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Intratumoral heterogeneity and intraclonal plasticity: from warburg to oxygen and back again

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See the article by Saga et al, on pages 1048–1056.

The golden age of biochemistry was characterized by the meticulous description of the main catabolic and anabolic cellular pathways.[1] During catabolism, for instance, under unfavorable environmental conditions, glucose and other immediate principles are degraded to produce energy, most significantly in the form of ATP. During anabolism, prior to cell division, energy is consumed to synthesize and assemble carbohydrates, proteins, and lipids.[1] The catabolic process of glucose utilization and the production of ATP may occur in normoxic conditions with the efficient production of ATP, or under hypoxic conditions leading to the production of pyruvate and lactic acid and yielding a much lower number of ATP molecules.

While these are biochemical features typical of normal cells, the classical studies by Otto Warburg[1] suggest that a reprogramming of metabolism occurs in most cancer cells. Warburg found that cancer cells use the anaerobic pathway (i.e., fermentation, resulting in the production of lactate) to metabolize glucose, even in the presence of a sufficient supply of oxygen. Why cancer cells should prefer the fermentation pathway when oxygen is abundantly available was not clear, but it was speculated to be related to the need for an anabolic metabolism to produce enough lipids, proteins, and carbohydrates to allow the safe division of cells during cancer proliferation.[2,3] We now know that solid tumors in general and gliomas in particular proliferate under hypoxic conditions,[4] so the shift from glucose metabolism to anaerobic conditions is probably required for cell proliferation in tumors.

Major progress in understanding the Warburg effect was made during the past decade, when the molecular pathways regulating this re-directed metabolism in cancer were described.[5] Importantly, the accumulating evidence suggests that genetic aberrations inherently related to cancer initiation and progression are important factors in the redirection of cancer metabolism in tumors.[6]

Inactivation of tumor suppressor genes plays an important role in the reprogramming of the metabolism of cancer cells, and some of these genes are partially responsible for the Warburg effect. For instance, p53 decreases glycolysis and increases the use of the tricarboxylic acid cycle and oxidative phosphorylation and, through p21 activation, regulates responses to abnormal redox potentials and high levels of reactive oxygen species.[6] Thus, loss of p53 function may lead to the Warburg effect. The loss of *PTEN*, another tumor suppressor gene in gliomas, and the concurrent increase of AKT-1 phosphorylation also favor the Warburg effect.[6]

On the other hand, the activation of hypoxia-inducible factors (HIFs)[7] and oncogenes such as *cMYC*[8,9] plays major roles in regulating the metabolism of cancer cells.[10] HIFs are regulated by the cellular hypoxic response, and among the HIF-regulated genes are 9 of the 10 enzymes that function in glycolysis and several other proteins that promote anabolism.[11] cMyc activates the transcription of more than a thousand genes that regulate many aspects of cellular biology, including cell metabolism. cMyc, which enhances the rate of protein synthesis, mitochondrial mass, and cell mass, may control both glycolysis and metabolism under aerobic conditions.[8] Therefore, HIFs and cMyc may compete or cooperate for the control of metabolic pathways in cancer cells under hypoxic conditions or with a better oxygen supply.[10]

Saga and colleagues, in this issue, report that they have identified two clonal populations in a mouse model of gliomas. Clone A displays rapid cell proliferation and relies on glucose uptake and anaerobic glycolysis and, accordingly, shows an abundance of activated hexokinase 2 (HK2), pyruvate kinase isozyme M2 (PKM2), and lactate dehydrogenase A (LDHA). In contrast, clone B is composed of slowly cycling stem cells and depends on mitochondrial respiration. The characteristics of these two populations immediately suggest that the master regulators in the metabolism of clones A and B are different: clone A is driven by HIFs because it adapts to survive under hypoxia, and clone B is driven by cMyc. From a therapeutic standpoint, this hypothesis is important because targeting either of these proteins exclusively would allow, in the best-case scenario, the complete eradication of one of the clones, possibly without affecting the natural history of the tumor due to the persistent growth of the other clone. Furthermore, Saga and collaborators report that even though the predominant feature of metabolism in each clone is different, cells from each clone can easily reverse their control of energy and anabolism by switching the main source of energy from glycolysis to oxygen-based processes and vice versa. Clearly, the plasticity of glioma cells and their potential to adapt to challenging situations are also present at the level of metabolic pathway

regulation.[12] Perhaps the silver lining of the data is the observation that HK2, PKM2, and LDHA are targets of both cMyc and HIFs[13,14] and, therefore, that inhibiting these downstream enzymes might efficiently choke cancer cells by simultaneously blocking—perhaps only partially—the regulation of glioma metabolism by two of these main master proteins.[15]

In summary, the report by Saga and colleagues offers solid evidence of the variable capability of glioma clones to regulate their metabolism through the mechanism described by Warburg. The authors also suggested that clones could switch from the Warburg effect to mitochondria-based energy production if the mechanisms controlling glycolysis are challenged. They provide evidence that the concept of cell plasticity at the metabolic level should be added to the multifaceted landscape of glioblastomas[12] and should always be kept in mind when therapeutic approaches or imaging systems that target glioma metabolism are being designed.

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