Review

Cancer Research

Nature and Nurture: What Determines Tumor Metabolic Phenotypes?

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Abstract

Understanding the genetic basis of cancer has led to therapies that target driver mutations and has helped match patients with more personalized drugs. Oncogenic mutations influence tumor metabolism, but other tumor characteristics can also contribute to their metabolic phenotypes. Comparison of isogenic lung and pancreas tumor models suggests that use of some metabolic pathways is defined by lineage rather than by driver mutation. Lung tumors catabolize circulating branched chain amino acids (BCAA) to extract nitrogen for nonessential amino acid and nucleotide synthesis, whereas pancreatic cancer obtains amino acids from catabolism of extracellular protein. These differences in amino acid metabolism translate into distinct pathway dependencies, as genetic disruption of the enzymes responsible for utilization of BCAA nitrogen limits the growth of lung tumors, but not pancreatic tumors. These data argue that some cancer metabolic phenotypes are defined by cancer tissue-of-origin and environment and that these features constrain the influence of genetic mutations on metabolism. A better understanding of the factors defining tumor nutrient utilization could be exploited to help improve cancer therapy. *Cancer Res; 77(12); 3131–4. ©2017 AACR.*

Introduction

When the first chemotherapy was developed to treat cancer, new drugs were identified through a combination of happenstance, observation, and deductive reasoning. Promising compounds were refined in the clinic, with effective regimens determined empirically and patients selected based on having a tumor with a specific site-of-origin and histologic classification (1). Early success came in the treatment of hematologic malignancies, with drugs such as the antifolates achieving stunning, but ultimately temporary remissions in some leukemias (2). With a limited understanding of these diseases at a molecular level, or how the drugs worked, physicians developed combination therapy regimens based on nonoverlapping toxicities to achieve longer remissions and even cures, although many patients were pushed to the brink of death by these treatments (1).

In the last three decades, the discovery of oncogenes and tumor-suppressor genes resulted in an improved understanding of how genetic events cause cancer, and dramatically shifted the approaches used to develop new cancer therapies (3, 4). The realization that cancer relies on mutations to corrupt existing pathways controlling development, cell growth, and proliferation suggested these same pathways might be targeted to treat cancer (5, 6). This resulted in the current paradigm where identifying the genetic changes driving tumor development leads to interventions that target vulnerabilities created by those mutations.

In some cases, identification and targeting of genetic drivers have been successful. For example, fusion oncogenes such as *BCR-ABL* in chronic myelongenous leukemia and *anaplastic lymphoma kinase tyrosine kinase receptor* (*ALK*) fusions in lung adenocarcinoma present unique druggable targets that have been exploited clinically with great effect (7). Tyrosine kinase inhibitors have also been effective therapies in cancers driven by mutations that activate growth factor signaling (7). However, it has been challenging to extend this paradigm to treat all cancers in part because tumor-suppressor mutations play a significant role in driving tumorigenesis, but remain difficult to target therapeutically (8). Nevertheless, there is hope that the broad application of tumor sequencing, even if it fails to identify directly targetable mutations, can further personalize treatment approaches to benefit a broader swath of patients (6, 9).

An alternative approach to developing therapies is to target pathways activated downstream of driver mutations or pathways that enable tumor phenotypes. Cancer metabolism represents one such area, although to date the most successful drugs targeting metabolism are chemotherapies that inhibit pathways involved in nucleotide metabolism (10). Changes in metabolism represent some of the first differences described between cancer and normal tissues, dating to Otto Warburg's initial observations that cancer tissues increase glucose uptake and have a tendency to ferment glucose despite the presence of oxygen (11). More recent work has connected increased glucose metabolism to oncogene activation (12), setting the stage for numerous studies detailing the role of oncogenes and tumor suppressors in regulating cancer cell metabolism to promote the accumulation of biomass necessary for enhanced proliferation (13–15). Because drugs are lacking to specifically treat patients with tumors harboring many mutations in genes such *KRAS* and *TP53*, one hope is to identify other pathway dependencies in these cancers (16–18). Both *KRAS* and *TP53* mutations result in metabolic changes, and efforts to target the downstream metabolic effects of these events have

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demonstrated preclinical potential and led to development of drugs in current clinical trials (19, 20). Yet there are also data to suggest that these approaches will not be successful in all *KRAS*-mutant tumors, raising the possibility that factors other than tumor genetics can contribute to cancer metabolic dependencies (21).

The majority of metabolic changes in cancer have been characterized in culture; however, nutrient availability differs dramatically between culture, tissues, and even within tissues or tumors (22, 23). Indeed, altering the culture environment changes metabolic preferences (24–26) and environment can influence the metabolic phenotypes of cancer cells with differences observed for the same cells in culture and in tumors (21). These studies argue that understanding the metabolic constraints on cancer cells within the native tumor environment will be important for identifying metabolic drug targets.

The Role of Tissue-of-Origin and Environment in Shaping Cancer Metabolism

Analysis of gene expression data from 22 different cancer types and paired normal tissue showed that cancer metabolic gene expression more closely resembles that of the parental tissue than it does of other cancers (27). These data argue that tumors adapt the normal metabolic program of their tissue-of-origin to support inappropriate cell proliferation. In fact, expressing different oncogenes in the same tissue (*MYC* and *MET* in the liver) as well as the same oncogene in different tissues (*MYC* in liver and lung) had distinct effects on glucose and glutamine metabolism, suggesting that both oncogene and tissue type contribute to the metabolic phenotype of cancers (28).

Elevated plasma branched chain amino acids (BCAA) were identified as an early event in pancreatic ductal adenocarcinoma (PDAC) in both mice and humans, a whole body metabolic change that results from increased muscle protein turnover in individuals with this cancer (29). To determine whether the BCAA elevation was unique to PDAC, isogenic mouse models of PDAC and non–small cell lung carcinoma (NSCLC) that are driven by both activating *Kras* mutations and *Trp53* disruption were analyzed, and in contrast to mice with early PDAC, mice with early NSCLC had decreased levels of plasma BCAAs (30). Tracing the fate of isotope-labeled BCAAs in animals with lung or pancreatic cancer showed that NSCLC tumors took up more free BCAAs compared with normal lung tissue, whereas PDAC tumors had decreased BCAA uptake compared with normal pancreas. Unlike PDAC tumors, NSCLC tumors incorporated these amino acids into proteins and used BCAA-derived nitrogen for nonessential amino acid and nucleotide synthesis. In contrast, PDAC tumors rely on the uptake and metabolism of protein in their environment to acquire amino acids (31) as well as nutrients secreted by stromal cells (32, 33). These findings argue that some metabolic phenotypes are dictated by the tissue-of-origin or environment, outside the purview of the initiating driver mutations. For BCAA metabolism, the metabolic preferences between lung and pancreatic cancer were reflected in enzyme expression differences (30). Importantly, there was no selection against expression of genes allowing BCAA metabolism in PDAC tumors, as activation of BCAA metabolism in PDAC tumor cells had no effect of tumor growth. However, deletion of *Bcat1* and *Bcat2*, enzymes involved in obtaining nitrogen from BCAAs, prevented NSCLC tumor formation *in vivo*, but had limited effect on PDAC tumor growth, arguing that some dependencies are hard-wired based on tumor lineage.

Implications and Perspective

Although most cells in an animal have identical genomes, each tissue and its composite cell types serve a specific physiologic role for the organism. These distinctions and functionalities are conferred by the differential expression of genes and the regulation of gene products. Among these gene products are a subset of all metabolic enzymes, which define the metabolic network available to support cell activities. A corollary to this is that various nutrient levels will vary by location, and levels of available nutrients will also affect which metabolic pathways are utilized by different cell types (34). In other words, there is a reciprocal interplay between the intrinsic set of metabolic enzymes expressed and their regulation by cell signaling, and extrinsic factors such as nutrient availability, which together shape the unique metabolism of each tissue (Fig. 1).

Tissue identity with regards to metabolism, then, can be defined by the core set of expressed metabolic enzymes that form pathways cells rely on to support their function. When challenged with changes in the environment such as nutrient limitation or hypoxia, different tissues can engage adaptive metabolic programs, such as lipid and protein scavenging (24, 25, 35) to compensate, and these responses also contribute to the metabolic identity of normal and disease tissues. Metabolic flexibility, however, is not infinite, and extreme or prolonged changes in nutrient availability or intrinsic limitations of the cell to adapt to stress will constrain metabolism in all cells. In addition, the limits of adaptability are unlikely to be the same across all cells and tissues.

Mutations in oncogenes and tumor suppressors that lead to tumor initiation and progression will act on the metabolic network within the cell, and thus the effects of these mutations on metabolism are subject to a set of constraints that are defined at least in part by tissue lineage and environment. These growth-promoting mutations may alter metabolic pathway activity, such as increased glycolysis or nutrient scavenging (24, 25), but do not drive convergence of tumor metabolism to a common proliferative program as tumors more closely resemble their parental lineage (27). Only those pathways that remain available based on the given tissue-of-origin can contribute to the tumor metabolic network and use available nutrients to generate a tumor.

Although selection based on genetics remains the current paradigm to develop new cancer treatments, other factors may be better for identifying patients for drugs targeting metabolism. In fact, tumor genetics has not been a successful way to find patients likely to respond to chemotherapies that target nucleotide metabolism, and giving these drugs based on tissue-of-origin has been the standard practice for decades (36). Some newer agents targeting metabolism also act on cancers in a way that is agnostic to cancer genotypes (10). Consistent with this idea, the metabolic constraints imposed by tumor lineage and environment, in addition to mutation status (28, 30), should be considered when examining potential pathways for therapeutic

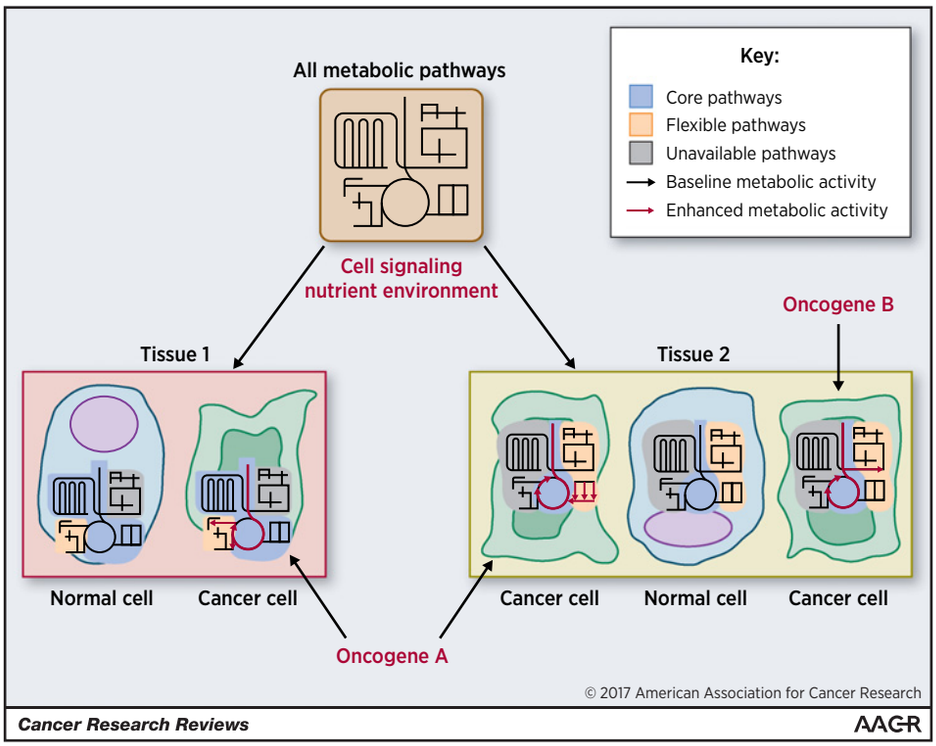

Figure 1.
Tissue-of-origin constrains the metabolic network available to tumors. Each tissue expresses enzymes, which form a core metabolic network that is utilized to support the physiologic function of the tissue. This network is subject to regulation by cell signaling, as well as nutrient and metabolite levels that are influenced by the tissue environment. Most cells maintain some metabolic flexibility and employ additional pathways in response to stress. Oncogenic mutations reshape metabolism to support tumor growth, but their effects are limited by network constraints imposed by tissue-of-origin and by available nutrients.

targeting. Furthermore, identifying those metabolic pathways that are most constrained and/or less flexible within specific tumors is critical to achieve both efficacy and a therapeutic window in patients.

The overall set of intrinsic metabolic constraints imposed by the tissue-of-origin and altered growth signaling, together with the extrinsic metabolic constraints imposed by the environment, may be more apparent *in vivo*. This could be because the types and quantities of nutrients available to cancer cells in tissues are more restricted than they are in culture. Thus, developing cell culture systems that better reflect the nutrient limitations of tumors (37, 38) or studies of tumors *in vivo* (39) may be a more reliable way to identify cancer metabolic targets. Furthermore, whole body metabolic investigations may reveal potential targets outside the tumor itself when cooperation between nontumor tissues are involved.

Cancer genetics, tumor microenvironment, and tissue-of-origin can all contribute to tumor metabolic dependencies. Both the intrinsic, genetic nature and the extrinsic, nurturing environment define normal tissues and the tumors that arise from them. Understanding the precise contributions of each factor across different cancers holds the best hope for matching the right patients with drugs targeting metabolism and to extend this avenue of precision-medicine to a broad array of cancers.

Disclosure of Potential Conflicts of Interest

M.G. Vander Heiden has ownership interest (including patents) in Agios Pharmaceuticals and is a consultant/advisory board member for Agios Pharmaceuticals and Aeglea Biotherapeutics. No potential conflicts of interest were disclosed by the other authors.

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