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Mitochondrial biogenesis and mitochondrial DNA maintenance of mammalian cells under oxidative stress

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Abstract

Mitochondrial biogenesis and mitochondrial DNA (mtDNA) maintenance depend on coordinated expression of genes in the nucleus and mitochondria. A variety of intracellular and extracellular signals transmitted by hormones and second messengers have to be integrated to provide mammalian cells with a suitable abundance of mitochondria and mtDNA to meet their energy demand. It has been proposed that reactive oxygen species (ROS) and free radicals generated from respiratory chain are involved in the signaling from mitochondria to the nucleus. Increased oxidative stress may contribute to alterations in the abundance of mitochondria as well as the copy number and integrity of mtDNA in human cells in pathological conditions and in aging process. Within a certain level, ROS may induce stress responses by altering expression of specific nuclear genes to uphold the energy metabolism to rescue the cell. Once beyond the threshold, ROS may cause oxidative damage to mtDNA and other components of the affected cells and to elicit apoptosis by induction of mitochondrial membrane permeability transition and release of pro-apoptotic proteins such as cytochrome *c*. On the basis of recent findings gathered from this and other laboratories, we review the alterations in the abundance of mitochondria and mtDNA copy number of mammalian cells in response to oxidative stress and the signaling pathways that are involved.

Keywords: Mitochondria; Biogenesis; Mitochondrial DNA; Oxidative stress; Somatic mutation; Copy number

Abbreviations: AP, apurine/apyrimidine; BER, base excision repair; CAMK, Ca^{2+}/calmodulin-dependent protein kinase; CREB, cyclic AMP response element-binding protein; CuZnSOD, copper/zinc superoxide dismutase; COX, cytochrome *c* oxidase; eNOS, endothelial nitric oxide synthase; GPx, glutathione peroxidase; hOGG1, human 8-oxoguanine DNA glycosylase; JNK, *c*-Jun N-terminal kinase; LPS, lipopolysaccharides; mtDNA, mitochondrial DNA; mtSSB, mitochondrial single-strand DNA binding protein; mtTFA, mitochondrial transcription factor A; MnSOD, manganese superoxide dismutase; nDNA, nuclear DNA; MPT, mitochondrial permeability transition; NER, nucleotide excision repair; NO, nitric oxide; NRF, nuclear respiratory factor; OXPHOS, oxidative phosphorylation; PGC-1, peroxisome proliferators-activated receptor γ coactivator-1; PI3K, phosphatidylinositol 3′-kinase; PKC, protein kinase C; POLG, DNA polymerase γ; ROS, reactive oxygen species; TCA, tricarboxylic acid

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1. Introduction

Mitochondria are the intracellular organelles responsible for biological oxidation in mammalian cells. They contain double membranes and several hundreds of proteins and 2–10 copies of mitochondrial DNA (mtDNA) in the matrix enclosed by mitochondrial inner membrane. Although mitochondria have their own genome, most of the proteins and enzymes that reside in mitochondrial membranes are nuclear gene products. Their principal function is to synthesize ATP through electron transport and oxidative phosphorylation (OXPHOS) in conjunction with the oxidation of metabolites by tricarboxylic acid (TCA) cycle and catabolism of fatty acids by β-oxidation. Part of the reactions of the biosynthesis of pyrimidines and hemes as well as the transcription, translation, and replication of mtDNA are also carried out in mitochondria. In addition to the production of energy, mitochondria are also the main intracellular source and immediate target of reactive oxygen species (ROS), which are continually generated as byproducts of aerobic metabolism in mammalian cells. The other important function of mitochondria is to act as an arbitrator in the initiation and execution of apoptosis. Mitochondria, thus, play a pivotal role in the determination of life and death of the mammalian cell (Lee & Wei, 2000).

Each mammalian cell contains several hundreds to more than a thousand mitochondria. The size, shape, and abundance of mitochondria vary dramatically in different cell types and may change under different energy demand and different physiological or environmental conditions. The abundance of mitochondria in a cell is determined by the biogenesis and division of the organelles (Attardi & Schatz, 1988). The abundance of mitochondria per cell is tightly controlled by the activation of specific transcription factors and signaling pathways (Attardi & Schatz, 1988; Moyes & Hood, 2003).

In this article, we review the main features of mitochondrial biogenesis, mtDNA maintenance, and the nuclear genes controlling these processes. Alterations in these processes in response to oxidative stress and the signaling pathways involved are also discussed.

2. Mitochondrial biogenesis and mtDNA maintenance

Mitochondria import most of their phospholipids from the cytoplasm to form and maintain their membranes (Moyes & Hood, 2003). Cardiolipin is an acidic and hydrophobic phospholipid required for the function of many mitochondrial proteins such as cytochrome *c* oxidase. The inner membranes of mitochondria are involved in the biosynthesis of cardiolipin and are rich in this phospholipid. The amount of cardiolipin in mitochondrial inner membrane is changed in response to the level of thyroid hormones, chronic contractile activity of muscle, and aging in the human (Paradies & Ruggiero, 1990; Takahashi & Hood, 1993; Paradies, Petrosillo, & Ruggiero, 1997).

Biosynthesis of mitochondrial proteins requires contributions from mitochondria and the nucleus, but most of them are encoded by nuclear genes and synthesized outside of the mitochondria. The proteins are imported into mitochondria by complex multiple mechanisms. On the other hand, 13 polypeptides including seven subunits of NADH dehydrogenase (ND1, ND2, ND3, ND4, ND4L, ND5, and ND6), three subunits of cytochrome *c* oxidase (COI, COII, and COIII), two subunits of F_0F_1 ATPase (ATPase 6 and ATPase 8), and cytochrome *b* are encoded by mtDNA and synthesized in the organelle (Attardi & Schatz, 1988). Mammalian mtDNA also codes for two rRNAs and a set of 22 tRNAs that are essential for protein synthesis in mitochondria. The assembly and functioning of the respiratory enzyme complexes in mammalian cells require coordinated expression and interaction between gene products of the mitochondrial and nuclear genomes (Poyton & McEwen, 1996). The gene expressions in mitochondria and the nucleus responds in a complex manner to a variety of physiological and developmental signals including growth activation (Luciakova, Li, & Nelson, 1992), neoplastic transformation (Shmookler & Goldstein, 1983; Torroni, Stepien, Hodge, & Wallace, 1990), muscle contraction (Williams, Salmons, Newsholme, Kaufman, & Mellor, 1986), cell differentiation, and hormone action (Wiesner, Kurowski, & Zak, 1992).

In mammalian cells, each mitochondrion harbors 2–10 copies of mtDNA, which is a circular double-strand DNA molecule (Robin & Wong, 1988). The replication of mtDNA occurs predominantly in the