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Review

Targeting cancer's metabolic co-dependencies: A landscape shaped by genotype and tissue context☆

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ABSTRACT

Tumors cells reprogram their metabolism to fuel rapid growth. The ability to trace nutrient fluxes in the context of specific alterations has provided new mechanistic insight into the process of oncogenic transformation. A broad array of complementary genetic, epigenetic, transcriptional and translational mechanisms has been identified, revealing a metabolic landscape of cancer. However, cancer metabolism is not a static or uniform process, including within a single tumor. Tumor cells adapt to changing environmental conditions, profoundly shaping the enzymatic dependencies of individual cells. The underlying molecular mechanisms of adaptation, and the specific interactions between tumor genotype, oncogenic signaling, and tissue/biochemical context, remain incompletely understood. In this review, we examine dynamic aspects of how metabolic dependencies develop in cancer, shaped both by genotype and biochemical environment, and review how these interlaced processes generate targetable metabolic vulnerabilities. This article is part of a Special Issue entitled: Cancer Metabolism edited by Dr. Chi Van Dang.

1. Introduction

Altered cellular metabolism is one of the most characteristic phenotypic changes that occurs during the process of tumor formation, progression and drug resistance. Beginning with the pioneering work of Otto Warburg in the 1940's and culminating in significant and rapidly accelerating progress in the past decade, a picture has begun to emerge of how cancer cells take up and use nutrients to drive cell autonomous growth and rapid adaptation to changing conditions. This line of inquiry has: 1) identified new drug targets; 2) shed light on interplay between mutated genes and altered metabolism; 3) highlighted the diversity of genetic, epigenetic, transcriptional, translational, and post-translational mechanisms that regulate tumor cell metabolism; 4) provided new insight into the flexibility of metabolic pathways that cancer cells use and 5) revealed the heterogeneity of the metabolic pathways used in different parts of a tumor [1–3]. These discoveries have moved the field beyond the initial phase of characterizing the metabolic landscape of tumor cells, into a new and exciting era of trying to understand how it works, with the ultimate goal of using this information to develop more effective cancer treatments.

Clear lessons have begun to emerge, framing the challenge ahead. Cancer cells stop behaving like normal cells in a multicellular organism and start behaving like single celled entities [3,4]. A molecular basis for this switch to cell autonomous metabolism and proliferation has also become clearer. Gain of function mutation and gene amplification of key components of the growth factor system, the very instructional cues that normal cells require for nutrient uptake and utilization, are frequent events in cancers of almost all histological types, providing a genetic basis for cell autonomous metabolism. How specific genetic alterations interact with the tumor microenvironment remains an open question. How does the biochemical milieu interact with corrupted growth factor signaling pathways to influence metabolic fluxes? How do they enable rapid adaption to changing conditions? What vulnerabilities do these adaptations expose and can they be targeted? The

Abbreviations: AML, Acute myeloid leukemia; BBB, blood-brain barrier; BCAAs, branched-chain amino acids; ecDNA, extrachromosomal DNA; FH, fumarate hydratase; GBM, glioblastoma multiforme; HIF1/2, hypoxia-inducible factor 1/2; IDH1/2, isocitrate dehydrogenases 1/2; LXR, liver X receptor; MTA, *S*-methyl-5′-thioadenosine; MTAP, methylthioadenosine phosphorylase; mTORC1/2, mammalian target of rapamycin complex 1/2; NSCLC, non-small cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; PHD, prolyl hydroxylase; PRMT5, protein arginine methyltransferase 5; R-2-HG, R(−)-2-hydroxyglutarate; ROS, reactive oxygen species; SCNA, somatic copy number alteration; SDH, succinate dehydrogenase; TCA, tricarboxylic acid; xCT, cystine-glutamate antiporter system xc-; α-KG, α-ketoglutarate

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challenge in the field is moving from the critical step of developing a biochemical map of cancer metabolism, towards a dynamic adaptive view of how tumor metabolism changes over the life of a cancer and in response to local cues, and how it can be therapeutically exploited. In this review, we focus on the dynamic aspects of how metabolic dependencies develop in a tumor shaped both by genotype and biochemical environment, and how these interlaced processes generate targetable metabolic vulnerabilities.

2. Gene amplification, deletion and mutation drive metabolic phenotypes

Nearly 90 years ago, Otto Warburg [5] showed that most cancer cells avidly consume glucose and convert it into lactate even in the presence of abundant oxygen, unlike normal cells that metabolize glucose to carbon dioxide via mitochondrial oxidative phosphorylation. The Warburg effect is a biochemical adaptation that benefits cancer cells by enabling them to generate the metabolic ingredients needed for building biomass for cell proliferation, while still yielding sufficient energy to power cellular reactions. Warburg's observation was the first, and probably the seminal demonstration that cancer cells have an altered metabolic phenotype. However, tumor cells also display major shifts in other metabolic facets, including in amino acid, nucleotide and lipid metabolism. Initially, a molecular basis for these biochemical shifts was not clear, but extensive research, particularly over the past 10 years, a molecular picture has emerged– common genetic alterations in tumor cells drive specific metabolic shifts.

The first major lesson to emerge, is that common genetic alterations in genes that encode core proteins in the growth factor signaling cascade, play a central role in cancer metabolic reprogramming. In multicellular organisms, growth factor signaling instructs cells to take up nutrients and direct them towards biomass generation, coupling nutrient flux with the transcriptional, translational and post-translational programs that regulate cell proliferation. In cancer, amplification and gain of function mutations of genes whose protein products are key components of the growth factor signaling system, including cell surface receptor tyrosine kinases such as EGFR, and downstream effectors PI3K and Akt, is a relatively common event, providing a mechanistic basis for the transition of tumors to cell autonomous nutrition. These activating lesions are often complemented by genetic deletion and/or loss of function mutations of PTEN, a suppressor of PI3K signaling (Fig. 1). This signaling cascade regulates the level and activity of nutrient uptake, such as levels of glucose transporters and helps determine which biosynthetic pathways will be utilized [6–12]. Other genes whose protein products are involved in nutrient uptake and utilization, including the signaling protein Ras and the transcription factor c-Myc, are also commonly amplified and or mutated in cancer [13,14], and determine other nutrient fluxes including glutamine and other amino acid uptake [15–21] and opportunistic pathways that have recently been described [22–25] (Fig. 1).

The second major lesson is that common genetic alterations in tumor cells co-opt signaling networks and transcriptional programs that control cellular metabolism through cooperative and tightly coordinated interactions. For example, recent work in glioblastoma, which is highly glycolytic [26], demonstrates how a genetic alteration in EGFR, which occurs in a high fraction of glioblastoma [27,28], drives glycolysis through three complementary pathways that integrate EGFR signaling through the PI3K pathway, with dysregulation of c-Myc. First, EGFRvIII, through and Akt-mTORC1-dependent pathway, leads to the splicing of the Myc interacting partner Max, generating a gain of function protein, Delta Max, that potently drives glycolysis in a c-Myc dependent fashion [29]. Second, EGFRvIII remodels the enhancer landscape of glioblastoma cells, potently driving SOX9 and FOXG1 to regulate c-Myc-dependent transcription [30]. Lastly, EGFRvIII promotes glycolysis in tumor cells through mTORC2-dependent acetylation of FoxO1 and subsequent regulation of c-Myc protein levels [31].

EGFRvIII-dependent metabolic reprogramming is not restricted to glycolysis. Cancer cells require not only glucose, but also amino acids, nucleotides and lipids in order to proliferate. Recent work sheds some light on how the same genetic alterations that regulate glycolysis, also coordinately regulate these other metabolic processes. For example, EGFRvIII coordinately regulates fatty acid synthesis through and Akt-SREBP1-dependent mechanism [32], and also controls intratumor cholesterol levels via an LDLR-dependent mechanism [33,34]. Considering the recent work linking c-Myc and mTORC1 with one carbon metabolism, amino acid regulation and nucleotide biosynthesis [35–38], it is possible that further studies will reveal an even more tightly regulated integration of a diverse set of metabolic events downstream of EGFRvIII in glioblastoma.

3. Metabolic co-dependency shaped by environment

A purely genotype-based view of cancer metabolism is missing half the picture. The metabolic phenotype of tumors is determined not only by the genotype of the cancer cells that it contains, but also by non-cell-autonomous environmental factors, such as nutrient availability, tissue context and biochemical environment. The interactions between these components determine the tumor's metabolic preferences and range of adaptive possibilities. It also generates metabolic dependencies of cancer cells that may be actionable drug targets.

3.1. Nutrient availability in microenvironment determines metabolic dependencies

Environments supply cells diverse nutrients, such as glucose, amino acids, lipids, O_2, and macromolecules, which the cells then use to produce ATP, synthesize macromolecules and modulate redox state for cell survival and proliferation (Fig. 2A). Cancer cells flux abundant nutrients, such as glucose, glutamine and fatty acids, for ATP and Intermediate metabolites [4]. Except for the essential amino acids and fatty acids, cancer cells can synthesis most of required metabolites from the intermediates. Lipids and amino acids of cancer cells can be achieved through synthesis from intermediates or import from environments. Nucleic acids of cancer cells are synthesized from glucose, glutamine and some non-essential amino acids. Under nutrient deprivation condition, cancer cells gain metabolic flexibility by remodeling their metabolic pathways to use alternative nutrient source from environment for cell survival and proliferation, which allows cancer cells to bypass the nutrient limitation and renders them dependent on available nutrients [39]. The tumor cell must balance what is available in the environment vs. what must be synthesized, and at what energetic cost. Thus, nutrient availability in microenvironment is a major factor in determining the metabolic state of tumor cells and its potential metabolic vulnerabilities.

The richness of potential biochemical interactions, the ability of enzymes to work in two directions, and the potentially wide array of metabolites make it very difficult to predict what a cancer cell will do, without considering its environmental context. For example, acetate and lactate are important alternative carbon sources for cancer cells. Glucose and glutamine, two main nutrients and substrates for metabolism, provides cancer cells major source of carbon. Acetyl-CoA, a precursor for fatty acid and cholesterol de novo synthesis, can be mainly acquired from glucose and glutamine though glycolysis and α-ketoglutarate, and represents a central node of carbon metabolism. Acetate was found as an important bioenergetic substrate for human glioblastoma and brain metastases [40]. Under low-oxygen and lipid-depleted conditions, cancer cells activate their utilization of acetate from microenvironments, providing one alternative source of acetyl-CoA for lipid synthesis and histone acetylation [41]. Depletion of Acetyl-CoA Synthetase 2 (ACSS2), one main enzyme to convert acetate to acetyl-coA and upregulated in a large proportion of tumors, inhibits cancer cells growth and suppresses tumor development [42]. Lactate