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Review Article

Deconvoluting the role of reactive oxygen species and autophagy in human diseases

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ABSTRACT

Reactive oxygen species (ROS), chemically reactive molecules containing oxygen, can form as a natural byproduct of the normal metabolism of oxygen and also have their crucial roles in cell homeostasis. Of note, the major intracellular sources including mitochondria, endoplasmic reticulum (ER), peroxisomes and the NADPH oxidase (NOX) complex have been identified in cell membranes to produce ROS. Interestingly, autophagy, an evolutionarily conserved lysosomal degradation process in which a cell degrades long-lived proteins and damaged organelles, has recently been well-characterized to be regulated by different types of ROS. Accumulating evidence has demonstrated that ROS-modulated autophagy has numerous links to a number of pathological processes, including cancer, ageing, neurodegenerative diseases, type-II diabetes, cardiovascular diseases, muscular disorders, hepatic encephalopathy and immunity diseases. In this review, we focus on summarizing the molecular mechanisms of ROS-regulated autophagy and their relevance to diverse diseases, which would shed new light on more ROS modulators as potential therapeutic drugs for fighting human diseases.

Contents

Abbreviations: 2DG, 2-Deoxy-D-glucose; 2-ME, 2-methoxyestradiol; 3NP, 3-nitropropionic acid; ASK1, apoptosis signal-regulating kinase 1; Atg, autophagy-related gene; ATM, ataxia-telangiectasia mutated; Bif-1, Bax-interacting factor-1; BNIP3, Bcl-2/E1B interacting protein 3; CoQ, coenzyme Q; Cu^{+}, reduced copper; cyto. *c*, cytochrome *c*; EDD, endothelium-dependent dilatation; ER, endoplasmic reticulum; ER-β, estrogen receptor beta; ERK, extracellular regulated kinase; Fe^{2+}, reduced iron; FIP200, focal adhesion kinase family interaction protein of 200-kDa; HE, hepatic encephalopathy; H_2O_2, hydrogen peroxide; JNK, c-Jun N-terminal kinase; LAMP1 and LAMP2, lysosomal-associated proteins 1 and 2; MAPK, mitogen-activated protein kinase; mETC, mitochondrial electron-transport chain; NO, nitric oxide; NOX, NADPH oxidase; $^1O_2$, singlet oxygen; $O_2^{-\bullet}$, superoxide; OH^-, hydroxyl radical; PI3KCIII, Class III phosphatidylinositol 3-kinase; PtdIns, phosphatidylinositol; ROS, reactive oxygen species; SOD, superoxide dismutase; ULK1/2, Unc51-Like Kinase 1/2; UVRAG, UV irradiation resistance-associated gene; XO, xanthine oxidase.

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Introduction

Reactive oxygen species (ROS) are a family of molecules that include highly reactive free oxygen radicals that are produced in cells through metabolism of oxygen and function as destructive molecules when at high levels [1]. After hydrogen peroxide was firstly demonstrated to be required for cytokine, insulin, growth factor and NF-κB signaling, it has become clear that ROS can regulate many biological processes [2]. Concurrent with ROS, the discovery that release of cytochrome *c* (cyto. *c*) can mediate apoptosis reveals that mitochondria seem to be an important redox signaling node [3]. Other mechanisms such as peroxisomes, endoplasmic reticulum (ER) and the NADPH oxidase (NOX) have been identified to intracellularly produce ROS including superoxide ($O_2^{-\bullet}$), hydroxyl radical (OH^-), nitric oxide (NO), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$). Consequently, redox signals help to integrate ROS function with autophagy, a selective lysosomal self-digestion of intracellular components to maintain cellular homeostasis, which is highly regulated by a limited number of autophagy-related (Atg) genes [4]. Autophagic pathways of cellular digestion are involved in the progression of various diseases affecting both cell survival and death; similarly, ROS have been identified as signaling molecules in various pathways regulating cell survival and death [5]. So far, autophagy has been found to be be induced in response to intracellular ROS such as H_2O_2, $O_2^-\bullet$ and NO and several molecular aspects modulating autophagic pathways by H_2O_2, $O_2^-\bullet$ and NO in diverse diseases have been revealed since some ROS-regulated autophagic pathways have been found in different diseases such as cancer, ageing, neurodegenerative diseases, type-II diabetes, cardiovascular diseases, muscular disorders, hepatic encephalopathy and immunity diseases [6].

Amazingly, ROS and autophagy were firstly described some years ago; however, precise mechanisms of ROS-regulated autophagy and effective therapeutic strategies still remain to be discovered. Herein, we focus on summarizing the molecular mechanisms of ROS-regulated autophagy and their relevance to diverse diseases, which would provide new clues to exploit more ROS modulators as potential drugs for fighting human diseases.

The generation of reactive oxygen species

Oxidative stress occurs in living cells in response to excessive production of ROS, which can be divided into two types: free radical ROS, such as $O_2^-\bullet$, OH^- and NO; highly reactive non-radical ROS, such as H_2O_2 and $^1O_2$, giving rise to radical forms of ROS [7]. Most intracellular ROS are derived from $O_2^-\bullet$, whose formation is mainly through NADPH oxidases (NOXs), xanthine oxidase (XO), and the mitochondrial electron-transport chain (mETC) in endogenous biologic systems [8–10].

O_2^- is short-lived and can be either through spontaneous dismutation or through the catalytic activity of superoxide dismutase (SOD) converted in H_2O_2, ultimately yielding the highly toxic OH^- in the presence of reduced iron (Fe^{2+}) or copper (Cu^+) through the Fenton reaction. Produced by NOXs or XO, $O_2^-\bullet$ is dismutated to H_2O_2 by the cytosolic CuZnSOD, whereas mitochondria have their own SOD, namely MnSOD, which functions specifically in H_2O_2 formation within the mitochondrial matrix [11]. NOXs are a family of multi-component enzymes that convert molecular oxygen to superoxide anion in cellular compartments. The NOXs family contains five members, namely Nox1 through Nox5, which are found to be expressed in different cell types [8]. The best-characterized NOX enzyme is Nox2 NADPH oxidase, which is widely expressed in phagocytes [12]. Nox2 NADPH oxidase is composed of a transmembrane catalytic complex, flavocyto-chrome b_{558} (comprising Nox2/gp91^{phox} and p22^{phox}), and cytosolic components p67^{phox}, p47^{phox}, p40^{phox} and Rac2, among which Nox2/gp91^{phox} can catalyze electron transfer from cytosolic NADPH to the oxygen molecules in the phagosomal lumen, generating $O_2^-\bullet$ [13]. Another enzyme, XO, can also produce superoxide anions since it can transfer electrons from hypoxanthine to oxygen molecules and form $O_2^-\bullet$ [9]. Found in the cytoplasm, perinuclear regions and intracellular vesicles, XO is involved in purine catabolism, converting hypoxanthine to xanthine as well as to urate.

Moreover, mETC, composed of four protein complexes (complexes I to IV), coenzyme Q (CoQ) and cyto *c*, is the main source of ROS in living cells, through which continuous aerobic respiration generates $O_2^-\bullet$ [10]. Large amounts of $O_2^-\bullet$ are produced at the mitochondrial complex I when the NADH/NAD^+ ratio is high or reverse electron transport occurs, while complex III can also produce superoxide but at a much lower level compared with complex I under physiologic conditions [14]. In mitochondria, electrons are transferred from NADH at complex I to complex II and through CoQ to complex III, and then by cyto. *c* to complex IV, where they are accepted by oxygen molecules to form water. Intermembrane space ROS theoretically has access to the cytosol, as they only need to cross the inner and outer mitochondrial membranes. Therefore, $O_2^{-\bullet}$ derived from site III CoQ and glycerol 3-phosphate dehydrogenase may possess an advantage with regard to signaling capacity in the cytosol. Other mitochondrial enzymes can also be sources of generation under certain conditions, such as α-ketoglutarate dehydrogenase, α-glycerophosphate dehydrogenase, and dihydroorotate dehydrogenase [15]. Peroxisomes are another major site of H_2O_2 generation. In addition, the ER luminal thiol oxidase Ero1 catalyzes the electron to the oxygen molecule, and forms disulfide bonds in substrates as well as H_2O_2 as a byproduct [16]. Under ER-stress conditions, ROS can be generated by Ero1, the mitochondria, and the Nox4 NADPH oxidase through the unfolded protein response [16]. Besides endogenous sources, exogenous sources of ROS also exist, such as UV and ionizing radiation, inflammatory cytokines, chemical irritants such as tobacco, environmental toxins, and various pharmaceutical agents (Fig. 1).

The relationship between reactive oxygen species and autophagic process

Of note, the autophagic process can be dissected into different steps, such as induction, vesicle nucleation, vesicle elongation, docking & fusion, and degradation & recycling [17]. The major