Cancer Metabolism as a Therapeutic Target: Finding the Right Target(s) in the Context of Tumor Heterogeneity, Evolution, and Metabolic Plasticity

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Since Otto Warburg first formulated his theory on the importance of metabolism in cancer, our knowledge of this process and of its complexity has expanded, as has our ability to target many metabolic pathways that are undoubtedly necessary for cancer proliferation.

“Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar. All normal body cells are thus obligate aerobes, whereas all cancer cells are partial anaerobes.” This is how Otto Warburg, at a 1966 meeting of Nobel laureates, described his theory on the origin of cancer as a metabolic disease.[1] The theory was based on the observation that, unlike the majority of normal cells, tumor cells derive energy via biochemical reactions characteristic “of the lowest living forms,” and which consist of the nonoxidative catabolism of glucose (glycolysis), the production of pyruvate, and the subsequent conversion of pyruvate to lactic acid. This biochemical process, named anaerobic respiration, or fermentation, generates several end products, including lactic acid itself, which are now known to contribute to various aspects of tumor progression.

Warburg’s pioneering work on the metabolism of cancer cells gave rise to important principles for the contemporary development of therapeutic drugs and diagnostic techniques. The extraordinary avidity of tumor cells for glucose serves as the basis of positron emission tomography (PET). In addition, drugs that target various metabolic pathways are currently being proposed as antitumor agents. Furthermore, evidence now suggests that metabolic reprogramming is not a “passenger” phenomenon in tumors, but that it actually drives the transformed phenotype by promoting adaptation in the nutrient- and oxygen-restricted microenvironment, by building tumor biomass and suppressing apoptosis and host immune responses. Undoubtedly, the idea that tumor cells have unique and well-defined metabolic needs is an attractive one, and is likely to generate new treatment options.

In this issue of ONCOLOGY, Drs. Batra, Rosen, and Shanmugam offer an insightful review of various therapeutic strategies aimed at perturbing the metabolism of tumor cells, identifying three major points of potential attack: 1) enzymes regulating glycolysis, 2) glucose transporters, and 3) compensatory metabolism. While the review covers a number of important studies underscoring the fact that chemical or genetic inhibition of various metabolic enzymes reduces tumor growth, it does not mention important open questions whose resolutions are key to moving the field forward. For example, metformin, a biguanide used for the treatment of type 2 diabetes, has received particular attention in the field and in this review. It has been proposed that metformin can improve cancer survival and prognosis, as well as potentiate antitumor responses when used in combination with other agents. However, many studies assessing cancer risk in diabetic patients treated with metformin are retrospective, nonrandomized, and as noted by others,[2] do not take into account the fact that the diagnosis of diabetes implies increased patient surveillance—and hence earlier cancer detection—which could explain the improved survival rates. Furthermore, some retrospective studies have actually raised doubts about the notion that metformin reduces cancer risk and mortality.[3] On the whole, the studies up until now that have attempted to correlate metformin administration with cancer outcomes have yielded conflicting results.[4] More importantly, though, the doses at which metformin exerts antitumor activity in laboratory settings are—stunningly—50- to 200-fold higher than those used for the treatment of diabetes.[5] There have only been a few exceptions in which the effects of metformin were seen at doses comparable to those used in diabetic patients. [6] Thus, metformin-mediated antitumor activity, if confirmed, will likely require much more aggressive treatment protocols, which might not be at all practicable because of side effects.
An even more critical issue is that the targeting of the tumor cell metabolism, as described by Batra and colleagues, will likely face the same challenges and difficulties encountered by conventional chemotherapeutic agents. I would argue that answering the following questions is of the utmost importance for advancing metabolic inhibitors to the next step of rational and effective therapeutic interventions:

- Are changes in the tumor metabolism similar across multiple cancer types?
- What impact does the phenomenon of resistance have on metabolic inhibitor-based therapies?
- Are tumors metabolically heterogeneous (as they are genetically), and if so, does this affect treatment outcomes?
- Can we measure cancer- or patient-specific metabolic alterations that would in turn guide appropriate therapeutic choices in a time- and cost-effective fashion?

The extent of metabolic reprogramming that occurs in tumor cells goes far beyond the glycolytic behavior, encompassing nearly all metabolic routes, including glutaminolysis, lipogenesis, fatty acid oxidation, gluconeogenesis, and the pentose phosphate pathway. Certain types of tumors are even strictly dependent on oxidative phosphorylation, in contradiction to Warburg’s original hypothesis.[7,8] Still, we do not entirely understand whether the specific metabolic requirements of tumor cells are dictated by alterations of the activity of oncogenes and tumor suppressors, which, as we know, occur in specifically defined cancer types, or whether they change dynamically during tumor evolution. These gaps in knowledge arise from the use of artificial experimental systems to study metabolic reprogramming; for the most part, these have involved the use of tissue culture cells or have been tumor transplantation experiments performed in nude mice. In this latter case, the metabolism of ensuing tumors is assessed outside of the “physiological” site of origin and can be followed only for a limited period of time. Nevertheless, there are important examples where the tumor metabolic reprogramming has been monitored in a dynamic fashion in murine models of cancer initiation, progression, or regression, following oncogene activation and then withdrawal.[9,10] These studies are paradigmatic in several ways. They have shown that different oncogenes, such as MYC or MET, each rely on distinct metabolic pathways for induction of tumorigenesis. Furthermore, the same oncogene may affect the metabolic requirement of cancer cells in a substantially different fashion depending on the tissue of origin, resulting in distinguishable differences between, for example, the lung and the liver.

Thus, as described by Batra and colleagues, there is indeed a growing list of metabolic inhibitors that might hypothetically be useful to attack many tumors, but ultimately it is an understanding of the differences in the metabolic profiles, dependent on the presence of a dominant “driver” genetic alteration, that will provide the next critical step toward the appropriate selection of the most effective category of metabolic inhibitor. The numerous examples listed by Batra and colleagues of targeting the tumor cell metabolism are not rationalized in accordance with these criteria. How, then, do we identify tumor-specific or patient-specific metabolic alterations? Unfortunately, while PET imaging provides a crude assessment of the general avidity of tumor cells for glucose, it does not offer any information on how glycolysis or other metabolic pathways are utilized inside tumor cells. The use of other technologies, such as magnetic resonance spectroscopy (MRS), to measure the concentration of specific metabolites noninvasively in tumors, in conjunction with metabolomic profiling of the serum or urine, may guide the selection of appropriate type(s) of inhibitors in a tumor- or patient-specific fashion.

Finally, Batra and colleagues touch on the concept of “compensatory” metabolism, mentioning that inhibitors targeting glycolysis might trigger metabolic reprogramming toward multiple other pathways. This important point perhaps deserves a more critical discussion. Tumors are extremely dynamic and heterogeneous, both genetically and metabolically. Metabolic heterogeneity was demonstrated in cervical carcinomas and correlated strongly with invasiveness and unfavorable prognosis.[11] Therefore, the targeting of one specific metabolic pathway will most certainly impose a great selective pressure for the emergence of resistant cells. Notably, the antitumor activity of caloric restriction that deprives tumors of energy is entirely abrogated by activation of the PI3 kinase or by inactivation of PTEN.[12] Furthermore, while the growth of many cancers is inhibited by dietary restriction of glucose, the same dietetic regimen can paradoxically lead to the appearance of more aggressive tumors if an isoform of protein kinase C is lacking, or if certain mutant forms of p53 are overexpressed,[13,14] suggesting that tumors that emerge after metabolic block might acquire even more aggressive behavior.

Since Otto Warburg first formulated his theory on the importance of metabolism in cancer, our knowledge of this process and of its complexity has expanded, as has our ability to target many metabolic pathways that are undoubtedly necessary for cancer proliferation. However, important
questions remain: how can we best strategize the clinical applications of metabolic inhibitors, and how effectively and for how long can they control tumor growth?

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