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Hypoxic mitochondria: accomplices in resistance

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Abstract. Mitochondria originated from a distant ancestor: the α-proteobacteria. They evolved over millions of years in a symbiotic relationship in eukaryotic cells by favoring consumption of oxygen by the electron transport chain with production of ATP. Contemporary mitochondria still play a crucial role in providing energy but also in apoptosis. Because of this symbiotic relationship and their pivotal function, mitochondria undoubtedly participate in tumorigenesis. Genetic defects in mitochondrial DNA, blockade of oxidative phosphorylation and mitophagy in tumor cells modify the production of damaging reactive oxygen species and restrain apoptosis. As the environment of tumor cells becomes more and more hypoxic, the hypoxia-inducible factor (HIF) is stabilized and participates in the reprogramming of cell metabolism. Recently, we became interested in asking whether HIF and hypoxia affect mitochondrial function. In this review, we show that hypoxia induces enlargement of mitochondria, due to abnormal fusion, which results in resistance to apoptosis and thus in survival. The role of hypoxia-induced BNIP3 and BNIP3L, proteins recently described as pro-survival proteins, in survival is also discussed. ▲

Key words: apoptosis, ATP, cell survival, hypoxia-inducible factor, mitochondria

Mitochondria and cancer

As populations of the Western world get older and are over-fed, age-related metabolic and degenerative diseases emerge. The incidence of diabetes, Alzheimer's disease, Parkinson's disease and cancer is steadily increasing, especially in industrialized countries. What is the link between aging and diet, and these diseases? The answer may lie in the organelle, the mitochondrion, a relic of proteobacteria [1], which is crucial for the survival of higher eukaryotic cells. Each human cell contains thousands of mitochondria that manage energy production and regulate cell death. Mitochondria are intriguing and complex factories generating energy by transforming fats and sugars into ATP [2]. Fats are metabolized to acetyl-CoA by β-oxidation and sugars are metabolized to pyruvate and then to acetyl-Co A. Acetyl-CoA enters the tricarboxylic acid cycle for oxidative phosphorylation in mitochondria *(figure 1)*. Energy is then generated along the electron transport chain through a series of redox reactions catalyzed by four different complexes, complexes I, II, III and IV, and the F_1F_0-ATP synthase. From one molecule of glucose, 38 ATP (2 from the glycolysis and 36 from oxidative phosphorylation) molecules are produced, representing more than 90 % of the intracellular ATP required for cells to grow [3]. Oxidative phosphorylation occurs essentially in the inner membrane but also in the outer membrane, and requires intact membranes.

Mitochondria are also the guardians of cell death. Stress conditions affect mitochondrial membrane permeabilization by triggering a decrease in the mitochondrial transmembrane potential that activates apoptosis *(figure 2)*. Under these conditions ATP synthesis stops and a flux of executioners, caspase-dependent and caspase-independent, from the inner membrane space of mitochondria are released into the cytoplasm to signal cell death [4]. The most critical activator is cytochrome *c*, which by forming a complex with apoptosis activating factor 1 (APAF-1) and pro-caspase 9 triggers a cascade of proteolytic cleavage and activation that turns on apoptosis. Many studies confirm this

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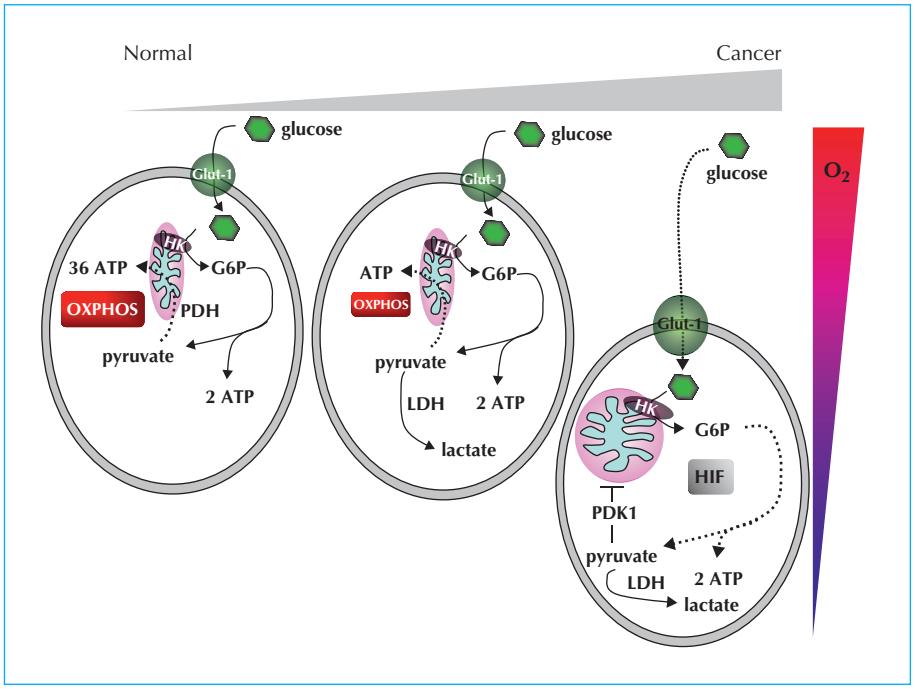

Figure 1. Metabolic characteristics of normal and cancer cells. Glucose is a major source of carbon that is metabolized in normal and cancer cells for the generation of energy. As glucose enters into cells through the glucose transporter (Glut-1), it is phosphorylated to glucose-6-phosphate (G6P) by hexokinase (HK) and then transformed into a final product, pyruvate, by multiples steps. In normal cells, the pyruvate enters into mitochondria after transformation by the pyruvate dehydrogenase (PDH) to finally, through the TCA cycle, produce ATP (36 + 2 ATP molecules). This process is called oxidative phosphorylation (OXPHOS). However, in tumor cells, OXPHOS is reduced and pyruvate is mostly converted into lactate. As tumor cells are often surrounded by hypoxia, the hypoxia-inducible factor (HIF) is stabilized triggering an increase in the turnover of glycolysis. Moreover, HIF, by inducing pyruvate dehydrogenase kinase 1 (PDK1), diminishes the entry of pyruvate into mitochondria, which favors lactate production.

mechanism, however how cytochrome *c* is released and if the mitochondrial permeability transition pore is involved, is still controversial. The Bcl-2 family members, such as Bcl-2 and Bcl-X_L, instead of the mitochondrial permeability transition pore, have been suggested to be involved in cytochrome *c* release. Bcl-2 and Bcl-X_L can bind to cytochrome *c* thereby avoiding its release whereas Bak, Bax and Bid can activate its release. The balance between cell death and survival will depend on the interaction with these proteins.

Mitochondria are also involved in necrotic cell death, which is dependent on the opening or closing of the mitochondrial permeability transition pore. When the mitochondrial permeability transition pore is open, due to uncoupling of oxidative phosphorylation, there is a loss of ions which is accompanied by mitochondrial swelling and decreased ATP production that subsequently triggers necrosis [5].

Undoubtedly, any mitochondrial dysfunction in mitochondrial metabolism or apoptosis gives rise to multiple defects. So what about mitochondria in cancer? Mutations in genes that encode for mitochondrial proteins have been directly linked to some hereditary cancers. Mutations in fumarate hydratase are linked to cutaneous and uterine leimyomas and renal cell carcinomas and mutations in the different subunits of succinate dehydrogenase (SDH), cytb membrane subunit (SDHD), coenzyme Q-binding membrane subunit (SDHC), iron-sulfur subunit (SDHB) of complex II are associated with paragangliomas and pheochromocytoma [2] while mutations in NADP+-dependent isocitrate dehydrogenase 2 (IDH2) are associated with glioblastoma [6]. Mutations in mitochondrial DNA, such as those in the mitochondrial encoded NADH dehydrogenase (ND1) mitochondrial gene, also modify oxidative phosphorylation and the electron transport chain and have been reported in many different cancer types such as colon cancer, head and neck tumors, breast tumors and prostate cancer [7]. Some of these mutations trigger an increase in production of reactive oxygen species, which is often linked to cancer