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Review

The H^+-ATP synthase: A gate to ROS-mediated cell death or cell survival ☆

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ABSTRACT

Cellular oxidative stress results from the increased generation of reactive oxygen species and/or the dysfunction of the antioxidant systems. Most intracellular reactive oxygen species derive from superoxide radical although the majority of the biological effects of reactive oxygen species are mediated by hydrogen peroxide. In this contribution we overview the major cellular sites of reactive oxygen species production, with special emphasis in the mitochondrial pathways. Reactive oxygen species regulate signaling pathways involved in promoting survival and cell death, proliferation, metabolic regulation, the activation of the antioxidant response, the control of iron metabolism and Ca^{2+} signaling. The reversible oxidation of cysteines in transducers of reactive oxygen species is the primary mechanism of regulation of the activity of these proteins. Next, we present the mitochondrial H^+-ATP synthase as a core hub in energy and cell death regulation, defining both the rate of energy metabolism and the reactive oxygen species-mediated cell death in response to chemotherapy. Two main mechanisms that affect the expression and activity of the H^+-ATP synthase down-regulate oxidative phosphorylation in prevalent human carcinomas. In this context, we emphasize the prominent role played by the ATPase Inhibitory Factor 1 in human carcinogenesis as an inhibitor of the H^+-ATP synthase activity and a mediator of cell survival. The ATPase Inhibitory Factor 1 promotes metabolic rewiring to an enhanced aerobic glycolysis and the subsequent production of mitochondrial reactive oxygen species. The generated reactive oxygen species are able to reprogram the nucleus to support tumor development by arresting cell death. Overall, we discuss the cross-talk between reactive oxygen species signaling and mitochondrial function that is crucial in determining the cellular fate. This article is part of a Special Issue entitled: 18th European Bioenergetic Conference.

1. Introduction

Oxidative stress is a phenotypic trait of many tumors. Main causes of this phenotype are the increased generation of reactive oxygen species (ROS) and the dysfunction of the antioxidant systems in cancer cells. ROS generation and scavenging are tightly connected to the metabolic state of the cell and especially to the activity of mitochondria. Nowadays, it is accepted that the roles played by cellular ROS are highly dependent on the level at which they are being produced. In this regard, it has been reported that high levels of ROS lead to increased cell death inhibiting tumorigenesis and metastasis [1], whereas low levels of ROS have an effect in promoting tumorigenesis by activating the signaling pathways that regulate proliferation, angiogenesis and metastasis [2,3], stressing the relevance of ROS as important signaling molecules that regulate cell fate. In this review we will briefly summarize: (i) the sites of production, mechanism of action and signaling pathways that are activated by ROS and (ii) the role of the mitochondrial H^+-ATP synthase in ROS-signaling cell death or cell survival paying, in the latter case, special attention to the new physiological function unveiled for the

Abbreviations: AIF, apoptosis inducing factor; Akt, v-Akt murine thymoma viral oncogene; AP-1, activator protein 1; ARE, antioxidant responsive element; ASK1, apoptosis signal-regulated kinase 1; ATM, ataxia telangiectasia mutated; Duox, Dual oxidase enzymes; DUSP3, dual-specific phosphatase 3; ETC, electron transport chain; GPXs, glutathione peroxidases; GSH, glutathione; GST, glutathione S-transferase; HIF1α, Hypoxia Inducible Factor 1; HO1, heme oxygenase-1; IER3, immediate early response gene; InsP3R, InsP3 receptor; IF1, ATPase Inhibitory Factor 1; IRE, iron-responsible elements; IRP, iron regulatory protein; JNK1, c-Jun N-terminal kinase 1, monoamine oxidase (MAO); mROS, mitochondrial reactive oxygen species; NFkB, nuclear factor kappa-light-chain-enhancer; NOX, NADPH oxidase; Nrf2, NFE2-like 2; O_2^-, superoxide radical; $^{\bullet}OH$, hydroxyl radical; OONO, peroxynitrite; OXPHOS, oxidative phosphorylation; p66Shc, 66 kDa proto-oncogene; SERCA, sarco/endo-plasmic reticulum Ca^{2+}-ATPase; Src, homologous-collagen homologue (Shc) adaptor; PI3K, phosphoinositide-3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PP2A, protein phosphatase 2A; PRXs, peroxiredoxins; PTEN, phosphatase and tensin homolog; PTP, permeability transition pore; PTP1b, phosphotyrosine protein phosphatase; Ref-1, redox factor-1; RNS, reactive nitrogen species; ROS, reactive oxygen species; RyR, ryanodine receptor; SODs, superoxide dismutases; UTR, untranslated region; VHL, von Hippel–Lindau; $\Delta\psi m$, mitochondrial membrane potential

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ATPase Inhibitory Factor 1 (IF1) as a main regulator of the oncogenic phenotype in some prevalent carcinomas.

2. ROS dynamics and signaling

2.1. Major cellular sites of ROS production

Most intracellular ROS are derived from the superoxide radical (O_2^-), which is the product of the one electron reduction of O_2 (Fig. 1). Superoxide is then converted to hydrogen peroxide (H_2O_2) by superoxide dismutases (SOD1, SOD2 and SOD3) (Fig. 1). The enzymes peroxiredoxins (PRXs), glutathione peroxidases (GPXs) and catalase are responsible for removing cellular H_2O_2 (Fig. 1), a process that is tightly regulated [4]. H_2O_2 can also react with iron to generate hydroxyl radicals ($^{\cdot}OH$) that are main drivers of the modifications in proteins, lipids and DNA that result in oxidative stress (Fig. 1).

Several enzymes produce superoxide radical in the cell. Among them, NADPH oxidase is the best described enzymatic source of superoxide that uses NADPH as an electron donor (Fig. 1) [5,6]. NADPH oxidases include the Nox family members (Nox1–5) and the Dual oxidase enzymes (Duox1–2) that are expressed in numerous tissues [6–8]. These enzymes play important roles in cell signaling, regulation of gene expression, cell death, differentiation and growth [9]. Nox enzymes have developed different regulatory mechanisms depending on their function [6,8,10–12]. ROS produced by Nox proteins can act both intra- and extra-cellularly. These enzymes generate superoxide at the plasma membrane, in endosomes and in the endoplasmic reticulum [13,14]. ROS produced by Nox2 have a main physiological role in the respiratory burst that occurs in phagocytes. Nox1 in the colon and Duox1 and 2 in the lung also play important roles in host defense [15]. However, ROS derived from Nox also participate in signaling as they can specifically and reversibly alter the activity, localization and half-life of proteins in response to various stimuli [9]. The phosphoinositide-3-kinase (PI3K) [16] and nuclear factor kappa-light-chain-enhancer of activated cell (NFkB) [13] pathways are two important signaling routes in which NADPH oxidases are involved. Fibroblasts over-expressing Nox1 displayed increased levels of superoxide and exhibited a transformed phenotype [17]. Moreover, it has been described that Nox1 signals angiogenic and tumorigenic effects through hydrogen peroxide [18]. Excess ROS produced by Nox5 have also been related to cancer [19,20].

A substantial portion of cellular ROS is generated in mitochondria. There are eight sites in mitochondria that have the ability to produce ROS [21]. The mitochondrial electron transport chain (ETC) is the major site of non-enzymatic formation of superoxide radical (Fig. 2). The ETC is composed of four multiprotein complexes (I–IV) located in the inner mitochondrial membrane. Complexes I, II and III have the ability to produce superoxide as a result of the flux of electrons through the ETC. Complexes I, II and III produce ROS within the mitochondrial matrix whereas complex III also generates ROS and releases it into the intermembrane space (Fig. 2) [22]. Importantly, ROS generated in the intermembrane space are supposed to access the cytosol in a faster way which may confer them signaling advantages [3,23]. ROS are released to the cytosol through voltage-dependent channels that are constituents of the permeability transition pore (PTP) and by the inner membrane anion channel (IMAC) [24,25]. The transition of ROS from mitochondria to the cytosol is crucial in the regulation of programmed cell death geared by mitochondria [25,26].

Other important sources of mitochondrial ROS (mROS) are p66Shc and monoamine oxidase (MAO) (Fig. 2). The protein p66Shc plays key roles in the oxidative stress response by inducing apoptosis under stressful conditions (Fig. 2) [27]. p66Shc acts as a redox protein due to its capability to interact and oxidize cytochrome c (Fig. 2) [28]. MAO is a flavoenzyme bound to the outer mitochondrial membrane that catalyzes the oxidative deamination of neurotransmitters and monoamines. MAO represents a significant source of ROS production in brain mitochondria where it has been shown to generate ROS in a much higher amount than the respiratory chain [29]. In fact, MAO is involved in multiple neuropathologies and myocardial diseases and its inhibition is likely to provide a promising target for the relief of the oxidative stress that is associated with these pathologies [30].

The overproduction of ROS in response to metabolic stress triggered by hypoxia or chemotherapy promotes an oxidative stress that has been invariably linked to multiple pathologies including neurodegenerative diseases, diabetes, cancer and premature aging [3]. Nowadays, it is indubitable that mROS are important signaling intermediates in the

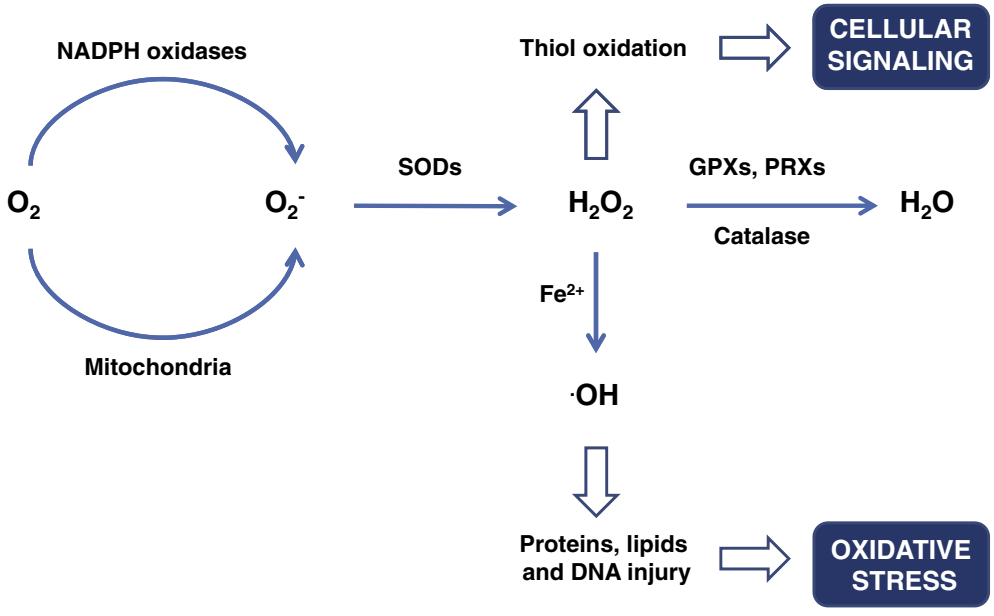

Fig. 1. The metabolism of oxygen. Superoxide is mainly produced by NADPH oxidases and by the mitochondrial respiratory chain. Superoxide is converted to hydrogen peroxide (H_2O_2) by superoxide dismutases (SODs). H_2O_2 is converted to water (H_2O) by glutathione peroxidases (GPX), peroxiredoxins (PRX) or catalase. H_2O_2 is the main player in ROS cellular signaling because it can promote posttranslational modifications in proteins by thiol oxidation. The reaction of H_2O_2 with iron (Fe^{2+}) generates hydroxyl radicals ($^{\cdot}OH$) that are responsible for lipid, protein and DNA damage, promoting oxidative stress.

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