On-line review: Energy metabolism and cancer

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Cancer and energy metabolism

In the early part of the 20th century, Otto Warburg originated a hypothesis that the cause of cancer is primarily a defect in energy metabolism. This hypothesis was based on the observation, since repeated and verified many times, that cancer cells show clear differences in energy metabolism when compared to normal cells.

Although Warburg's hypothesis has been overshadowed by support for the mutational theory of carcinogenesis (including the discovery of oncogenes and tumor suppressor genes) his original observations still have merit, and recent discoveries concerning the participation of mitochondria in the phenomenon of apoptosis raises again the question of the role of energy metabolism in the process of carcinogenesis. Cavalli and Liang [1], for example, suggest three ways that mitochondria could impact carcinogenesis: through mitochondrial DNA acting as transposable elements and modifying the nuclear genome, through mitochondrial maintenance of the tumorigenic phenotype, and through the role of mitochondria in apoptosis.

The mitochondrial genome

In terms of the mitochondrial genome, there is some evidence for the transfer of mitochondrial DNA into the nuclear genome, even in human cells [2]. There is also abundant evidence for alteration of transcription rates for the mitochondrial genome in cancer cells. For example, transcription of mitochondrial genes has been shown to occur at a lower rate in renal tumor cell lines, while transcription of nuclear genes involved in oxidative phosphorylation takes place at an increased rate [3]. One study has suggested similarities between fetal liver mitochondria and hepatoma mitochondria in terms of gene expression [4]. Among the genes showing increased transcription was the adenine nucleotide transporter gene ANT2, suggesting a connection between ATP uptake and development of the neoplastic phenotype. Other mitochondrial enzyme levels (NADH

cytochrome c reductase, succinate cytochrome c reductase, and cytochrome c oxidase) have been shown to change also during exposure to carcinogens, with cytochrome c oxidase levels remaining elevated even after discontinuation of exposure [5].

Mitochondrial DNA may also be more susceptible to mutation [6]. This may be due either to its supercoiled structure [7] or the paucity of repair mechanisms for mitochondrial DNA [8]. Another contributing factor may be the relatively constant exposure of mitochondrial DNA to free radicals produced by the respiratory chain. Finally, study of hamster kidney tumor cells indicates that there is a reduction in mitochondrial DNA in those cells, which may have implications for functional energy metabolism in those cells [9].

Modifications in glycolysis and the citric acid cycle

Since the days of Warburg, studies have continued to show alterations of functional energy metabolism in cancer cells. Among these differences are an increased rate of glycolysis [10] [11], and shifts in LDH isozyme patterns [12]. The high glycolytic rate maintained by both proliferating cells and tumor cells [13] may possibly be due to altered expression of enzymes. Glycolysis may be stimulated by availability of ADP (a rate-limiting step), and it has been suggested that either inefficient ATPase activity (the Na^+/K^+ ATPase in Ehrlich ascites tumor cells) leading to increased ATP hydrolysis [14] or increased ATPase activity may contribute to the increase in ADP levels [15].

LDH activity in tumor cells has been examined in several studies. Alteration of the Glycerol-3-phosphate and malate-aspartate shuttles (reducing transport of H^+ into the mitochondria) may require tumor cells to reoxidize NADH in the cytosol by LDH [16]. In one study, LDH activity was shown to be increased, and different isozyme patterns displayed in biopsies of brain tumor cells compared to normal tissue [12]. Additional studies have shown that glycolytic tumors show enzyme forms similar to those in fetal tissues [17]. Recently, c-Myc- regulated increases in LDH-A expression has been demonstrated in a variety of tumor cells including transformed fibroblasts, lymphoblasts, and Burkitt lymphoma cell lines [18]. Other studies, though, have shown reduced LDH levels in tumor cells [19].

Likewise, although hexokinase activity in human gliomas was shown in one study to be 2-4 times lower than normal rat brain tissue [20], hexokinase II isoform was

found to be elevated along with the glutamate I transporter in tumor cell line AH130 [21]. Other studies have also indicated high levels of hexokinase activity in cancer cells, and have shown that drugs that detach hexokinase from mitochondrial membranes may decrease cell viability [22]. According to Golshani-Hebroni and Bessman [23], binding of hexokinase to mitochondria may allow a continuous ATP flux and provide energy for phosphorylation of glucose, and thus and increased glycolytic rate. This, in turn, might stimulate protein synthesis (since several amino acids are products of intermediates of glycolysis and the Krebs cycle).

Effects on oxidative phosphorylation

In terms of mitochondrial energetics, glioma mitochondria have been reported to be tightly coupled (have a high RCR), but are fewer in number compared to normal cells [20]. Other studies have also identified similar differences between normal and neoplastic cells. For example, mitochondria from human hepatocellular carcinoma cells have been shown to have a decreased ATPase activity level which seems to be related to a decrease in ATPase content. This is accompanied by an increase in expression of the ATPase inhibitor protein IFI [24].

The membrane potential of mitochondria seems to be increased in some tumor mitochondria [25], a phenomenon that may be due to the tendency of tumor cells to accumulate lipophilic cations. Reduction of this increased membrane potential has been shown to lead to cell cycle arrest. This is particularly interesting in view of the evidence that different cell cycle phases may have different ATP levels, pointing to the possible existence of "energy checkpoints" at G1-S or G2-M [26]. Interestingly, glucose deprivation causes normal fibroblasts to arrest in G0/G1 but induces c-myc transformed cells to undergo apoptosis. This apoptosis is blocked by bcl-2 and induced by increased expression of LDH-A [27].

Other differences between tumor cell and normal mitochondria have also been identified. Mitochondria from leukemic leukocytes have been shown to use pyruvate as a substrate where normal leukocytes cannot [28]. This appears to be due to the absence of pyruvate dehydrogenase complex in normal leukocyte mitochondria [28]. Glutamine oxidation is a major source of energy in HeLa cells [29]. HeLa mitochondria apparently

lack NAD-linked stimulation of State 3, also, indicating an apparent defect in complex I [30].

Apoptosis

Given the role of mitochondria in apoptosis, several studies have investigated the potential links between differences in respiratory function and susceptibility to apoptosis (particularly chemotherapy-induced apoptosis). In one study, brain and breast tumor cells were treated with ethidium bromide to deplete mitochondrial DNA [31]. These cells, which retained the ability to undergo apoptosis, showed increased sensitivity to cytotoxic compounds, implicating mitochondria in chemosensitivity. Another study, however, indicated that HeLa cells lacking mitochondrial DNA were, in fact, less sensitive to adriamycin and photodynamic therapy-induced cell death [32]. In another study, cyanide induces apoptosis in terminally differentiated but not in undifferentiated PC12 cells [33].

The actions of TNF-α may also be related to mitochondrial function. It is well known that many tumor cells show resistance to TNF-α [34]. This resistance can be conferred by increased metallothionein levels [35], or by reduced hsp90 levels. Overexpression of hsp70 in murine fibroma cells has been shown to inhibit TNF-α-induced activation of phospholipase A [36]. Drug-resistant leukemic lines have increased respiratory rates and are more sensitive to killing by TNF-α; normal cells with increased respiration are also more susceptible to killing by TNF-α [37].

TNF-α has been shown to lower mitochondrial glutamate dehydrogenase activity [38], to stimulate lactate production, glucose uptake, and lactate dehydrogenase activity in Sertoli cells. Following exposure to TNF-α, mitochondria cluster around the nucleus. Without this translocation, cell death is delayed [39]. Other studies have shown that the cytotoxicity of TNF-α depends on the mitochondrial permeability transition [40].

Other studies have focused on the characterization of how cells which are resistant to chemotherapy, radiation, or photodynamic therapy differ from nonresistant cells in terms of mitochondrial function. For example, fibrosarcoma cells which are

resistant to photodynamic therapy are smaller, and produce more ATP than non-resistant cells [41]. However, oxygen uptake remains unchanged.

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