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Mitophagy: Link to cancer development and therapy

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ABSTRACT

Mitophagy, the selective degradation of mitochondria via the autophagic pathway, is a vital mechanism of mitochondrial quality control in cells. Mitophagy is responsible for the removal of malfunctioning or damaged mitochondria, which is essential for normal cellular physiology and tissue development. Pathways involved in the regulation of mitophagy, tumorigenesis, and cell death are overlapping in many cases and may be triggered by common upstream signals, which converge at the mitochondria. The failure to properly modulate mitochondrial turnover in response to oncogenic stresses can either stimulate or suppress tumorigenesis. Thus, the analysis of crosstalk among the processes of mitophagy, cell death and tumorigenesis is important for the identification of targets responsible for the stimulation of cell death and selective elimination of cancer cells. In the present review, we analyze the mechanisms of mitophagy regulation, the pathways underlying the utilization of damaged mitochondria, and how intervention with mitophagy can affect tumor cell resistance to treatment.

Contents

1. Introduction

The control of mitochondrial quality is of substantial importance for the normal development of cells and tissues. Mitochondria, in addition to energy production in the form of ATP, participate in the regulation of Ca^{2+} homeostasis, fulfilling the role of safety devises against Ca^{2+} overload. Leakage of electrons from the respiratory chain of damaged mitochondria causes formation of the reactive oxygen and nitrogen species (RONS), contributing to oxidative stress. In addition, mitochondria are key organelles in initiation and execution of various forms of cell death. Malfunctioning mitochondria represents a danger for cells, since inadequate supply of

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ATP, or extensive production of ROS and NOS can be a cause of a number of abnormalities, such as neurodegenerative diseases, cancer, and autoimmune disorders. Thus, the removal of malfunctioning or damaged mitochondria is vital for the normal cellular physiology and tissue development. This review is devoted to analysis of the mitophagy process, the pathways underlying the removal of damaged mitochondria [1] or excessive mitochondria during starvation [2], and how intervention with mitophagy pathways might make tumor cells more susceptible to treatment and the induction of cell death.

2. The mechanisms of mitophagy regulation

Mitophagy, mitochondrial macroautophagy, is a process of selective degradation of mitochondria via autophagic pathway [3]. Autophagy is accompanied by formation of autophagosomes, double-membrane structures intended for the digestion and degradation of cellular proteins and organelles. Delivery of defective mitochondria into autophagosomes is regulated by various intracellular mechanisms. The most important of these mechanisms is regulated by LC3 (microtubule-associated protein light chain 3) family proteins, which includes LC3A, LC3B, LC3B2, LC3C proteins. Cytosolic LC3A forms a complex with phosphatidylethanolamine that results in formation of LC3B form, which directly associated with autophagosome membrane. Lipidated LC3 contributes to the closure of autophagosomes [4], and enables the docking of specific cargos and adaptor proteins such as p62 [5]. LC3 participation in autophagy is regulated by phosphorylation. It has been shown that mammalian sterile-20 kinases STK3 and STK4 phosphorylate LC3 at threonine 50 (Thr50). Loss of phosphorylation at this site blocked autophagy by impairing fusion of autophagosomes with lysosomes [6]. A recent study conducted in a mouse model of myocardial infarction showed that STK4 can block autophagy by directly phosphorylating Beclin1, which is integral for activation of the autophagy pathway [7]. The integration of LC3B into the autophagosome membrane can be inhibited by protein kinase A mediated phosphorylation of Ser15, whereas both metabolic (rapamycin) and pathological (MPP+) inducers of autophagy caused dephosphorylation of endogenous LC3 [8].

A breakthrough in autophagy investigation was a discovery of specific autophagy receptors that sequester cargo into forming autophagosomes (phagophores). A key role in the selectivity determines the LC3-interacting region (LIR) motif, which ensures the targeting of autophagy receptors to LC3 (or other ATG8 family proteins) anchored in the phagophore membrane [9]. Mitophagy receptors on the outer mitochondrial membrane (OMM) such as PINK/Parkin, AMBRA1, BNIP3, NIX, FUNDC bind to autophagosomes also via LIR fragments. Some of these receptors are translocated from the cytoplasm to mitochondria upon induction of mitophagy; others are constitutively attached to the OMM via the transmembrane domain and can bind LC3 directly.

3. Mechanisms of autophagy regulation

Currently the most studied pathway of mitophagy initiation involves serine-threonine kinase PINK1 (PTEN-induced putative kinase 1) and E3 ubiquitin ligase Parkin. This ligase is expressed in many organs and tissues such as brain, skeletal muscle, heart, and liver. Mutations in the gene encoding Parkin, PARK2, are known to cause a familial form of Parkinson's disease [10]. It is also involved in the regulation of mitochondrial morphology [1]. The pathway engaging PINK1 and Parkin leading to mitochondrial fragmentation is induced by mitochondrial membrane depolarization. The initiator of this process is PINK1 [11]. In healthy mitochondria PINK1 is imported through the OMM via the TOM complex, and partially through the inner mitochondrial membrane (IMM) via the TIM complex, so it then spans the IMM. The process of import into the IMM is associated with the cleavage of full-length PINK1 with formation of 60-kDa fragment. PINK1 is then cleaved by intramembrane protease PARL generating a 52-kDa cleavage product that is rapidly degraded by the proteasome [12]. It has been shown that the level of the 52-kDa processed form of PINK1 increases upon inhibition of the proteasome activity with the inhibitor MG-132. Mitochondrial depolarization leads to the accumulation of PINK1 on the OMM. Once localized at the mitochondria, PINK1 phosphorylates Parkin at Ser 65, homologous to the site where ubiquitin was phosphorylated, which activates Parkin by inducing dimerization and an active state. This allows for Parkin-mediated ubiquitination on other proteins resulting in autophagic destruction of the dysfunctional organelles (Fig. 1).

The details of the regulation of this process are still elusive and to some extent controversial. Thus, it has been shown that activated

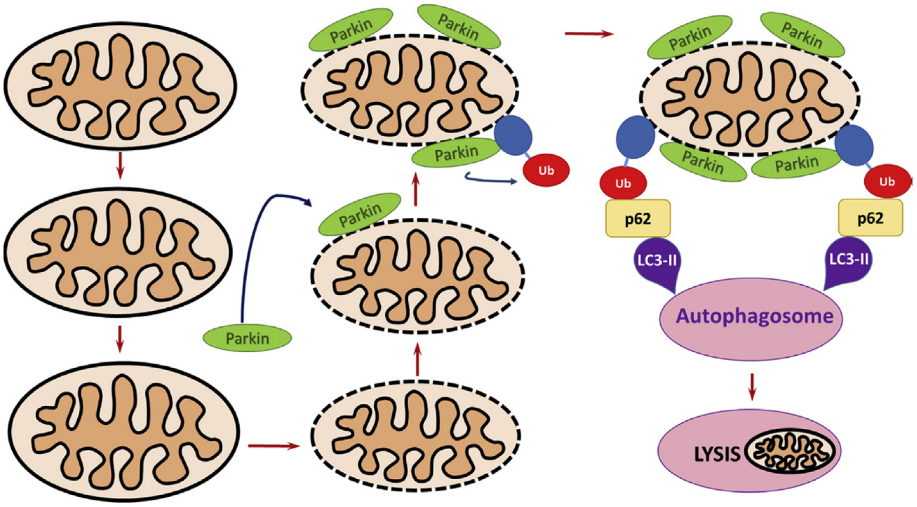

Fig. 1. Schematic representation of PINK1 stabilization on the membrane of damaged mitochondria. When mitochondria undergo any stress that leads to the loss of the membrane potential, PINK1 accumulates on OMM and recruits Parkin from the cytosol. Parkin ubiquitynates proteins at OMM. These ubiquitinated proteins are recognized by p62. LC3-II locates on autophagosome membrane and this binding provides fusion of mitochondria and autophagosomes.