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Mini Review

Mitochondrial ROS generation for regulation of autophagic pathways in cancer

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ABSTRACT

Mitochondria, the main source of reactive oxygen species (ROS), are required for cell survival; yet also orchestrate programmed cell death (PCD), referring to apoptosis and autophagy. Autophagy is an evolutionarily conserved lysosomal degradation process implicated in a wide range of pathological processes, most notably cancer. Accumulating evidence has recently revealed that mitochondria may generate massive ROS that play the essential role for autophagy regulation, and thus sealing the fate of cancer cell. In this review, we summarize mitochondrial function and ROS generation, and also highlight ROS-modulated core autophagic pathways involved in ATG4–ATG8/LC3, Beclin-1, p53, PTEN, PI3K–Akt–mTOR and MAPK signaling in cancer. Therefore, a better understanding of the intricate relationships between mitochondrial ROS and autophagy may ultimately allow cancer biologists to harness mitochondrial ROS-mediated autophagic pathways for cancer drug discovery.

1. Introduction

Mitochondria, recognized as cellular energy power houses, may regulate cellular redox signaling to ascribe to cell survival, and also orchestrate programmed cell death (PCD), including apoptosis and autophagy [1]. Autophagy, a term from Greek "auto" (self) and "phagy" (to eat), refers to an evolutionarily conserved, multi-step lysosomal degradation process in which cell degrades long-lived proteins and obsolete organelles such as mitochondria [2,3]. Macroautophagy (hereafter referred to autophagy), a major regulated catabolic mechanism, is highly regulated by a limited number of autophagy-related genes (ATGs), with an astonishing number of links to cancer [4,5].

ROS are highly reactive oxygen free radicals or non-radical molecules that are generated by multiple mechanisms, with the nicotinamide adenine dinucleotide phosphate oxidases (NOX) and mitochondria as the major cellular sources [6]. These ROS, as important multifaceted signaling molecules, can regulate a number of cellular pathways and thus playing critical roles in determining the fate of cell [7]. Depending on different cell type and context, autophagy may play the Janus role for regulation of ROS-mediated survival or death pathways in cancer [8,9].

In this review, we focus on describing mitochondrial function and mitochondria-generated ROS, and further highlight mitochondrial ROS-modulated autophagic pathways in cancer, such as ATG4–ATG8/LC3, Beclin-1, phosphatase and tensin homolog (PTEN), p53, PI3K–Akt–mTOR and MAPK signaling. Because space is limited, the readers interested in NOX-produced ROS-mediated autophagy can be referred to some recent reviews [6,7].

2. Mitochondrial function

Mitochondria, the primary energy-generating mechanism of eukaryotes, are important organelles that may regulate several critical cellular processes [10]. Also, mitochondria are known to play the key roles in triggering cell death via disrupting electron transport and energy metabolism, releasing or activating apoptosis-related proteins, as well as altering cellular redox potential. The connections between mitochondria and apoptosis have been explored that mitochondria can release a series of apoptosis-related proteins such as cytochrome *c* and AIF. Therefore, they may display cryptic cytotoxic activities after escaping from the mitochondrial inter-membrane space into the cytoplasm, and thus culminating in cell death [11,12].

Additionally, mitochondria are considered as the main source of ROS, which is a multiple-effective element in cellular signaling and thus playing a dual role in cell survival and death [13]. Recently, bulks of accumulating data have demonstrated that massive ROS generated by mitochondria may critically mediate several core autophagic pathways in cancer initiation and progression [14].

3. Mitochondrial ROS and cell physiology

ROS, chemically-reactive molecules containing oxygen, include oxygen ions and peroxides highly reactive in signaling pathways

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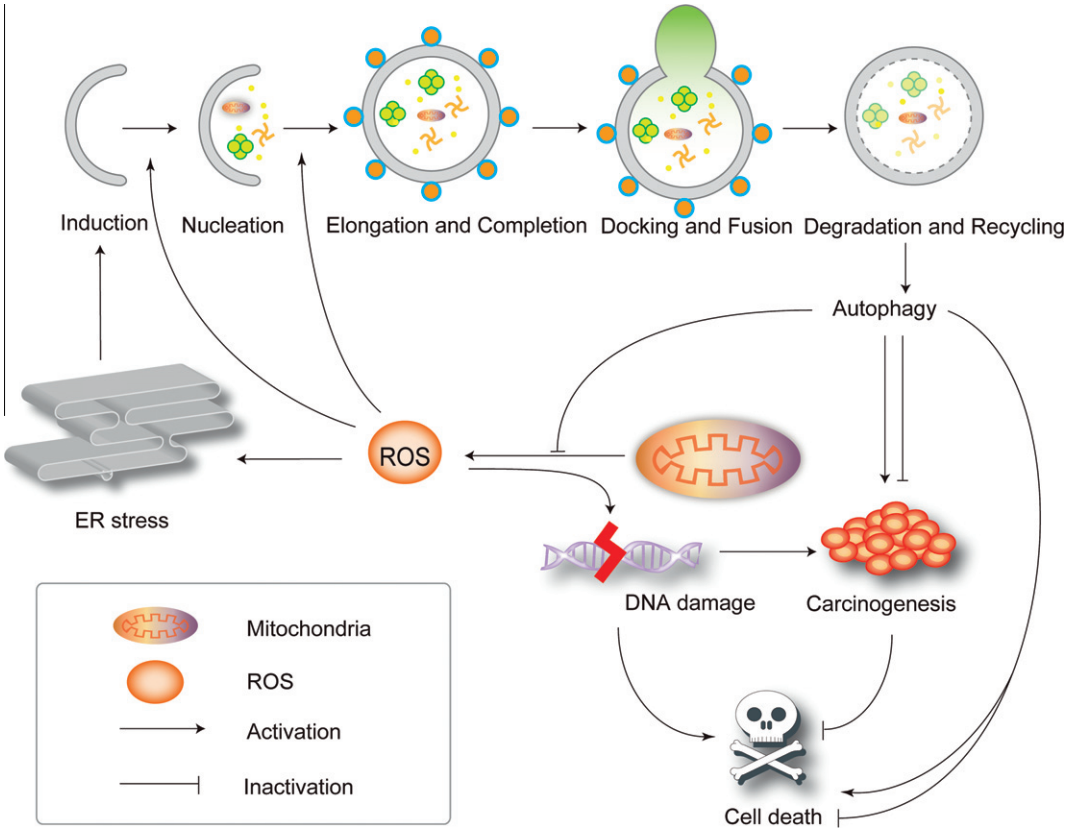

Fig. 1. The relationships between mitochondrial ROS generation and autophagic process in cancer. Mitochondria may generate massive ROS that play the key roles in several cellular processes, such as autophagy. Within the context of cancer, mitochondrial ROS may directly initiate autophagy via inducing the early autophagic stages or indirectly promote autophagy via ER stress. Additionally, mitochondrial ROS may lead to DNA damage, cell death or replication mutations. Autophagy induction may remove excessive ROS and maintain continuous nutrition supply; thereby inhibiting cell death and playing the multifaceted roles in carcinogenesis.

for regulating cell growth, differentiation, survival and death. Major sites of endogenous ROS production during normal homeostasis are mitochondrial electron transport chain (ETC), Ero1–DPI oxidative folding system in endoplasmic reticulum (ER) and nicotinamide adenine dinucleotide phosphate oxidases (NOX) complex at the membrane [13].

Recently, mounting evidence has revealed that mitochondria may produce massive ROS that can modulate autophagy process [11] (Fig. 1). Whilst, the increased levels of ROS, also called oxidative stress, may damage some organisms and thus resulting in oxidations of amino acids in proteins, polydesaturated fatty acids in lipids, as well as DNA damage and apoptosis [9]. Additionally, the metabolic pathways may lead to ROS production, and ETC in the membrane of mitochondria can be regarded as the main source [14]. Moreover, UV light, cytotoxic treatment or anoxia reperfusion may arise the defects of ETC (blockade of complex I, oxidation of complex I or II substrates), and remarkably increase mitochondrial ROS production [9].

4. Mitochondrial ROS and cancer

4.1. ROS-mediated autophagic pathways

Of note, autophagy can be stimulated in response to ROS injury in cancer cells and thus playing a relevant role in the control of cellular redox balance (Fig. 2). During amino acid starvation, H_2O_2-generated by mitochondria can directly modulate the cysteine protease Atg4, resulting in inhibition of Atg4 delipidating activity, whereas the initial processing of LC3 (priming) by Atg4 is not altered [6]. Also, ROS-dependent accumulation of LC3–PE on the autophagosomal membrane adjunct to mitochondria is aroused, thereby facilitating the first step in autophagosome formation [8]. Additionally, other ATGs such as Beclin-1 have been reported to be upregulated in response to ROS in cancer cells. And, Bcl-X_L and Bax may be involved in this process, suggesting that ROS may have synergetic effects in apoptosis and autophagy [15].

Moreover, ROS can directly induce dephosphorylation of mTOR and p70 ribosomal protein S6 kinase in a Bcl-2/E1B 19 kDa interacting protein 3 (BNIP3)-dependent manner in C6 glioma cells. And, BNIP3 has the capacity to inhibit mTOR activity, and then mTOR inhibition leads to autophagic induction [16]. In ROS-induced autophagy, the hypoxia-dependent factor-1-dependent expression of BNIP3 and the constitutive expression of Beclin-1 and ATG5 are necessary. Also, ROS can inhibit PTEN, which activates autophagy via downregulation of PI3K–Akt–mTOR signaling [7].

Increased ROS may lead to PARP activation, indicating the involvement of SRC-dependent JNK and ERK is involved in ROS production and autophagic death in zVAD-treated L929 cells [16]. However, increased ROS can activate the apoptosis signal-regulating kinase 1 (ASK1)–c-Jun N-terminal kinase (JNK)/p38 pathway, which suggests a connection between ROS-induced autophagy and apoptosis. Recently, AMP-activated protein kinase (AMPK) activity, ROS levels, and autophagic markers have been monitored in confluent bovine aortic endothelial cells (BAEC) treated with the glycolysis blocker 2-deoxy-D-glucose (2-DG). Then, AMPK is shown to be required for ROS-triggered autophagy, which may increase cell survival [6]. Also, mitochondrial ROS generation has been shown to activate p38, which subsequently activates p53 in cancer cells [12].

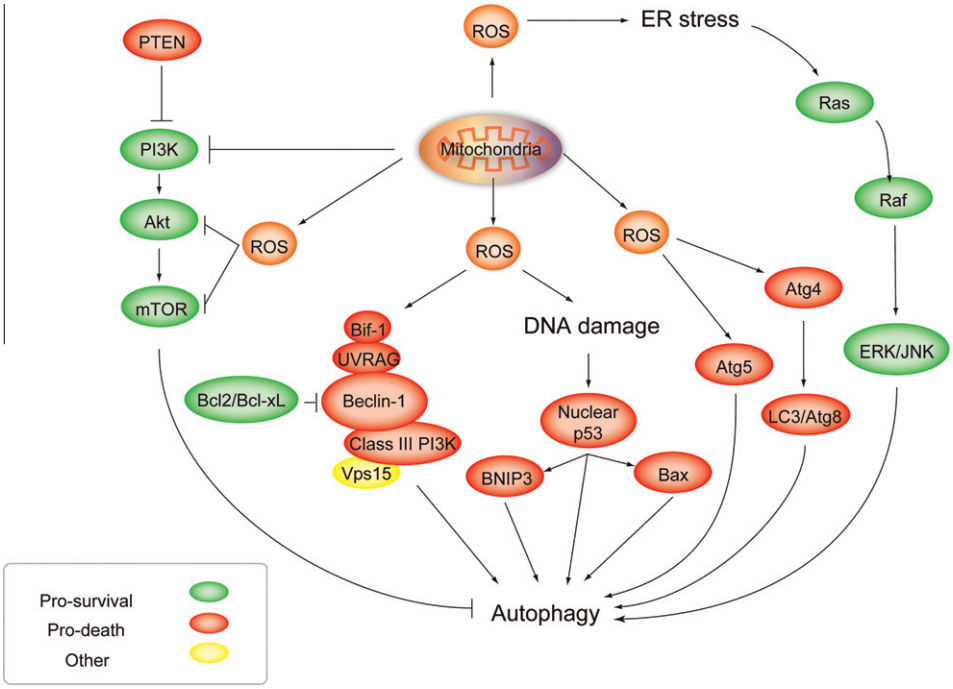

Fig. 2. Targeting mitochondrial ROS-induced autophagic pathways for cancer therapy. Mitochondria-generated ROS may play the Janus role (pro-survival or pro-death) in cancer initiation and progression. Subsequently, these ROS may regulate several core autophagic pathways, such as ATG4–ATG8/LC3, Beclin-1, p53, PTEN, PI3K–Akt–mTOR and MAPK signaling. Thus, these autophagic pathways connect with each other and may be further integrated into the mitochondrial ROS-modulated autophagic network for the discovery of potential novel cancer drug targets.

Another molecular mechanism of ROS-induced p53 has been explored that ROS generation can cause the oxidative DNA damage by abstraction of an H atom from the methyl group of thymine and each of the C–H bonds of 2′-deoxyribose, leading to genome instability or genetic replication mutations. Subsequently, the expression of p53 can participate in gene repair or cell death program in apoptosis and autophagy [13,17].

4.2. Mitochondrial ROS-induced autophagy and cancer

ROS are well-characterized to involve in autophagy induction; on the other hand, autophagy also impacts on ROS production. When mitochondrial ROS are remarkably elevated, mitochondrial membrane is damaged, resulting in ROS leakage into the cytosol; thereby damaging other organelles [11]. In addition, autophagy selectively targets and removes these obsolete organelles such as mitochondria and ER; thereby, limiting ROS amplification [7] (Fig. 1).

Recently, the high levels of ROS are proposed to be involved in cancer metastasis. Mitochondrial ROS can oxidize the critical targeted molecules such as PKC and protein tyrosine phosphates (PTPs) in cancer cell invasion. Also, mitogen-activated protein kinases (MAPKs) and p21 activated kinase (PAK), two classes of downstream molecules regulated by ROS, are established to be the major signaling pathways for driving cancer cell metastasis. Notably, DNA damage caused by excessive ROS may be another important inducer in carcinogenesis [6].

Due to massive ROS production in cancer cells, the effective redox adaptation mechanisms would be coped with noxious environment. The specific blockade on its adaptation mechanism may result in constant and irreversible high levels of ROS; thereby leading to cell death [8]. Furthermore, cancer cells are more vulnerable to oxidative stress caused by exogenous ROS-generating agents. Due to differential redox states between normal and cancer cells, the therapeutic strategies would be reconsidered to selectively utilize these aforementioned agents for cancer therapy [7,18].

5. Outlook for the future

Autophagy has been well-characterized to play the Janus role, acting as either guardian or executioner in cancer therapy [19,20]. Mounting evidence has demonstrated that mitochondria, the main source of reactive oxygen species (ROS), may orchestrate the autophagy process in cancer initiation and progression. Excessive mitochondrial ROS are harmful to cells because of their capacity for damaging cellular components, whereas ROS are beneficial as important signaling molecules for regulating a series of downstream pathways critical for cell survival or death. For instance, mitochondrial ROS may act as a tumor suppressor by activating pro-autophagic genes and blocking anti-autophagic genes in carcinogenesis; however, similar to the Roman God Janus, ROS also play a pro-tumor role under certain circumstances. Thus, mitochondrial ROS may play the multifaceted roles as the ‘molecular switch’ for regulation of several core autophagic pathways (e.g., ATG4–ATG8/LC3, Beclin-1, PTEN, p53, PI3K–Akt–mTOR and MAPK signaling) that may jointly seal the fate of cancer cell (Fig. 2). Within this context, further elucidating molecular mechanisms behind mitochondrial ROS and targeting ROS-modulated autophagy would be a promising avenue for the discovery of potential novel cancer drug targets.

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