Convergence of Cancer Metabolism and Immunity: an Overview

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Abstract

Cancer metabolism as a field of research was founded almost 100 years ago by Otto Warburg, who described the propensity for cancers to convert glucose to lactate despite the presence of oxygen, which in yeast diminishes glycolytic metabolism known as the Pasteur effect. In the past 20 years, the resurgence of interest in cancer metabolism provided significant insights into processes involved in maintenance metabolism of non-proliferating cells and proliferative metabolism, which is regulated by proto-oncogenes and tumor suppressors in normal proliferating cells. In cancer cells, depending on the driving oncogenic event, metabolism is re-wired for nutrient import, redox homeostasis, protein quality control, and biosynthesis to support cell growth and division. In general, resting cells rely on oxidative metabolism, while proliferating cells rewire metabolism toward glycolysis, which favors many biosynthetic pathways for proliferation. Oncogenes such as MYC, BRAF, KRAS, and PI3K have been documented to rewire metabolism in favor of proliferation. These cell intrinsic mechanisms, however, are insufficient to drive tumorigenesis because immune surveillance continuously seeks to destroy neo-antigenic tumor cells. In this regard, evasion of cancer cells from immunity involves checkpoints that blunt cytotoxic T cells, which are also attenuated by the metabolic tumor microenvironment, which is rich in immuno-modulating metabolites such as lactate, 2-hydroxyglutarate, kynurenine, and the proton (low pH). As such, a full understanding of tumor metabolism requires an appreciation of the convergence of cancer cell intrinsic metabolism and that of the tumor microenvironment including stromal and immune cells.

Key Words: Cancer, Metabolism, Tumor suppressor, Oncogenes, Immunometabolism

INTRODUCTION

Almost 100 years ago Otto Warburg, through studying human and animal cancer tissue slices *ex vivo*, found that tumors tend to convert most glucose to lactate through fermentation, which ordinarily would only occur under hypoxic conditions (Koppenol *et al*., 2011). Pasteur, through carefully executed experiments with baker yeast, found that the production of alcohol – significantly important for the French wine industry – was suppressed in the presence of oxygen that mediates oxidative metabolism of sugary nutrients (Pasteur, 1879). Pasteur's observations are now known as the Pasteur effect, while the observations of Warburg is now regarded as the Warburg effect or the propensity of cancer cells to convert glucose to lactate despite the presence of oxygen. In this regard, while Warburg acknowledged in published work that oxidative metabolism played a role in maintenance of tumors, he subsequently suggested that damaged mitochondrial func-

tion leading to glycolysis is fundamental and hence causal for tumorigenesis. This simple conceptual framework, however, over-simplifies the complexity of cancer, which is now known to consist of at least 200 diseases owing to the diversity of tissues that are amenable to cancer formation (Alexandrov *et al*., 2013).

Each normal tissue and organ serves a specific function relying on the epigenetic and metabolic make up of that tissue or organ driven by the same germline genome. For example, the liver is a highly metabolic organ given its central role in processing nutrients absorbed through the gastrointestinal track. It functions to process, store and distribute nutrients and plasma proteins for the rest of the body. By contrast, the kidney, which has evolved to rid the body of metabolic waste products, has specific tissues and specialized cells that excrete toxins into urine and re-absorb precious nutrients as well as provide pH homeostasis for the body. The tumors that arise from these different tissues are distinctly different genomically, epigenom-

Fig. 1. Diagram of central metabolic pathways involved in cell growth and proliferation. Ac-CoA: acetyl-CoA, ACYL: ATP citrate lyase, ARG: arginase 1, ASL: argininosuccinate lyase, ASS1: argininosuccinate synthase 1, CAD: carbamoyl-phosphate synthase, GLS: glutaminase, GLUD: glutamate dehydrogenase 1, GOT2: glutamic-oxaloacetic transaminase or aspartate aminotransferase, HK2: hexokinase 2, LDHA: lactate dehydrogenase A, PFK: phosphofructokinase, PK: pyruvate kinase, SHMT1/2: serine hydroxymethyltransferase 1/2, SLC1A5: solute carrier family 1 member 5 or sodium-dependent neutral amino acid transporter type 2, SLC2A1: solute carrier family 2 member 1 or glucose transporter1 (GLUT-1).

ically, and metabolically (Yuneva *et al*., 2012; Davidson *et al*., 2016; Hensley *et al*., 2016). Hence, the complexity of genomic alterations can re-wire metabolism differently in different cancers involving different organs and tissues. For example, kidney cancers tend to silence gluconeogenic pathways, while liver cancers could consume ketone bodies (Huang *et al*., 2016). Notwithstanding the tissue-specific complexity, general principles of maintenance and proliferative metabolism, as found in normal and cancer, respectively, have been derived from simple systems and generally provide a conceptual framework for the field of cancer metabolism. Herein, these general concepts are summarized and the complexities and nuances overlying this framework will be discussed.

MAINTENANCE METABOLISM

Perhaps most instructive about Warburg's historical work is his comparison of normal adult mammalian tissues and cancer tissues, not accounting for the proliferative fraction of these tissues. A century ago, Ki67 or other proliferative markers did not exist, and hence tissues grossly appear static, masking the more dynamic nature of cancer tissues. The comparison of normal versus cancer tissue as such did not

take into account the difference between homeostatic, maintenance metabolism of largely non-proliferative normal tissue versus a cancer tissue that differed measurably in the fraction of cells that actively proliferated. Invasion of host defense cells further complicates the tumorigenic scene. In this regard, it is notable that glycolysis tends to be quite high during embryonic development, which then yields to more oxidative metabolism in differentiated non-proliferating tissues. Warburg, in fact, studied the metabolism of many systems including embryonic development (Warburg, 1956). In general, resting differentiated tissues use oxidative metabolism to generate substantial energy to maintain membrane potential and drive protein and biosynthesis to sustain turnover of damaged organelles or macromolecules undergoing the wear-and-tear of constant usage (Hosios *et al*., 2016). Thus, maintenance metabolism favors oxidative metabolism of glucose or lactate (which is converted to pyruvate) over glycolytic metabolism of glucose. Glutamine is yet another amino acids among many that could be oxidatively metabolize, but fatty acids are chief among the oxidative substrates capable of generating many ATP molecules per fatty acid chain. It should be noted that while many studies focused on the utilization of glucose and glutamine, other nutrients such as minerals and vitamins are also vitally important for maintenance and proliferative metabolism (De-

Berardinis and Chandel, 2016).

PROLIFERATIVE METABOLISM

By contrast to oxidative maintenance metabolism, cell growth and proliferation impose additional demands on cellular metabolic pathways (Fig. 1). Specifically, instead of just sustaining membrane potentials with ATP from various nutrient sources, proliferative cells require an increased in uptake of glucose, amino acids, minerals, vitamins, and fatty acids for de novo synthesis of all components of a cell for its replication with fidelity (Hosios *et al*., 2016). As such, the research performed over the past decade using simple systems and metabolomics has generated a general conceptual framework that appears generally applicable to many systems. The findings suggest that glucose is primarily converted to lactate in proliferative metabolism. The fate of glucose in proliferating cells trifurcates toward the pentose phosphate pathway, glucosamine biosynthesis, and glycolytic degradation to lactate. The pentose phosphate pathway generates an essential component of nucleic acids: ribose, which would then be reduced to deoxyribose by deoxyribonucleotic reductase. Glucosamine, which is at the crossroads of glucose and glutamine metabolism, is critical for carbohydrate synthesis and posttranslational modification via O-linked glycosylation, for example. The conversion of glucose to lactate with the regeneration of NAD^+ from NADH ensures the upstream glycolytic flux through GAPDH, which depends on NAD^+, continues to funnel pyruvate downstream for its conversion to lactate by lactate dehydrogenase (Fig. 1). These pathways essentially churn glucose into building blocks for the proliferating cells, ribose for nucleic acid synthesis, glucosamine for carbohydrate, and glycerol from glucose carbons for lipid biosynthesis.

Further down the central metabolic pathway, pyruvate could be converted to lactate via LDH, transaminated to produce alanine, or transported into the mitochondrion by mitochondrial pyruvate carriers (MPCs). Pyruvate is then converted by pyruvate dehydrogenase (PDH) to acetyl-CoA, a key energetic currency that is further catabolized by the tricarboxylic acid (TCA) cycle for the production high energy electrons and ATP (Fig. 1). Further, the TCA cycle intermediates provide the backbone for the synthesis of fatty acids and nucleotides for cell proliferation. De novo protein synthesis relies on freshly imported amino acids through transporters. Amino acids could also serve as energetic substrates. For example, branched chain amino acids (BCAAs) could enter into the mitochondria to be catabolize. Conversely, TCA cycle intermediates could reciprocally produce BCAAs. Citrate generated in the TCA can be transported into the cytosol for its conversion to acetyl-CoA by acetyl-CoA lyase (ACLY); cytosol acetyl-CoA in turn provides the 2-carbon building blocks for de novo fatty acid synthesis via malonyl-CoA carboxylase (ACACA) and fatty acid synthase (FASN). Importantly, de novo nucleotide biosynthesis relies on aspartate for base synthesis, and aspartate is generated by transamination of oxaloacetate.

Glutamine, which is required for *in vitro* cell proliferation and likely for specific tissues *in vivo*, can be converted to glutamate by mitochondrial glutaminase (GLS) (Fig. 1). Glutamate is metabolized to α-ketoglutarate by glutamate dehydrogenase or by transamination via glutamate-oxaloacetate transaminase (GOT) or glutamate-pyruvate transaminase

(GPT). α-Ketoglutarate generated from glutamine could hence support TCA cycling, particularly when glucose is limiting as found under hypoxia when a reverse carboxylation of α-ketoglutarate generates isocitrate and citrate to support lipid biosynthesis. In addition to its role in feeding the TCA cycle, glutamine is also important as a nitrogen donor for glucosamine and nucleic acid base synthesis.

Although it is generally believed that availability of oxygen drives exclusively oxidative metabolism *in vivo*, measurements of oxygen levels in tissues indicate that many tissues in fact exist at the boundary (~3-6% oxygen) between sufficiency and deficiency of oxygen that induces the hypoxia inducible factors (HIFs) (Semenza, 2012; Nakazawa *et al*., 2016). Hence, a more realistic perspective would be that HIFs play a natural regulatory at this boundary, adjusting and modifying oxidative metabolism as oxygen tension fluctuates *in vivo*. Importantly, activation of HIFs, particularly HIF-1, induces a hypoxic transcriptome for metabolic adaptation to low oxygen tensions. HIF-1 induces most glycolytic genes as well as shunting pyruvate away from the mitochondrion by activating pyruvate dehydrogenase kinases (PDKs), particularly PDK1, which phosphorylate and inactivate PDH (Shen and Kaelin, 2013; Chan *et al*., 2016). Further, HIF-1 could also transcriptionally modulate the mitochondrion for maximal efficiency under limiting oxygen concentrations.

ONCOGENIC METABOLISM

A key distinction between normal proliferative metabolism and oncogenic metabolism is the loss of integrity of normal feedback regulatory loops in cancer cells owing to constitutive oncogenic signaling. In normal cells, proliferative (proto-oncogenic) signals are counter-balanced by growth suppressive signal (via tumor suppressors) depending on the presence of growth factors and nutrients. Studies to date suggest that proto-oncogenic signaling is silenced by absence of growth factor stimulation or nutrient deprived states. In stands to reason that evolution has selected well-behaved metazoan cells that exist in a social environment that synchronously diminish the need to feed when food is scarce.

It is documented that the MYC oncoprotein level could be diminished by glucose, glutamine, or oxygen deprivation. In this context, diminished MYC under these conditions through feedback loops and checkpoints ensures any proliferative signal in normal cells would be turned off when nutrients to make building blocks are unavailable, despite the presence of growth factors. By contrast, however, constitutive expression of MYC, which is known to induce metabolic pathways broadly to support protein and nucleic acid synthesis – driving ribosomal biogenesis, causes MYC-deregulated cells to sustain constitutive program of biomass accumulation regardless of the availability of the nutrient pipelines. MYC also induces mitochondrial biogenesis, while seemingly inhibits lysosomal biogenesis (Li *et al*., 2005; Wolf *et al*., 2013). Hence, it was postulated and experimentally documented that MYC-overexpressing cells, driven to undergo biosynthesis, as compared to parental non-transformed cells, tend toward cell death when deprived of glucose or glutamine. Therefore, one key distinction between normal proliferative cells and cancer cells is that the latter are genetically constrained by constitutive oncogenic signaling or loss of tumor suppressive functions, such

as loss of PTEN that causes essentially of the PI3K pathway.

Other oncogenes, PI3K, BRAF, and KRAS activate signaling pathways involving AKT, which favors glycolytic metabolism through increased glucose transport and glycolysis (Pavlova and Thompson, 2016). MYC, being downstream, has been implicated as being essential for the function of these oncogenes, likely through it transcriptional drive of biosynthesis. Although HIF is induced by hypoxia, increased translational of HIF downstream of PI3K is thought to contribute to metabolic rewiring toward glycolysis along with MYC induction. Thus, oncogenic drivers impinge on glycolysis and TCA cycling of metabolism to support cell growth and proliferation, but in a constitutive fashion that unveils vulnerabilities to metabolic disruptions.

IN VIVO VERSUS *IN VITRO* TUMOR METABOLISM

A number of recent studies uncovered significant differences in the metabolic profiles of *in vivo* tumors versus comparable *in vitro* models, which generally have adapted to a high dependency on glutamine (Altman *et al*., 2016). For example, glutamine drives proliferation of lung cancer cells *in vitro*, but use of glutamine *in vivo* does not seem as important. Glucose, on the other hand, appears to be largely oxidized *in vivo* as compared to its higher conversion to lactate *in vitro*. These recent findings challenge the prevailing notion that the Warburg effect and glutaminolysis dominate the cancer metabolic profile.

It is intriguing that these recent findings and interpretations stand in contrast to Cori's and Warburg's *in vivo* metabolic studies of cancers. Cori and Cori (1925) (JBC) measured glucose and lactate in axillary veins of chickens bearing unilateral sarcomas and found that the blood from the vein ipsilateral to the tumors had lower glucose and higher lactate levels. Similarly, Warburg's studies in rats showed metabolite differences between efferent arterial and afferent venous blood coming from sarcomas (Warburg *et al*., 1927). Specifically, as compared to arterial and venous blood from normal tissues, glucose was more highly extracted by tumors and more lactate was produced and found in venous blood draining tumors. The historical studies perhaps should be replicated with modern tools using metabolic tracers, particularly since recent studies rely on modeling of levels of metabolites after an infusion that is complicated by metabolism of metabolites by red blood cells, normal organs and the tumors themselves.

Intriguingly, the same oncogene – KRAS – in different tissues could induce metabolic profiles that are distinct from one to the other (Davidson *et al*., 2016). The caveat of *in vivo* models is the complexity of cell constituents in the tumor tissue, which can consist of stromal cells and immune cells. How much of the *in vivo* metabolic re-wiring is an emergent property of a tissue remains to be dissected with better technologies which have now been developed to study single cell transcriptomes. Short of ideal solutions to resolve this issue, it is possible that use of reconstituted experimental systems mimicking cancer tissues might provide new insights into the emergent properties of tumor tissues which are highly complex in composition in additional to the varied metabolic backgrounds of the tissue of origin of specific cancers (eg, kidney versus liver as discussed) (Zhang *et al*., 2005).

Recent advances in studying human cancer metabolism *in vivo* and *ex vivo* have also added to the complexity of our conceptual framework of tumor metabolism. For example, glucose oxidation appears to be key to several human cancers as gleaned by metabolic tracing experiments (Sellers *et al*., 2015; Hensley *et al*., 2016). These observations question the prevailing notion that tumors are highly Warburg-like or glycolytic. After all, careful study of Pasteur's original reveals that oxidative yeast metabolism yielded more cell mass that strictly glycolytic metabolism greatly favored by wineries and of course, oenophilic connoisseurs (Pasteur, 1879). As such, the mitochondrion, historically marginalized by Warburg, still has a central role in cancer metabolism.

IMMUNITY AND THE CANCER METABOLIC SECRETOME

As interest in cancer metabolism research re-invigorated over the past several decades, immunologist and cell biologists realize that proliferating immune cells must somehow utilize pathways similar to those used by cancer cells (Murray *et al*., 2015; O'Neill *et al*., 2016). However, foundational metabolic studies of immune cells, illustrating the dependency of activated lymphocytes on glucose and glutamine, had already existed before this resurgence of interest (Ardawi and Newsholme, 1983). Indeed, growth factor signaling in various tissues parallels B and T cell receptor signaling in intriguing metabolic re-wiring. For example, activation of normal T cells through the T cell receptor triggers glycolysis and glutaminolysis in a MYC, but note HIF, dependent manner (Wang *et al*., 2011). Beyond B and T cells, tumor macrophages have different metabolic profiles depending on whether they are pro-inflammatory as in the case of glycolytic M1 macrophages or anti-inflammatory as with oxidative M2 macrophages (O'Neill *et al*., 2016). Because Tregs, which are anti-inflammatory, also rely on oxidative metabolism and myeloid derived suppressive cells, which are pro-tumorigenic, rely on fatty acid oxidation, a general conceptual framework has emerged that inflammatory states tend to be glycolytic, while immuno-suppressive states tend to be oxidative. In this regard, the intriguing suggestive evidence that metformin, which inhibits mitochondrial oxidative metabolism, has anti-tumor effects may not be the result of cancer cell autonomous response, but rather due to modulation of the immune repertoire within the tumor.

The tumor microenvironment has been shown experimentally in many (but not all) settings that it is hypoxic, acidity and bathed with tumor metabolites such as lactate and kynurenine, which are both immunosuppressive (Murray *et al*., 2015). As such, a deeper understanding of the cancer cell metabolic secretome and its effect on stromal and immune cells is essential for a richer appreciation of tumor susceptibility and resistance to therapies.

METABOLIC INTERPLAY BETWEEN CANCER AND TUMOR-ASSOCIATED STROMA

Albeit highly disorganized, cancer cells co-exist and interact with diverse cell types including immune cells, fibroblasts, and endothelial cells within the tumor microenvironment. Extensively altered metabolism in highly proliferative cancer cells may create metabolically imbalanced, challenging microenvi-

ronment, which forces surrounding stromal cells to form an alliance with cancer cells for metabolic symbiosis or compete for precious nutrients. Similar to cancer cells, cancer-associated fibroblasts (CAFs) have been shown to exhibit elevated glycolysis and glucose consumption in a HIF-1-dependent manner. Highly glycolytic CAFs then secret lactate, which can then be utilized by presumably less glycolytic cancer cells (Zhang *et al.*, 2015). However, opposite metabolic relationship between cancer cells and CAFs also has been reported, highlighting complexity and context-dependence of cancer-stromal metabolic interplay. Beyond lactate, various amino acids including glutamine and alanine have been implicated in metabolic exchange between cancer cells and CAFs (Sousa *et al.*, 2016). To metabolize and mobilize amino acids, cells needs to activate autophagy. Indeed, CAFs exhibit highly increased autophagy in various human cancers including pancreatic and prostate cancers. Amino acids derived from autophagy or de novo biosynthesis, secreted from CAFs feed cancer cells to sustain cellular bioenergetic as well as anabolic demands.

Angiogenic activation is one of the hallmark microenvironmental features of actively growing tumors. Given the highly proliferative and migratory capacity of cancer-associated endothelial cells (CAECs), one can assume that CAECs and cancer cells share similar metabolic alterations. For instance, CAECs have highly activated glycolytic metabolism to support their proliferation and anabolic demands (Wong *et al.*, 2017). Intriguingly, targeting glycolysis by genetic or pharmacological inhibition of PFKFB3, a potent glycolytic activator, induced endothelia quiescence resulting in reduced vessel sprouting and tumor vascular normalization (Missiaen *et al.*, 2017). This highlights the prominent roles of glycolysis in activated tumor endothelial cells. It remains to be determined if reciprocal metabolic interaction exists between cancer cells and CAECs as seen in cancer cell-CAFs.

As cancer cell-stroma interaction is anticipated to be highly complex and context-dependent, and further influenced by non-cellular components such as oxygen tension, pH, stiffness, and interstitial pressure, it is challenging to illuminate actual metabolic link among various cellular component in the tumor microenvironment. Yet, better understanding of both intrinsic and reciprocal metabolic regulation will greatly improve our capacity to design more effective therapeutic strategy for targeting cancer metabolism.

THERAPEUTIC IMPLICATIONS OF TUMOR METABOLISM

It is the hope of the field that cancer metabolism would lead to tangible clinical impact that reduces the burden of cancer. While alter metabolism has been exploited for clinical cancer imaging, such as fluoro-2-deoxyglucose PET imaging, the promise of metabolic therapy for cancers is still awaiting clinical validation beyond the very special case of IDH mutations found in gliomas and acute myelogenous leukemia. For example, a glutaminase inhibitor – CB839 (Gross *et al.*, 2014)– has proven in the clinic to have palpable activity in kidney cancer. The mitochondrial inhibitor CPI-613, a lipoate, appears to have significant activity in early Phase I studies (Alistar *et al.*, 2017). Other compounds such as those targeting acetyl-CoA carboxylase or fatty acid synthase or lactate dehydrogenase awaits definitive clinical development and clinical studies. An

important consideration for therapeutic targeting of cancer metabolism includes richer understanding of metabolic inhibitors on the immune system which could be tipped metabolically to be anti-tumorigenic or pro-tumorigenesis. Despite these challenges and complexities, a richer and deeper understanding of cancer and immune cell metabolism have emerged in recent years holding promise that in the correct context some of metabolic drugs will help reduce the burden of cancer.

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