Mitophagy in health and disease

Mitochondria are cellular organelles specialized for energy production, and critically influence several features of cellular metabolism and physiology. Maintenance of a healthy mitochondrial pool is a prerequisite for cellular and tissue homeostasis. Compromised mitochondrial function results in the transformation of cellular powerhouses to “hotspots” of metabolic stress. Hence, it is not surprising that mitochondrial damage is associated with a broad spectrum of pathological conditions, including premature ageing, myopathies, cardiovascular, metabolic and neurodegenerative diseases among others.

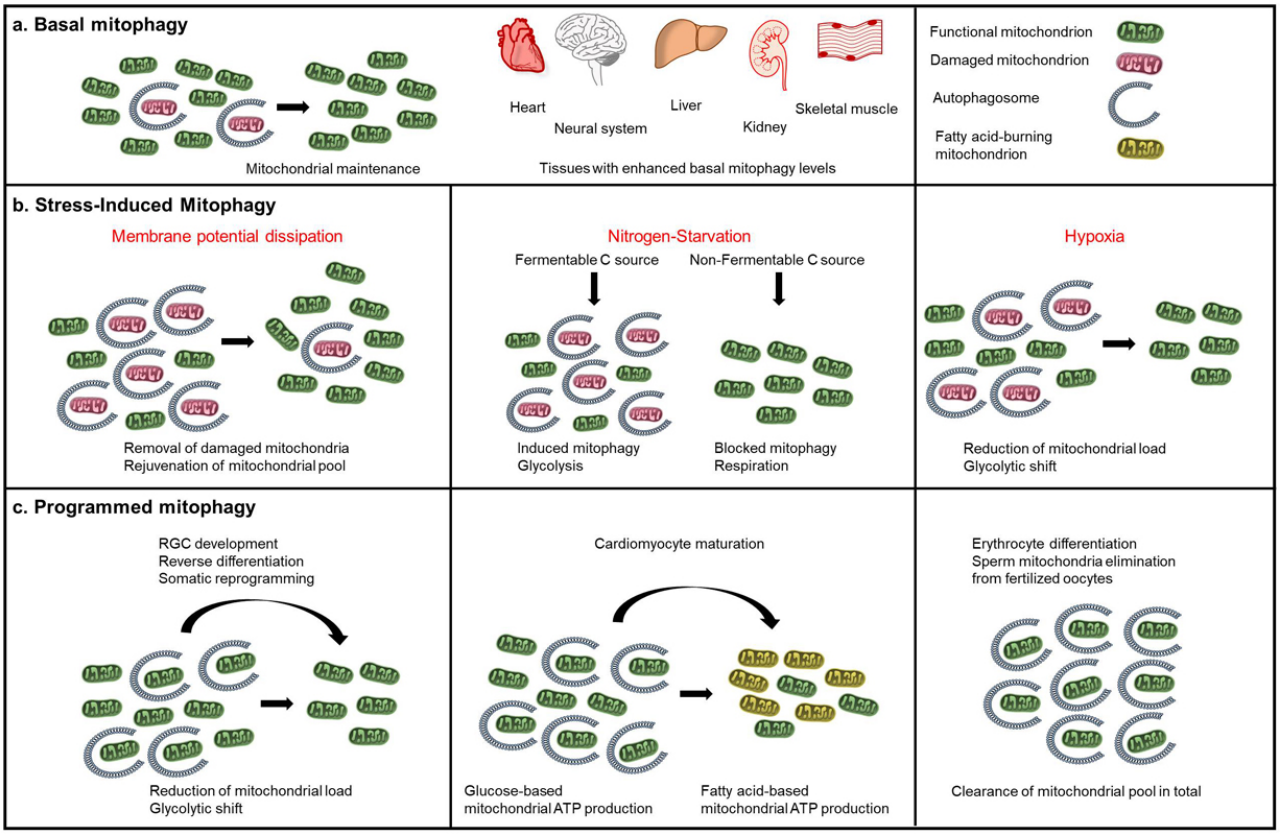

Fig. 1. Physiological roles of mitophagy. a. Basal mitophagy: Tissues of enhanced mitophagy levels including heart, neural system, liver, kidney, and skeletal muscle are depicted. b. Stress-induced mitophagy: Mitophagic effects during dissipation of mitochondrial membrane potential. c. Programmed mitophagy: Mitophagic effects during retinal ganglion cell development (RGC), reverse differentiation towards pluripotency during somatic reprogramming, cardiomyocyte maturation, erythrocyte differentiation and sperm mitochondria elimination are depicted.

Given that the consequences of defective mitochondrial function can be detrimental for cellular

survival, redundant quality control mechanisms have been evolved to restore and sustain energy metabolism. Although these homeostatic pathways may be sufficient to repair mitochondrial damage, uncontrolled and persistent defects trigger the removal of entire organelles through mitophagy. Failure to properly carry out mitophagy deregulates mitochondrial function and causes progressive accumulation of defective organelles leading to the deterioration of biological systems, often culminating in tissue collapse.

Several molecular mechanisms of mitophagy have been identified indicating that different stimuli can promote mitophagy through multiple signalling cascades, in distinct cellular contexts. The PINK1/Parkin pathway is the most well-studied molecular mechanism that regulates mitochondrial degradation upon stress. Moreover, several studies have documented the existence of PINK1- and Parkin-independent signalling cascades revealing multiple mitochondrial proteins (e.g. FUNDC1, BNIP3, NIX, PHB2) or lipids (e.g. cardiolipin) that serve as mitophagy receptors in response to environmental and/or developmental stimuli.

Depending on the physiological context mitophagy can be classified as basal, stress-induced and programmed. Recent studies in nematodes, flies and rodents showed that most types of cells experience basal levels of mitophagy as part of their constant mitochondrial maintenance. However, steady-state mitophagy levels vary between tissues and between different cell types within the same tissue (Fig. 1a). Stress-induced mitophagy facilitates maximum mitochondrial quality control upon stress and supports adjustment of cellular metabolism to the external challenge. Starvation, hypoxia, heat, oxidative and mitochondrial stress are well-studied conditions known to potently induce mitophagy (Fig. 1b). Programmed mitophagy is stimulated in several cell types as part of their developmental programs (Fig. 1c). Emerging findings shown that sperm-derived mitochondria are degraded through mitophagy upon oocyte fertilization in nematodes, flies and mice. Furthermore, mitophagy removes total mitochondrial content during erythrocytes differentiation. Metabolic rewiring and reformation of the entire mitochondrial population are mainly regulated by mitophagy during cardiomyocytes maturation, retinal ganglion cell (RGC) differentiation and macrophage polarization. Therefore, fine-tuning of mitophagy levels is critical to organismal development and viability.

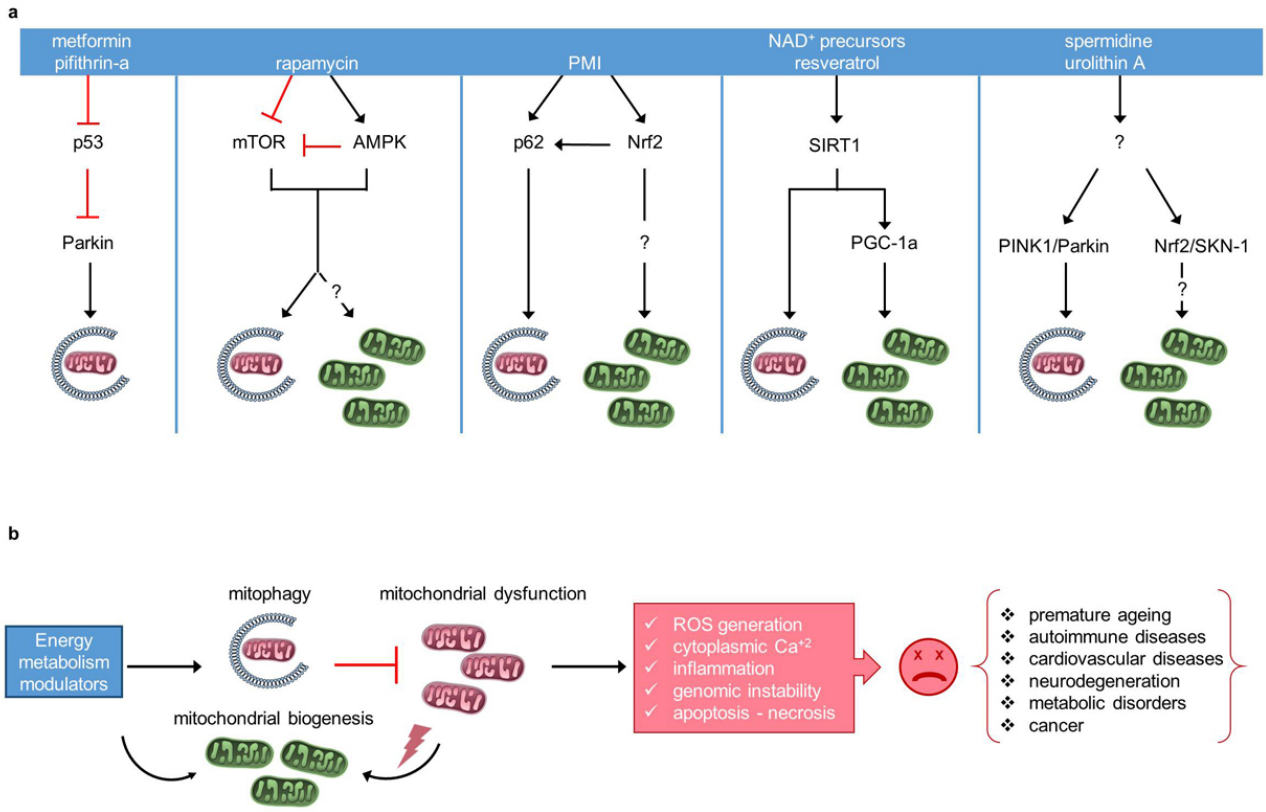

Fig. 2. Chemical modulators of energy metabolism. a. The molecular mechanisms and mitophagic/biogenic capacities of several energy modulators, such as metformin. b. Administration of chemical compounds, which modulate mitophagy and mitochondrial biogenesis, sustains energy metabolism leading subsequently to cellular and organismal survival.

Pharmacological screenings are taking place to identify novel chemical agents that may be used to manipulate and restore the efficient elimination of dysfunctional organelles. To this direction, several synthetic (e.g. NAD^+ precursor molecules, PMI, metformin, pifithrin-a, iron chelators) and natural chemical (e.g. antibiotics, resveratrol, urolothin A, spermidine) molecules have been identified to modulate mitophagy (Fig 2a). Identifying novel mitophagy modulators might establish novel therapeutic intervention strategies targeting a variety of mitochondrial-associated pathologies and provide critical insights with broad relevance to human health and quality of life (Fig. 2b).

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