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INTRODUCTION

Mitochondria in cancer

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Prominent features of cancer cells include metabolic imbalances and enhanced resistance to mitochondrial apoptosis. The fact that tumors rely heavily on glycolysis to meet their metabolic demands has been recognized since the beginning of the twentieth century, yet a complete elucidation of the so-called Warburg effect has not been achieved. Several mechanisms have been proposed to explain this phenomenon, including the upregulation of rate-limiting steps of glycolysis, the accumulation of mutations in the mitochondrial genome, the hypoxia-induced switch from mitochondrial respiration to glycolysis or the metabolic reprogramming resulting from the loss-of-function of enzymes like fumarate and succinate dehydrogenases. How aerobic glycolysis and apoptosis resistance are linked remains to be elucidated. On the one hand, these alterations may be acquired independently by cancer cells during multistep oncogenesis. On the other hand, the suppression of the intrinsic apoptotic program may be achieved through mechanisms that directly lead to the Warburg phenotype. Cancer-specific mitochondrial alterations and bioenergetics may be taken advantage for the development of two novel classes of antineoplastic agents. A first approach would target glycolysis and/or revert the Warburg phenomenon, whereas a second approach would aim at inducing apoptosis by targeting mitochondrial proteins and membranes. In both instances, encouraging pre-clinical results have been obtained.
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As a first hint that mitochondria may play an important role in cancer cell biology, it was discovered in the 1920s that cancer cells constitutively upregulate glucose metabolism, even in the presence of abundant oxygen (Warburg, 1930). Thus, cancer cells tend to synthesize ATP mainly through 'aerobic glycolysis', a metabolic state that is linked to high glucose uptake and local acidification owing to lactate production. Increased glucose breakdown provides building blocks for the synthesis of nucleotides (via the pentose phosphate pathway) and amino and fatty acids (from intermediates formed in the glycolytic and tricarboxylic acid cycles). In addition, local acidification of the tumor microenvironment may facilitate tumor invasion. The enhanced activity of the pentose phosphate shunt may lead to an elevated production of NADPH and glutathione (which would increase the resistance of tumor cells against oxidative insults and some chemotherapeutic agents).

Aerobic glycolysis in cancer, the so-called Warburg effect, is not just a historical reminiscence or a biochemical curiosity. Rather, the Warburg effect is actually the basis for the widespread application of positron emission tomography in which a glucose analog tracer (2-^{18}fluoro-2-deoxy-D-glucose) is used to differentiate between normal and tumor tissue. The molecular and cellular mechanisms of the Warburg phenomenon have not been fully explained. At present, the following non-exclusive hypotheses have been forwarded to explain the Warburg effect:

- Cancer cells often upregulate the rate-limiting processes and enzymes of glycolysis, including glucose transporters, for instance as a result of the constitutive signaling through the Akt pathway or as a result of the expression of oncogenes including Ras, Src or Bcl-Abl (Pelicano *et al*., 2006).
- Cancer cells accumulate defects in the mitochondrial genome, leading to deficient mitochondrial respiration and ATP generation (Brandon *et al*., 2006; Chatterjee *et al*., 2006). In some cases, mitochondrial germline mutations have been shown to provide a genetic predisposition to cancer development (Brandon *et al*., 2006). In most cases, however, such mutations are acquired during or after oncogenesis. It appears that acquired mutations in mitochondrial DNA fall into two classes. A first category includes severe mutations that inhibit oxidative phosphorylation, increase the production of reactive oxygen species (ROS) and promote tumor cell proliferation. Another category of milder mutations could permit tumors to adapt to new microenvironments, especially when tumors progress and metastasize (Brandon *et al*., 2006).
- Cancer cells may adapt to decreased oxygen tension (hypoxia) that is characteristic of most, if not all solid tumors as the pre-malignant lesion grows progressively further from the blood supply. Thus, the way through which cells adapt to hypoxia would be to durably shut down mitochondrial respiration and to switch on glycolytic metabolism (King *et al*., 2006; Robey and Hay, 2006).
- In specific cases, mitochondrial enzymes can act as tumor-suppressor proteins whose mutation indirectly engenders aerobic glycolysis. The inactivating mutation of mitochondrion-specific proteins such as succinate dehydrogenase (SDH subunits B, C or D) and fumarate dehydrogenase is an oncogenic event, causing phaeochromocytoma (in the case of SDH

mutations) and leiomyoma, leiomyosarcoma or renal carcinoma (in the case of fumarate dehydrogenase mutations). The loss of function of succinate or fumarate deyhdrogenases results in the accumulation of fumarate and succinate in the cytosol, respectively. This, in turn, favors the activation of the transcription factor hypoxia-inducible factor (HIF) and hence generates a pseudohypoxic state accompanied by HIF-dependent reprogramming of the metabolism towards aerobic glycolysis (King *et al*., 2006).

In the last decade of the twentieth century, it was discovered that the mitochondria from cancer cells are often resistant against the induction of mitochondrial outer membrane permeabilization (MOMP), a process which mediates the intrinsic pathway of apoptosis (Zamzami *et al*., 1998; Green and Kroemer, 2004). MOMP is an extremely complex phenomenon that is regulated by proteins from the Bcl-2 family (Cheng *et al*., 2006), proteins contained in the permeability transition pore complex (Brenner and Grimm, 2006), proteins that affect mitochondrial dynamics (fusion and fission) (Alirol and Martinou, 2006; Cereghetti and Scorrano, 2006) and even transcription factors (such as the tumor-suppressor protein p53) that can translocate from the nucleus to mitochondria to stimulate MOMP (Moll *et al*., 2006). MOMP inhibition resulting in disabled apoptosis is important for the development of solid tumors. Moreover, it plays a major role in the development of hematological cancers, including in the switch from pre-neoplasia (such as low-grade myelodysplastic syndrome), in which cells spontaneously undergo apoptotic MOMP, to overt neoplasia (such as acute myeloid leukemia developing from a myelodysplastic syndrome), in which MOMP is inhibited (Fontenay *et al*., 2006).

The mechanistic link between aerobic glycolysis and MOMP resistance is not clear yet. The following hypothetical explanations may be put forward to explain the simultaneous presence of the Warburg effect and MOMP inhibition in cancer:

- During multistep oncogenesis, cancer cells could acquire metabolic alterations and MOMP inhibition independently. In this scenario, respiratory defects and increased ROS production, induced for instance by mitochondrial DNA mutations, would increase the likelihood of cancer cells to undergo apoptotic MOMP, and MOMP inhibition would be required to enhance the fitness of cells. Alternatively, suppression of the apoptotic pathway might be permissive for genomic instability (Zhivotovsky and Kroemer, 2004), and the Darwinian selection of genetically instable cells would then favor the accumulation of cells manifesting the Warburg phenomenon.
- In a putative one-step scenario, cancer cells might suppress the intrinsic (mitochondrial) apoptotic program through mechanisms that simultaneously engender the Warburg phenomenon. One suggestion in favor of this hypothesis is provided by the observation that mitochondrial DNA mutations may cause, through unknown mechanisms, a reduction of spontaneous or chemotherapy-induced apoptosis in cancer cells (Ohta, 2006). Another possible link between aerobic glycolysis and MOMP suppression is provided by hexokinase II that simultaneously increases glycolysis and inhibits MOMP when it associates with the voltage-dependent anion channel (VDAC) in the mitochondrial outer membrane. This interaction may be favored by the cancer-specific overexpression of mitochondrion-binding hexokinase isoenzymes (Mathupala *et al*., 2006) or by activation of the Akt pathway, which stimulates the interaction between hexokinase and VDAC (Robey and Hay, 2006). Another hint to a possible one-step scenario comes from the observation that members of the Bcl-2 family have apoptosis-unrelated functions (or 'day jobs') that may connect metabolic control and apoptosis regulation, although the details of this crosstalk remain largely unexplored (Cheng *et al*., 2006).

These facts and hypotheses do not constitute a merely academic playground. Rather, cancer-specific alterations in mitochondria and bioenergetics can be taken advantage of to develop two new strategies for antineoplastic therapy:

- First, it is conceivable to inhibit glycolysis for therapeutic purposes, either by targeting glycolytic enzymes (Pelicano *et al*., 2006) or by attempting to release hexokinase from its mitochondrial receptor, VDAC (Robey and Hay, 2006). Inhibitors of glycolytic enzymes that have been successfully used to slow down the growth in human tumors transplanted to mice include 3-bromopyruvate (an inhibitor of hexokinase) and oxythiamine (an inhibitor of the transketolase-like enzyme) (Pelicano *et al*., 2006). Some glycolytic inhibitors are being evaluated in clinical trials. This applies to 2-deoxyglucose (an inhibitor of the initial steps of glycolysis) as well as to lonidamine (TH-070), an inhibitor of glycolysis that also has direct pro-apoptotic properties.
- Second, it is conceivable to therapeutically induce MOMP (and hence apoptosis) in cancer cells by targeting mitochondrial membranes, members from the Bcl-2 family and components of the permeability transition pore complex (Debatin *et al*., 2002). MOMP inducers can be positively charged α-helical peptides, agents designed to mimic the BH3 domain of Bcl-2-like proteins, ampholytic cations, metals as well as steroid-like compounds. Such molecules can induce apoptosis by themselves (monotherapy) or facilitate apoptosis induction in combination therapies, bypassing chemoresistance against DNA-damaging agents, as demonstrated in preclinical studies (Fantin and Leder, 2006; Fontenay *et al*., 2006; Galluzzi *et al*., 2006). In addition, it is possible to design molecules that mimic the action of the pro-apoptotic mitochondrial protein Smac/DIABLO (Fulda and Debatin, 2006) or that release the pro-apoptotic mitochondrial protein AIF from its inhibition by heat shock protein 70 (HSP70) (Galluzzi *et al*.,

2006). One particularly seducing perspective would be to target MOMP-inhibitory proteins such as Bcl-2 causing them to switch from an anti-apoptotic to a pro-apoptotic function (Moll *et al*., 2006). Another fascinating possibility consists in the development of drugs that target cytotoxic agents first to a tumor-specific surface receptor and then to mitochondria to induce MOMP (Fantin and Leder, 2006). Several among the MOMP inducers or facilitators are currently undergoing clinical evaluation.

The long process that has led from the discovery of cancer-related mitochondrial abnormalities to the clinical exploration of novel anticancer therapies illustrates how the slow accumulation of fundamental knowledge eventually generates medically exploitable information. It can be anticipated that the readers of *Oncogene* as well as the authors of this Special Issue on 'Mitochondrial and Cancer' will help accelerating the pace of drug discovery and therapeutic application in this specific area of research.

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