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Review article

Mitochondrial composition and function under the control of hypoxia

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ABSTRACT

Hypoxia triggers several mechanisms to adapt cells to a low oxygen environment. Mitochondria are major consumers of oxygen and a potential source of reactive oxygen species (ROS). In response to hypoxia they exchange or modify distinct subunits of the respiratory chain and adjust their metabolism, especially lowering the citric acid cycle. Intermediates of the citric acid cycle participate in regulating hypoxia inducible factors (HIF), the key mediators of adaptation to hypoxia. Here we summarize how hypoxia conditions mitochondria with consequences for ROS-production and the HIF-pathway.

1. Introduction

Hypoxia imposes stress to cells and organisms, which occurs under both, pathological and non-pathological conditions. The lack of oxygen is linked to diseases like cancer, diabetes, or inflammation but constitutes also a challenge for people living at high altitude. Cells within organisms adapt to hypoxia by altering their metabolism. This is facilitated by changes in protein expression occurring at the transcriptional or translational level, mRNA- or protein stability as well as enzyme activity. Sensors and adaptors towards decreased oxygen availability are prolylhydroxylases (PHD), also known as Egl nine homolog 1 proteins (EGLN). Their loss of activity stabilizes the transcription factors hypoxia inducible factors (HIF) under hypoxia. HIFs enter the nucleus to enhance transcription of a variety of target genes, including mitochondrial components.

Major consumers of oxygen in the cell are mitochondria. Consequently, they are severely affected by decreased oxygen availability. Along those lines, hypoxia alters mitochondrial fusion and fission, mitophagy, and oxidative phosphorylation (OXPHOS). OXPHOS is adapted to hypoxia by remodeling the electron transport chain (ETC) as well as the activity of the TCA cycle. The mitochondrial respiratory chain was originally described as flavin- and cytochrome-containing proteins in the inner mitochondrial matrix [1]. This model proposed the four major complexes, i.e. NADH-coenzyme Q reductase (complex I), succinate-coenzyme Q reductase or succinate dehydrogenase (complex II or SDH), ubiquinol cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV) of the respiratory chain randomly dispersed in the matrix, being connected by the redox active enzymes coenzyme Q (CoQ) and cytochrome c [2,3]. This model was refined with complex I, III, and IV forming supercomplexes that allow an effective electron transport with a minimum of superoxide (O_2^-) production. Nevertheless, ROS (if not specified the term refers to both, superoxide and H_2O_2) from complex I, II, and III appear not only as an accidental escape of electrons from the ETC and their transfer to molecular oxygen, but are now considered as important mediators in physiological cell signaling. ROS production needs to be tightly controlled to avoid its overproduction, provoking damage of mitochondrial and extramitochondrial macromolecules and eliciting cell death [4]. Considering that ROS signaling is linked to the HIF system, it allows anticipating multiple layers of reciprocal interaction. Each ETC complex adapts to hypoxia by replacing distinct proteins, which alter the function of the complex. Using this system, it is not necessary to build an entire new complex to adapt, making these processes fast, reversible, and highly effective. Another adaptive response to hypoxia is the reduction of mitochondrial mass, by mitophagy [5]. This specialized form of autophagy involves factors such as nucleoporin p62, beclin1, microtubule-associated protein1A/1B-light chain 3 (LC3), BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), or BNIP3 ligant [6,7]. These components are part of the phosphatidylinositide 3-kinase class III complex-mediated autophagosome formation. The autophagosome docks to lysosomes, followed by fusion and subsequent digestion of trapped macromolecules/organelles. Some proteins eliciting autophagosome formation like BNIP3 are HIF-regulated, suggesting that mitophagy under hypoxia is at least partly HIF-driven [8–10]. In this review, we address fundamental changes and adaptive mechanisms of mitochondria and mitochondrial ROS production to hypoxia and refer to the crosstalk between mitochondria and the HIF-system (Fig. 1).

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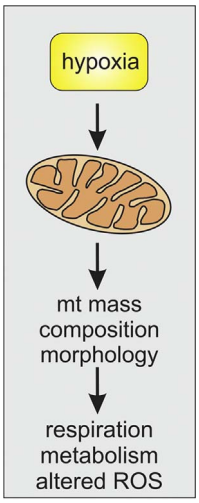

Fig. 1. Hypoxia and mitochondria. Hypoxia acts on mitochondria in multiple ways. It changes the protein composition of the electron transport chain, mitochondrial morphology, and mitochondrial mass. Consequences comprise an altered rate of respiration, changes in the mitochondrial intermediary metabolism, and an adjusted increased or decreased ROS-producing capacity. These changes determine mitochondrial biology with an outreaching impact on cell physiology. *Abbreviations: mt: mitochondrial, ROS: reactive oxygen species.*

2. Mitochondrial ROS production in brief

Besides NADPH oxidases, mitochondria emerged as a powerful source of ROS. Fig. 2 provides an overview towards ROS-production by the ETC and ROS-detoxifying enzymes. Deficiencies in assembling ETC components, mutations in distinct ETC subunits, or the specific inhibition of the ETC can increase ROS production. The molecular details of ROS production at distinct ETC complexes are elaborated in review articles [11–16]. Individual targets, experiencing oxidative modifications in response to complex I and III ROS have been identified [17]. Complex I ROS oxidize TCA cycle associated proteins like subunits of pyruvate dehydrogenase or isocitrate dehydrogenase as well as 2-oxoglutarate dehydrogenase complex component E2 [17]. Apparently, complex I ROS are predominantly oxidizing proteins that are localized in the matrix. Complex III ROS in turn oxidize proteins such as voltage-dependent anion channel 3 and mitochondrial import inner membrane translocase subunit TIM50 but also NDUFB10 and NDUFS3, both components of complex I, which are located in the mitochondrial inner membrane [17]. The voltage-dependent anion channel 3 in the outer mitochondrial membrane was proposed as a marker for oxidative stress, occurring in the intermembrane space [18]. Conclusively, distinct sources of ROS modify divergent proteins and thus, alter discrete signaling pathways (Fig. 3).

3. Regulation of HIF

HIF proteins are key determinants of a cellular response to hypoxia. Once stabilized, they induce multiple target genes, thereby affecting intermediary metabolism e.g. by increasing the expression of proteins involved in glycolysis and decreasing oxygen-dependent pathways by altering the ETC complex structure and activity. The fundamental concepts of HIF regulation are outlined in Fig. 4.

4. Fusion and fission

Besides changes at the protein level, that affect the quarterly structure of protein aggregates, hypoxia impacts on the mitochondrial morphology, including cristae structure (Fig. 5) [19]. Under normoxia,

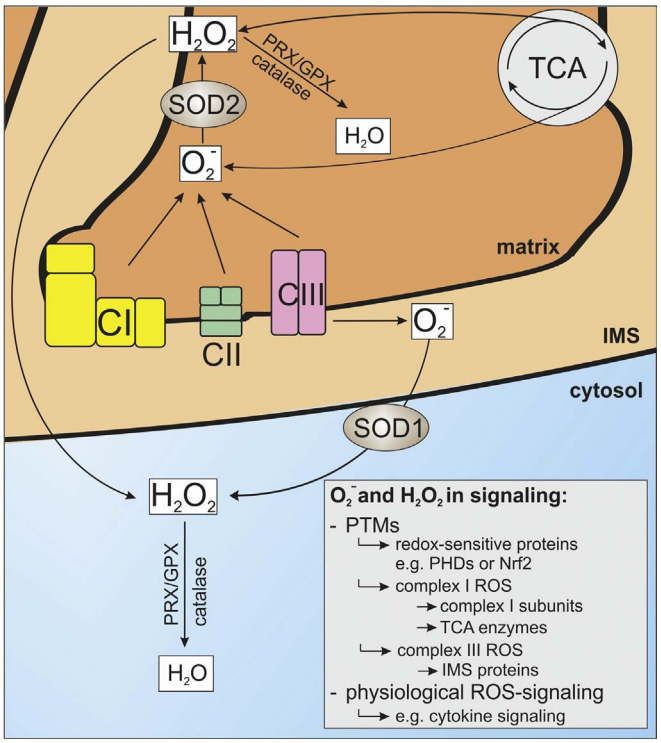

Fig. 2. Mitochondrial ROS. Complexes I, II, and III of the respiratory chain are shown to release O_2^- either into the matrix (CI, CII, CIII) or into the intermembrane space (CIII) [11]. To avoid damage of mitochondrial proteins, lipids, or DNA, effective defense mechanisms are in place. Mitochondrial or cytosolic SOD disproportionate O_2^- to molecular oxygen and H_2O_2. In turn, H_2O_2 is efficiently removed by catalase and/or the PRX/GPX system. Nevertheless, ROS may cause PTMs of redox-sensitive proteins, e.g. components of the ETC or transcriptional elements such as Nrf2 or PHDs. ROS cannot only be regarded as damaging agents, as they appear critical for physiological redox-signaling, e.g. during cytokine formation to protect cells from pathogen invasion. Interestingly, cancer cells were shown to protect mitochondria under hypoxic conditions by an increased expression of antioxidative proteins [28]. Thus, cytoplasmic and intermembrane space SOD1 and matrix SOD2 are transcriptionally upregulated under hypoxia, enhancing superoxide detoxification but producing H_2O_2. Although this review concentrates on ROS produced by the ETC, it should be mentioned that NAD-linked dehydrogenases of the TCA cycle such as 2-oxoglutarate dehydrogenase and pyruvate dehydrogenase are potential sites of electron leakage and thus, ROS formation [29]. *Abbreviations: ETC: electron transport chain, GPX: glutathione peroxidase, Nrf2: Nuclear factor erythroid derived 2, IMS: mitochondrial intermembrane space, PHD: prolyl hydroxylase, PRX: peroxiredoxin, PTM: posttranslational modification, ROS: reactive oxygen species, SOD: superoxide dismutase, TCA: citric acid cycle.*

mitochondria form tubular networks favoring OXPHOS and ATP production. Under hypoxia, mitochondria undergo fission and appear as single organelles, possibly to promote mitophagy, to keep ROS production at a physiological low level, and to maintain integrity by a decrease in respiratory activity.

5. Crosstalk between HIF and mitochondria

Ongoing research in the areas of metabolomics, assembly, and structure of ETC components provide multiple links between mitochondria and the HIF pathway, as depicted in Fig. 6. HIF gets stabilized by a decreased PHD activity, an enzyme demanding metabolites of the mitochondrial TCA cycle for catalysis. In turn, HIF induces the expression of proteins, which impinge on both, metabolism and structure of mitochondria as described in detail in the following figures.