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Organelles in focus

# Mitochondria: Much ado about nothing? How dangerous is reactive oxygen species production?☆

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ABSTRACT

For more than 50 years, reactive oxygen species have been considered as harmful agents, which can attack proteins, lipids or nucleic acids. In order to deal with reactive oxygen species, there is a sophisticated system developed in mitochondria to prevent possible damage. Indeed, increased reactive oxygen species levels contribute to pathomechanisms in several human diseases, either by its impaired defense system or increased production of reactive oxygen species. However, in the last two decades, the importance of reactive oxygen species in many cellular signaling pathways has been unraveled. Homeostatic levels were shown to be necessary for correct differentiation during embryonic expansion of stem cells. Although the mechanism is still not fully understood, we cannot only regard reactive oxygen species as a toxic by-product of mitochondrial respiration anymore.

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**Key facts**

- Reactive oxygen species are produced in various cell compartments.
- Previously thought of as harmful agents only, they are now considered as important signaling molecules with potential therapeutic effect.

**Organelle facts**

- Mitochondria produce vital energy in the form of ATP via oxidative phosphorylation.
- Mitochondria have their own genome, called mitochondrial DNA.
- Mitochondria are responsible for most of the reactive oxygen species via oxidative phosphorylation.
- Mutations in nuclear encoded genes of mitochondrial proteins potentially result in inherited diseases, with an incidence of 1 in 10,000, most of them causing neuropathies or myopathies.
- Mitochondrial diseases of oxidative phosphorylation can be connected with increased ROS
- Mitochondria have their own ROS defense system.

## 1. Introduction

The discussion about reactive oxygen species (ROS) started around the year 1956 (Harman, 1956) with the finding that 2% of the oxygen which is used up by the respiratory chain in mitochondria can be released and transformed into a superoxide radical anion $O_2^{\bullet -}$ by consuming a single electron coming from the respiratory chain. Traditionally, most of the ROS production is believed to originate from the electron transport chain in mitochondria, especially from complexes I and III. Later on, many other proteins were

*Abbreviations:* I, complex I; II, complex II; III, complex III; IV, complex IV; α-KGDH, α-ketoglutarate dehydrogenase; AO, alternative oxidase; cyt, cytochrome; DHODH, dihydroorotate dehydrogenase; ETF, electron transfer flavoprotein; GLRX, glutaredoxin; GPx, glutathione peroxidase; GSH GSSG, glutathione; GSR, glutathione reductase; mGPDH, mitochondrial glycerophosphate dehydrogenase; MAO, monoamine oxidase; NADH DH, external NADH dehydrogenase; NOS, nitric oxide synthase; OXPHOS, oxidative phophorylation; PDH, pyruvate dehydrogenase; PRXIII, peroxiredoxin III; ROS, reactive oxygen species; TXN2, thioredoxin 2; TXNRD2, thioredoxin reductase.

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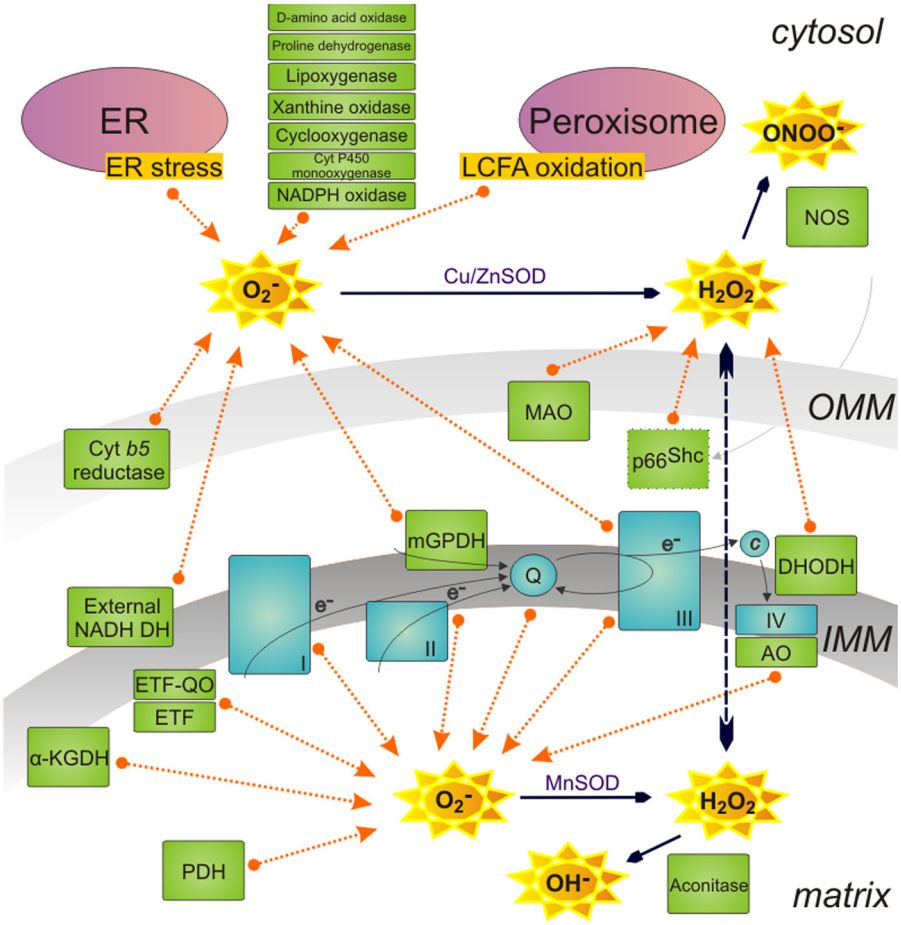


**Fig. 1.** Sites of ROS production. Many different sites of ROS production exist within a cell. Most of them are located in the mitochondrial environment such as the complexes of the respiratory chain: complex I (I), complex II (II), complex III (III), or mitochondrial glycerophosphate dehydrogenase (mGPDH) next to α-ketoglutharate dehydrogenases (α-KGDH), electron transfer flavoprotein (ETF) and ETF ubiquinone oxidoreductase, pyruvate dehydrogenase (PDH), aconitase, alternative oxidase (AO), complex IV (IV), dihydroorotate dehydrogenase (DHODH), external NADH dehydrogenase (NADH DH), protein $p66^{Shc}$, cytochrome (cyt) *b5* reductase, monoamine oxidase (MAO) and nitric oxide synthase (NOS). Other proteins or organelles can also contribute to ROS production. Respiratory chain complexes are displayed in blue, other ROS contributors in green, organelles in violet. (For interpretation of the references to color in figure legend, the reader is referred to the web version of the article.)

described as potential ROS producers, but the exact contribution from different sites is not yet fully understood. Many ROS producers arise with disruption of cell homeostasis, but, in contrast, several proteins produce ROS to restore this homeostasis. Here, we summarize sites of reactive oxygen species production and mitochondrial defense mechanisms and focus on described roles of ROS in cell signalization as a beneficial, yet often overlooked effect of ROS in cell metabolism.

## 2. Organelle function: mitochondrial sites of ROS production

Mitochondria play a key role in aerobic cellular metabolism. The incomplete oxidation of oxygen to water results in superoxide production, virtually ROS. Even though it is still unclear if ROS are only harmful or beneficial, many ROS producing sites were described (Fig. 1). However, an exact contribution of each enzyme is not yet known. Complexes of the respiratory chain in mitochondria are considered as main producers, especially complex I in several sites of the enzyme (Koopman et al., 2010), complex III in subunits interacting with coenzyme Q (Raha et al., 2000; Turrens et al., 1985) and complex II under low substrate conditions (Quinlan et al., 2012) as well.

Within mitochondria, minor ROS producers can also be found. First of all, one protein, which is able to transfer electrons to the coenzyme Q pool as well as to contribute to the ROS formation, is the mitochondrial glycerolphosphate dehydrogenase (Drahota et al., 2002). It is located in the inner membrane facing the intermembrane space. Another significant contribution to ROS production occurs during fatty acid oxidation due to electron transfer flavoprotein (ETF) that accepts electrons from different dehydrogenases and transfers them through its membrane partner ETF ubiquinone oxidoreductase to the coenzyme Q pool in the inner membrane (Ruzicka and Beinert, 1977). Next, there is a multisubunit pyruvate dehydrogenase complex (Starkov et al., 2004) and a structurally similar membrane bound enzyme complex of α-ketoglutarate dehydrogenase (α-KGDH) which has been proposed as a source of superoxide and hydrogen peroxide under low availability of $NAD^+$, the natural electron acceptor of α-KGDH (Starkov et al., 2004). Many of the aforementioned proteins contain flavin in their active site, which is directly interacting with electrons and plays a possible role in the electron leakage.

Aconitase, an enzyme in the mitochondrial matrix, is able to transform hydrogen peroxide into hydroxyl radicals during a Fenton reaction with its iron–sulphur cluster. Aconitase, though, is easily inhibited by the presence of superoxide (Vasquez-Vivar et al., 2000). The function of many proteins is changed upon oxidative stress in cells. Redox disbalance and subsequent oxidation of, for example, protein $p66^{Shc}$, which plays an important role in the regulation of apoptosis, translocates it into the intermembrane space to produce $H_2O_2$ (Pelicci, 2005).