**Tumor Energy Metabolism**

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Reprogramming of the cellular metabolic activities to meet the energy demands imposed by cancer, involves a drastic redesign of energy metabolism. This involves normally, an increased contribution of glucose transport and glycolysis, a decreased efficacy of the mitochondrial tricarboxylic acid cycle and an increase in the supply of metabolic precursors for anabolic activities supporting the enhanced cellular proliferation. Optimal reprogramming of energy metabolism is currently thought to provide a selective advantage for the transformed cell, supporting survival in a hostile microenvironment, progression, invasion and metastasis. The mechanisms underlying accelerated glycolysis in fast growing tumor cells may involve; (i) Increase in the isoform expression of glycolytic enzymes and glucose transporters, (ii) Decreased expression of mitochondrial oxidative enzymes and transporters, (iii) Lowering of the mitochondrial content per cell, (iv) Inhibition of oxidative phosphorylation by glycolysis activation (Crabtree effect), (v) Increased amount of the natural inhibitor protein (IF1) of the mitochondrial ATPase and (vi) Higher sensitivity of mitochondrial DNA to oxidative stress.

In solid tumors in vivo, the additional role of limited perfusion through the caotic neovasculature and the resulting heterogeneous microenvironment must be additionally considered. In this lecture I shall provide an introduction to the mechanisms underlying the reprogramming of energy metabolism in tumors and their repercussions in MRS and MRI examinations, as well as on their potential use as therapeutic targets. Several review articles provide an adequate coverage of the topic.

Glucose transport and cytosolic aerobic glycolysis in tumors.

It was the Nobel Prize winner, Otto Warburg who first described for in the 1920’s that tumors produce larger amounts of lactate than normal tissues, even in the presence of sufficient oxygen. Enhanced aerobic glycolysis appears to rely on augmented transcription of all enzymes and transporters involved, as well as on a different isoenzyme profile. In particular, tumoral transformation includes the several fold overexpression of GLUT1 transporter, hexokinase I and II, Fosfofuctokinase 2, Aldolase, Phosphoglycerate mutase and fetal M2-pyruvate kinase.

High aerobic glycolysis provides important advantages for the tumor cell, including (i) Improved survival under fluctuating oxygen tensions, (ii) increased production of lactic acid and carbonic acid, acidifying the extracellular environment and favoring invasion and metastasis, (iii) increased pentose phosphate pathway activity, generating NADPH, required for increased reduced glutathion GSH detoxifying activities and nucleic acid and lipid biosynthesis, (iv) use of glycolitic intermediates, upstream of embryonic M2PK for anabolic reactions including the biosynthesis of glycogen and lipids. Increased GLUT1 transport provides additionally the basis for the $^{18}$Fluoro-deoxygluose (FDG) tumor detection by PET scanning. Indeed most tumors show enhanced $^{18}$FDG uptake by PET, a molecular imaging approach that has improved enormously clinical tumor detection and the follow up of therapy efficacy.

Mitochondrial Tricarboxylic Acid Cycle in tumors.

The ultimate role of the mitochondrial tricarboxylic acid cycle is to provide reducing equivalents to support oxidative phosphorylation at the mitochondrial electron transport chain. Pyruvate transport and pyruvate dehydrogenase activities are reduced in tumor cells, the later most probably though the increase in pyruvate dehydrogenase kinase I, an enzyme that inhibits PDH activity by phosphorylation. Moreover, the tumoral tricarboxylic acid cycle seems truncated after citrate synthase, favoring the extrusion of citrate to the cytosol to generate cytosolic acetyl-CoA for lipid synthesis and malate, which then returns to the
mitochondria for further metabolism. Long-chain fatty acid transport to the mitochondrial matrix (and subsequent β-oxidation) are also reduced in tumors, mainly because the reduction in carnitine palmitoyl transferase (CPT1A). Notably, even the lowest oxygen concentrations available in hypoxic areas, are sufficient to maintain the respiratory chain and cytochrome oxidase activity (Km O2 ca 1 μM). On these grounds, it seems that average ranges of tumoral hypoxia (8 < [O2] < 57 μM) do not limit, in most cases, the operation of the respiratory chain. Importantly, some tumors (sarcomas, lung carcinomas, breast cancer, skin melanomas, uterine cervix cancers) depict an oxidative phenotype, their bioenergetics relying mainly on oxidative energy metabolism rather than glycolysis.

**Role of the Hypoxia Inducible Factor HIF-1 and others.**

The Hypoxia Inducible Factor (HIF-1) is a transcription factor, known to play a central role coordinating the cellular responses to hypoxia. HIF-1 is a heterodimer consisting of constitutive, stable β subunits and unstable α subunits which are synthesized and degraded sequentially under normoxic conditions by oxygen dependent proll-hydroxylases and the ubiquitin ligase. HIF-1 becomes stabilized under hypoxic conditions triggering a phelotra of peliotropic gene expression effects. HIF-1 is also activated by growth factors and cytokines through the PI3 kinase/Akt/mTOR axis. HIF-1 increases anaerobic glycolysis by upregulating the glucose transporter isoform 1 (GLUT1), Hexokinase I and II, lactate dehydrogenase (LDH A) the monocarboxylate/proton extruding transporter, the Na+/H+ exchanger, carbonic anhydrase IX and XII, decreasing oxidative phosphorylation and β-oxidation. Other transcription factors as p53 and c-MYC provide complementary inhibition of oxidative phosphorylation and overexpression of some glycolytic enzymes.

**Therapies targeting energy metabolism.**

The differential charactereristics of tumor energy metabolism makes it an ideal target for antitumoral therapies, after adjusting inevitable side effects in normal cells. More precisely, increased glucose uptake and glycolysis may be inhibited by 2-deoxyglucose, a compound with radiosensitizing and chemosensitizig effects. Hexokinase (I and II), Pyruvate kinase and Lactate dehydrogenase may be inhibited by 3-bromopyruvate, somatostatin and its derivative TT-232, and siRNA. HIF may be inhibited by Echinomycin or through activation of PHDs by reversal of the fumarate or succinate mediated inhibition of PHDs. Finally, hypoxic regions may be targeted by increasing the cytotoxic effects of compounds enriched in hypoxic cells as Tirapazamine (TPZ) a hypoxia activated pro-drug. The use of ketogenic diets to decrease glucose anaerobic metabolism in the tumor in a therapeutic manner has also been proposed.

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**Bibliography**