity of mitochondria in highly dynamic networks, striking a balance between fission and fusion processes. Mitochondrial fission is regulated by proteins such as mitochondrial fission 1 protein (Fis1), mitochondrial fission factor (MFF), and dynamin-related protein 1 (Drp1). Mitochondrial fusion is regulated by dynamin-related GTPases, namely mitofusins (Mfn1 and Mfn2), and optic atrophy protein 1 (OPA1). These processes also play a role in apoptosis, with activation of mitochondrial fission and inhibition of fusion.

As adult cardiomyocytes rarely divide, controlling mitochondrial content is crucial due to the oxidative damage mitochondria may endure. Mitophagy and mitochondrial biogenesis, opposing processes determining the number of mitochondria, are key regulators of mitochondrial turnover and quality. Damaged or senescent mitochondria divide into one healthy organelle that fuses with other healthy mitochondria, and one severely depolarized that is eliminated by autophagosomal engulfment (*Figure 1*). Consequently, new mitochondria are generated by biogenesis to replace degraded mitochondria. Imbalances

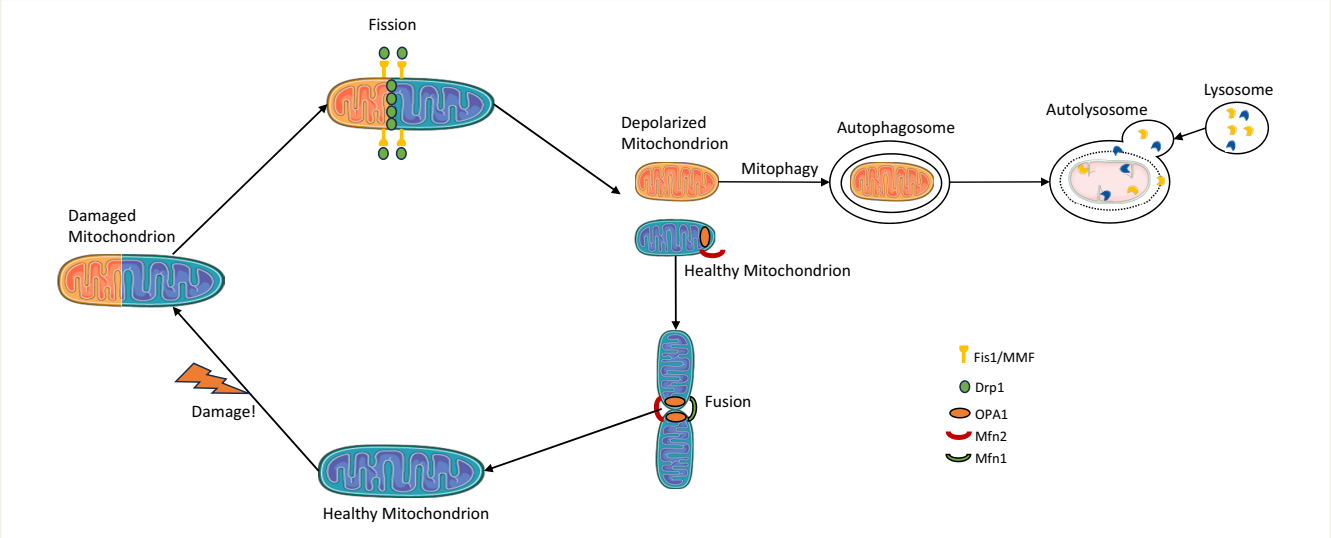

Figure 1 Illustration of mitochondrial fission, fusion and autophagy

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between mitochondrial fusion and fission lead to hyperelongated or hyperfragmented mitochondria. In pathological conditions, the accumulation of damaged mitochondria in the cytosol of cardiomyocytes or endothelial cells can trigger excessive inflammatory responses, leading to cell death and pathological tissue loss.

Mitochondria and cardiovascular disease

Considering this central role of mitochondria, it is not surprising that dysfunctional mitochondria have been reported in several cardiovascular diseases. For instance, heart failure is associated with disorders in substrate uptake and utilization by mitochondria, oxidative phosphorylation, and energy shuttling via mitochondrial phosphotransfer systems. Alteration of mitophagy is closely related to cardiomyopathy progression, frequently reported in dilated cardiomyopathy, hypertrophic cardiomyopathy, desmin-related cardiomyopathy, and restrictive cardiomyopathy. Mitophagy is also implicated in the pathogenesis of atherosclerosis, contributing to increased plaque formation and elevated ROS levels from damaged mitochondria across all cell types. In myocardial infarction and ischaemia–reperfusion injury, the occlusion of coronary arteries can lead to multi-component consequences, including mitochondrial Ca^{2+} overload and the opening of the mitochondrial permeability transition pore, causing myocardial cell death and injury.

Despite our extensive knowledge of mitochondrial mechanisms underlying the pathophysiology of cardiac diseases, treatment options remain limited. While pre-clinical tests for several antioxidants to prevent oxidative stress, apoptosis, and damages in oxidative phosphorylation exist, few clinical trials on these molecules have been carried out so far, with disappointing results except for coenzyme Q10, elamipretide, and vitamin C. This underscores the need for a deeper understanding of the molecular mechanisms behind mitochondrial processes, the pharmacodynamics and pharmacokinetics of molecules, and even the pathophysiology of some cardiovascular disorders for new drug discoveries.

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.