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Determinants of nutrient limitation in cancer

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Abstract

Proliferation requires that cells accumulate sufficient biomass to grow and divide. Cancer cells within tumors must acquire a variety of nutrients, and tumor growth slows or stops if necessary metabolites are not obtained in sufficient quantities. Importantly, the metabolic demands of cancer cells can be different from those of untransformed cells, and nutrient accessibility in tumors is different than in many normal tissues. Thus, cancer cell survival and proliferation may be limited by different metabolic factors than those that are necessary to maintain non-cancerous cells. Understanding the variables that dictate which nutrients are critical to sustain tumor growth may identify vulnerabilities that are could be used to treat cancer. This review examines the various cell-autonomous, local, and systemic factors that determine which nutrients are limiting for tumor growth.

Introduction

For most proliferating cells, survival and proliferation rate can be dictated by nutrient availability (Vander Heiden and DeBerardinis 2017). That is, if a cell is unable to obtain a sufficient quantity of a nutrient upon which it is dependent, the cell will not be able to survive, or divide as rapidly, as it would if given an excess of that nutrient. This effect can be mediated by a lack of substrate availability necessary to produce the macromolecules needed for biomass accumulation, or may affect critical signaling pathways that respond to nutrient levels and are required to orchestrate the processes needed for cell growth and proliferation (Torrence and Manning 2018). Regardless of mechanism, proliferation is reduced when the intracellular levels of some nutrients fall below a certain threshold. This threshold is dictated by two terms: cellular demand for that nutrient and the ability of the cell to access that nutrient or its precursors from the environment (Figure 1). Both of these terms are affected by a multitude of cell-intrinsic and cell-extrinsic factors. As a result, proliferating cells in different tumors and tissues are not universally limited by the availability of the same nutrients. Understanding which nutrients are most limiting for specific cells and determining the contexts that dictate those limitations is critical to find metabolic treatments for cancer.

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Declaration of Interests

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that take advantage of tumor-specific nutrient requirements and effectively starve malignancies without substantially damaging normal tissues.

**Nutrient demand**

The demand for specific nutrients by cancer cells in tumors is determined by the complex interplay of many factors that influence metabolic pathway use (Figure 2). Here we will examine key variables that affect nutrient demand, including tumor-promoting mutations, chromosomal abnormalities, cancer-specific phenotypic programs, and tissue of origin.

**Demands imposed by mutations that drive tumor progression**—Tumorigenesis is driven by genetic alterations (Hanahan and Weinberg 2011). Many of these genetic changes occur in growth-promoting signaling pathways that also activate metabolic pathways to enable biomass production. Genetic changes in cancer can also occur directly in the metabolic pathways that carry out reactions important for biomass accumulation and can alter the metabolic demands of a cell. Comprehensive descriptions of the metabolic changes that occur due to specific oncogenic mutations are explored in-depth elsewhere (Cairns et al. 2011; Nagarajan et al. 2016); here, we discuss representative examples of tumor-promoting genetic changes found in many cancers and highlight how these genetic changes impact nutrient demand in the tumor.

**MYC and its upstream activators:** MYC is a transcription factor that regulates the expression of a broad range of genes required for proliferation; when dysregulated, MYC can thus act as an oncogene (Wolpaw and Dang 2018). Alterations leading to constitutive MYC expression occur frequently in cancer, and MYC is the third-most commonly amplified gene across all cancers studied in The Cancer Genome Atlas (Zack et al. 2013). Constitutive MYC expression can occur through somatic gene amplification (Zack et al. 2013) or as a result of mutations in upstream signaling pathways such as the mitogen activated protein kinase (MAPK) pathway (Wolpaw and Dang 2018). Thus, common mutations in proto-oncogenes that are a part of the MAPK pathway, such as KRAS and BRAF, yield similar metabolic effects as MYC activation (Dang et al. 2009; Bryant et al. 2014; Santana-Codina et al. 2018). When active, MYC serves to stimulate broad metabolic remodeling (Nikiforov et al. 2002; Liu YC et al. 2008; Dang et al. 2009) that can alter the metabolic demands of the tumor. One prominent example is that constitutive MYC expression generates a higher requirement for consumption of the amino acid glutamine in cultured cells (Yuneva et al. 2007). We speculate that this effect could potentially be driven by MYC-associated expression of xCT, a cell-surface transporter that takes cystine into the cell while exporting glutamate (Ji et al. 2018). In the presence of environmental cystine, high expression of xCT leads to rapid export of glutamate, which imposes a need for increased glutamine consumption in order to replenish glutamate levels (Muir et al. 2017; Sayin et al. 2017). Regardless of the specific mechanism, altered metabolism in tumors with constitutive MYC activity can create new demands for certain metabolites, such as glutamine.

**TP53:** The most commonly mutated tumor suppressor gene in cancer is TP53; at least 50% of tumors display some sort of alteration in the TP53 gene (Ciriello et al. 2013). The TP53 gene product, p53, is a protein with myriad functions as a transcription factor and as a
cytosolic protein (Kastenhuber and Lowe 2017). Among its many functions, p53 allows cells
to adapt to nutrient deprivation (Kruiswijk et al. 2015). For instance, in response to stress
conditions, p53 downregulates glycolysis through multiple mechanisms including direct
inhibition of glucose transporters (Schwartzenberg-Bar-Yoseph et al. 2004) and induction of
glycolysis inhibitors such as TIGAR (Bensaad et al. 2006). Metabolic genes downstream of
p53 can also play a role in triggering p53-induced cell death (Jiang L et al. 2015). p53 can
directly or indirectly influence expression of genes involved in lipid metabolism, amino acid
transport and synthesis, and other metabolic pathways (Puzio-Kuter 2011), making it
difficult to predict a priori exactly how nutrient demands are altered by p53 loss. Further
complicating the effect of p53 on nutrient demand, specific mutations of TP53 can have
different effects on tumor metabolism (Humphton et al. 2018; Schofield et al. 2018).
Additional study of the complex changes caused by loss of TP53 will shed light the specific
metabolic demands that are altered by this critical tumor suppressor.

**KEAP1/NFE2L2 axis:** Another common alteration that occurs in cancer with implications
for nutrient demand is the activation of NFE2L2, which encodes the transcription factor
NRF2 that is involved in the cellular response to oxidative stress (Venugopal and Jaiswal
1996; Itoh et al. 1997; Raghunath et al. 2018). NRF2 activity can also be induced by loss of
function mutations in KEAP1, which encodes a ubiquitin ligase that regulates NRF2 levels
by targeting it for proteasomal degradation (Itoh et al. 1999; Kobayashi et al. 2004). KEAP1
contains reactive cysteine residues that are sensitive to oxidative stress and prevent NRF2
degradation when in the oxidized state. KEAP1 is often mutated in tumors, particularly non-
small cell lung cancer, leading to accumulation of NRF2 independent of cellular redox state
(Singh et al. 2006; Kansanen et al. 2013). NRF2 activation leads to increased expression of
genes involved in the response to oxidative stress, which includes such processes as
xenobiotic detoxification and glutathione synthesis (Raghunath et al. 2018). Further, NRF2
activation leads to induction of ATF4, a transcription factor involved in the response to both
nutrient deprivation and endoplasmic reticulum stress (He et al. 2001). As a result, NRF2
activation yields ATF4-dependent metabolic remodeling, including induction of de novo
serine synthesis (DeNicola et al. 2015) and increased expression of xCT (Romero et al.
2017; Sayin et al. 2017) resulting in an increased dependence on glutamine metabolism as
described above. Thus, alteration of the KEAP1/NRF2 signaling axis leads to metabolic
changes that modify cellular demands for some amino acids. These examples typify
characteristic alterations to metabolic demand created by oncogenic mutations. Given the
pleiotropic, complex effects of tumor-promoting mutations, further work to develop a more
thorough understanding of the metabolic consequences of these mutations is warranted.

**Metabolic demands driven by chromosomal abnormalities**—The tumor-
promoting mutations described above activate pathways that coopt normal physiology to
satisfy the metabolic requirements of cell growth and proliferation. Thus, cancer cells and
some untransformed, proliferating cells may share metabolic alterations that allow them to
adapt to the metabolic demands imposed by growth signaling pathway activation (Fendt
2017). However, some tumor-promoting mutations occur through loss of large chromosomal
segments, which can result in deletion of genes in regions adjacent to tumor suppressors.
These large deletions sometimes include metabolic genes, which can affect metabolic
pathway use (Muller et al. 2015). Beyond specific focal deletions of chromosomal regions, many cancers exhibit large-scale changes in chromosome number, known as aneuploidy (Sansregret and Swanton 2017), that can create tumor cell characteristics that are not recapitulated in normal tissues (Knouse et al. 2014). Because these events are not associated with a physiological metabolic program, they may create unique nutrient demands for cancer that differ from those found in all other normal cells.

**Collateral mutation of metabolic genes: CDKN2A and MTAP:** The most commonly deleted chromosomal locus across cancers is 9p21, due to the presence of the tumor suppressor gene CDKN2A in that region (Beroukhim et al. 2010; Zack et al. 2013). CDKN2A codes for two proteins, p16\(^{INK4A}\) and p14\(^{ARF}\) (Duro et al. 1995; Mao et al. 1995; Quelle et al. 1995; Stone et al. 1995), each of which is a tumor suppressor (Serrano et al. 1993; Serrano et al. 1995; Stott et al. 1998). CDKN2A deletions are often accompanied by deletion of surrounding genes (Zhang H et al. 1996), including the enzyme methylthioadenosine phosphorylase (MTAP), which is responsible for metabolizing methylthioadenosine that is produced as a byproduct of polyamine synthesis (Pegg and Williams-Ashman 1969a, 1969b; Carrera et al. 1984; Pegg 2009). Deletion of MTAP as a consequence of CDKN2A loss leads to dysfunctional salvage of methylthioadenosine. As methylthioadenosine accumulates, it inhibits the protein arginine methyltransferase PRMT5, rendering cancer cells particularly sensitive to knockdown of PRMT5 and related proteins (Marjon et al. 2016; Mavrakis et al. 2016). MTAP deletion also causes global changes in metabolism that may be caused by altered epigenetic state or by perturbed methionine metabolism (Sanderson et al. 2018); in either case, MTAP deleted cells may exhibit differential nutritional demands that cells must meet through adaptation of other metabolic pathways.

**Collateral mutation of metabolic genes: SMAD4 and ME2:** Another tumor suppressor that is commonly deleted in cancer is SMAD4 (Hahn et al. 1996). SMAD4 is a part of the TGF-β signaling pathway, and SMAD4 deletion can promote tumor progression in a variety of cancers, particularly pancreatic ductal adenocarcinoma (Bardeesy et al. 2006; Zhao et al. 2018). Among the genes located proximal to SMAD4 is malic enzyme 2 (ME2) (Dey et al. 2017), a mitochondrial enzyme that is one of three isoforms responsible for interconversion of malate and NAD(P)\(^+\) with pyruvate, NAD(P)H, and CO\(_2\) (Moulder et al. 1945; Hsu 1982; Taroni et al. 1987). Loss of ME2 has been suggested to limit both NADPH production and lipid synthesis in cancer (Jiang P et al. 2013), and cancer cells with ME2 deletion become sensitive to depletion of malic enzyme 3 (ME3) (Dey et al. 2017). This suggests that the demand to produce NADPH through other metabolic pathways must be increased in SMAD4/ME2 deleted tumors. Understanding how cancers cope with ME2 loss could identify metabolic liabilities to target therapeutically in SMAD4-deleted cancers.

Beyond focal deletions involving tumor suppressors, some larger chromosomal regions are consistently lost in specific cancers (Beroukhim et al. 2010; Zack et al. 2013; Cai et al. 2016). These losses can also eliminate expression of metabolic genes (Boots-Sprenger et al. 2013; Muller et al. 2015; Branzoli et al. 2019) and create potential therapeutic targets (Muller et al. 2012; Lin et al. 2018). Further examination of how metabolic pathways are...
affected by chromosomal segment deletions has the potential to uncover novel metabolic demands for certain cancers, and may uncover cancer-specific auxotrophies.

**Aneuploidy:** Aneuploidy produces a broad range of stresses affecting nearly every facet of biology (Zhu et al. 2018). One of the changes that occurs in aneuploid cells is widespread remodeling of metabolism (Sheltzer 2013; Zhu et al. 2018). For instance, aneuploidy results in increased levels of ceramide lipid species, rendering aneuploid cells more dependent on pathways that normalize ceramide levels (Tang et al. 2017). Similarly, in yeast, aneuploidy imposes an increased demand for certain sphingolipid species, and increases demand for the amino acid serine, which is required for *de novo* sphingolipid synthesis (Hwang et al. 2017). These findings illustrate how abnormal chromosome number and chromosomal rearrangements can alter nutrient demand, and may represent a targetable type of metabolic remodeling that is specific to cancer cells.

**Nutrient demands determined by cellular programs that are important in some cancers**—In addition to genetic changes that can alter metabolic demands, cancer cells often exhibit phenotypic changes that impact metabolism. Some prominent examples of phenotypes observed across cancers include the epithelial to mesenchymal transition (EMT) (Brabletz et al. 2018), adoption of stem-cell like properties (Batlle and Clevers 2017), and the development of drug resistance (Brown et al. 2014; Mansoori et al. 2017). Cells that have undergone EMT, cancer cells with stem-like properties, and drug resistant cancer cells all exhibit altered metabolism, frequently driven by expression of the same genes (Morandi et al. 2017). For example, each of these states is characterized by high expression of the enzyme dihydropyrimidine dehydrogenase (DPYD), which degrades the nucleobases uracil and thymine into dihydropyrimidines (Mani et al. 2008; Li et al. 2013; Shaul et al. 2014). Increased activity of DPYD alters levels of dihydropyrimidines relative to uracil and thymine (Shaul et al. 2014), and suggests that these cells may have an increased demand for consumption of these nucleobases. Some cellular programs alter nutrient demand in ways that impose increased requirements for certain enzymes. For instance, drug resistant cells have an increased demand for the amino acid cysteine and the tripeptide glutathione; as a result, these cells are highly dependent on pathways that prevent lipid peroxidation and cell death via ferroptosis, an iron-dependent form of programmed cell death (Hangauer et al. 2017). Broadly, the various phenotypic states adopted by tumors can result in different metabolic demands that affect which nutrients are limiting for tumor growth or survival.

**Metabolic demands dictated by tumor tissue of origin**—Beyond genetic changes and phenotypic states of tumors, some nutrient demands are shaped by the cell or tissue type from which a tumor arose (Hu et al. 2013; Gaude and Frezza 2016). Thus, these characteristics may not be shared across all tumor types, even those driven by the same oncogenes. For instance, tissue of origin can determine the extent to which tumors are dependent on particular amino acids, including non-essential amino acids such as glutamine (Yuneva et al. 2012), as well as essential nutrients such as branched chain amino acids (Mayers et al. 2016). In the case of branched chain amino acids, tumors arising from lung require the enzyme required to catabolize branched chain amino acids, while tumors arising from the pancreas do not (Mayers et al. 2016). This discrepancy in the requirement for
branched chain amino acid transamination may be to fulfill differential demands for products of branched chain amino acid breakdown, such as acquisition of nitrogen or production of the amino acid glutamate. Thus, tissue of origin can be an important determinant of nutrient demand in tumors.

**Nutrient accessibility**

In order to meet varying metabolic demands, tumor cells must be able to acquire relevant nutrients from their environment. Thus, as alluded to above, the second factor that determines which nutrients are limiting for cancer cell proliferation is the accessibility of nutrients in the tumor. The nutrients available to a tumor can not only directly affect tumor growth, but can also affect the essentiality of other genes and metabolic pathways (Birsoy et al. 2014; Arroyo et al. 2016; Kory et al. 2018). Accessibility of nutrients is itself affected by two variables: cell-extrinsic metabolite availability in the environment and cell-intrinsic ability to obtain and effectively use those metabolites (Figure 3).

**Circulating nutrient levels**

**Diet:** Nutrient availability to the tumor is dependent on the abundance of circulating metabolites in the blood. The macronutrient content of diet can lead to complex changes in circulating nutrient levels. For instance, consuming diets with varying caloric content and different calorie sources can alter the lipid profile in blood (Raeini-Sarjaz et al. 2001; Appel et al. 2005; Ma et al. 2006). In fact, the levels of most circulating metabolites are influenced by diet, and subtle changes in dietary nutrients can have a profound effect on the metabolic content of blood (Sullivan, Danai, et al. 2019). Further, depletion or supplementation of certain nutrients in the diet can lead to a concomitant change in circulating nutrient abundance. In the most extreme example, the circulating levels of nutrients that cannot be synthesized by humans are strongly influenced by diet (Fitzpatrick et al. 2012). As a result, dietary vitamin levels can impact tumor growth, because although vitamins are typically not consumed by enzymatic reactions, each newly formed cancer cell must be able to obtain a sufficient supply of vitamins to support its enzymatic reactions. For example, dietary folic acid supplementation was noted to exacerbate childhood leukemia in the 1940s (Farber et al. 1947; Farber et al. 1948), and can accelerate the development of murine breast tumors (Hansen et al. 2017). However, given the pleiotropic effects of vitamin deprivation on overall animal health, dietary levels of folic acid have been reported to both positively and negatively affect the risk of developing tumors in humans (Ulrich 2007; Lamm et al. 2015; Ashkavand et al. 2017).

The dietary content of some non-essential nutrients can also influence circulating levels of those metabolites. Feeding mice a diet lacking the amino acids serine and glycine results in lower serine levels in circulation (Maddocks et al. 2013). Reduced serine accessibility in this setting can slow tumor growth without grossly affecting animal health (Maddocks et al. 2013; Maddocks et al. 2017; Sullivan, Mattaini, et al. 2019), consistent with tumors having a high demand for serine that they are not able to meet given a diminished accessibility of serine in the circulation. This principle can also be applied more generally in fasted animals. Long-term fasting broadly alters circulating metabolite levels in both mice and humans (Broer S and Broer 2017; Steinhauser et al. 2018), shifting nutrient accessibility in a manner
that decreases tumor proliferation in mice (Lee et al. 2012; Sun et al. 2017). Other dietary changes that broadly alter nutrient availability, such as the ketogenic diet, have been shown to both increase and decrease the rate of tumor progression in mice (Klement 2017; Hopkins et al. 2018), further highlighting the complex role that diet can have on tumor progression.

**Hormonal control of metabolism:** Circulating nutrient levels are not solely determined by the diet. Instead, complex hormonal mechanisms influence the levels of some nutrients in blood. Perhaps the most well-studied example of hormonal regulation of metabolism is in the control of circulating glucose levels. Glucose levels in the blood are tightly regulated by the action of the hormones insulin and glucagon. Insulin stimulates glucose uptake in many cell types and broadly functions to clear glucose from circulation (Wilcox 2005). Conversely, glucagon stimulates glucose release into the bloodstream from hepatic glycogen stores and de novo glucose synthesis through the process of gluconeogenesis (Han et al. 2016). Glucose is not the only metabolite regulated by hormones. In fact, it has long been recognized that endocrine signaling influences the concentrations of amino acids in blood (Friedberg and Greenberg 1947). As a result, circulating amino acid levels are largely held within a certain range of concentrations independent of the composition of diet. Systemic metabolism does not fully control circulating amino acid levels, as within this normal range, amino acid levels can fluctuate over the course of the day in response to normal feeding and fasting (Sullivan, Mattaini, et al. 2019), and certain amino acids such as serine, glycine, and alanine vary over a wider range than other amino acids (Broer S and Broer 2017). However, consistent with the importance of hormonal regulation of amino acid levels, derangement of whole-body metabolism in obesity or cancer alters circulating levels of branched chain amino acids (Newgard et al. 2009; Mayers et al. 2014). Beyond regulation of metabolite levels, hormonal processes mediate the effects of dietary and environmental perturbations on circulating nutrient levels. For instance, fasting has been shown to inhibit leukemia progression by altering expression of leptin receptor (Lu et al. 2017), a protein which binds to the hormone leptin and is involved in maintenance of whole-body energy homeostasis (Kelesidis et al. 2010). Thus, in addition to directly setting the circulating levels of many metabolites, hormonal mechanisms may also mediate the effects of diet and other environmental factors on nutrient accessibility in tumors.

**Influence of the microbiome on systemic metabolite levels:** Systemic metabolism can be influenced by the actions of the gut microbiome. The microbiome carries out many metabolic reactions, and can affect which nutrients in the diet end up in circulation, or produce metabolites that do not directly reflect the content of diet (LeBlanc et al. 2013; Fujisaka et al. 2018). Microbiome composition may also affect systemic metabolism, as fecal microbiota transplants are sufficient to predictably alter non-fasting glucose levels in mice (Ussar et al. 2015). Thus, the behavior of the microbiome appears to also influence tumor nutrient accessibility.

**Fluctuating metabolite levels due to circadian rhythms:** Nutrient availability in circulation is not constant throughout the day. In fact, circadian rhythms exhibit a profound effect on the plasma levels of metabolites, with some nutrients displaying greater than 2.5 fold differences in circulating concentration throughout the day (Dallmann et al. 2012; Masri
and Sassone-Corsi 2018). In contrast, some metabolites largely do not fluctuate throughout the day (Dallmann et al. 2012). Given the variability in circadian fluctuation between nutrients, certain metabolites could be less accessible and thus more limiting for tumor growth at particular times during the day. For this reason, it may be advantageous for tumors to reprogram circadian metabolism to promote more favorable nutrient accessibility. Indeed, lung adenocarcinoma has been observed to alter hepatic circadian rhythms in a way that alters whole-body metabolism (Masri et al. 2016). For these reasons, when examining nutrient accessibility with the goal of understanding metabolic limitations on tumors, it is important to consider the effects that circadian rhythms have on circulating metabolite levels.

Nutrient levels in the tumor microenvironment—Though systemic metabolism can impact blood nutrient levels, tumors do not have straightforward access to all of the nutrients present in circulation (Sullivan, Danai, et al. 2019). The delivery of nutrients to tumor cells is complicated by altered vasculature and competition for metabolites between various cells within the tumor microenvironment. Indeed, the metabolic composition of tumor interstitial fluid, the nutrient bearing substance that directly carries nutrients between the tumor cells and circulation (Wiig and Swartz 2012), is different from that of blood (Sullivan, Danai, et al. 2019). Here we examine some of the factors in the local tumor microenvironment that alter nutrient accessibility.

Tumor vascularization and lymphatics: In contrast to normal tissues, tumors have irregularly spaced, poorly functioning blood vessels (Fukumura et al. 2010). As a result, tumors may not be able to efficiently exchange nutrients and waste products with the circulation. Further compounding the abnormal vasculature is the presence of dysfunctional lymphatics in tumors. Lymphatic ducts are responsible for returning fluid and metabolites that drain from a tissue into the blood (Wiig and Swartz 2012). Solid tumors are typically highly compressed and, as a result, can be deficient in functional lymphatics. This further increases tumoral interstitial pressure, which inhibits nutrient uptake from the blood (Fukumura et al. 2010; Wiig and Swartz 2012). As a result, the accessibility of nutrients to the tumor depends both on the extent of vascularization and the effectiveness of the blood vessels present in the tumor.

Competition for nutrients between cell types in the tumor microenvironment: Once nutrients are delivered to the local tumor microenvironment, all cells within the tissue, including stromal and immune cells compete for nutrients within the tumor. For example, some immune cells important for restricting tumor growth, such as activated T cells, acquire metabolic characteristics that are similar to tumor cells and are often driven by the same transcriptional programs that exist in cancer (Wang et al. 2011; Le Bourgeois et al. 2018). Thus, these cells compete with tumor cells for the same nutrients. Beyond competition, some immune cells degrade or sequester critical nutrients in the tumor microenvironment (Lyssiotis and Kimmelman 2017). For instance, myeloid derived suppressor cells (MDSCs) deplete the amino acids arginine, tryptophan, and cystine from the tumor microenvironment beyond their own metabolic needs (Kumar et al. 2016). Degradation of these nutrients has an
immunosuppressive effect that can favor tumor progression; however, tumors must also cope with this altered nutrient availability.

**Nutrient sharing between cell types in the tumor microenvironment:** Stromal cells in the tumor microenvironment can also alter nutrient accessibility in a way that is favorable to cancer cells (Lyssiotis and Kimmelman 2017). For example, primary chronic lymphocytic leukemia (CLL) cells have a limited ability to uptake the amino acid cystine due to low expression of the cystine-glutamate antiporter xCT. Bone marrow stromal cells that are present in the CLL niche, in contrast, are capable of importing cystine using xCT and then excreting cysteine, the reduced form of cystine that can be transported using the ASC family of amino acid transporters (Barker and Ellory 1990; Zhang et al. 2012). This allows the CLL cells to take up cysteine, providing increased access to a crucial amino acid. Further examples of how cell populations within a tumor might exchange nutrients in a symbiotic relationship are also prominent in the literature (Sonveaux et al. 2008; Tardito et al. 2015; Sousa et al. 2016; Yang et al. 2016).

**Uptake of nutrients**—Rather than relying upon local delivery or microenvironmental production of specific metabolites, tumor cells can increase the accessibility of nutrients by more effectively taking up metabolites from their environment. For instance, xCT deficient CLL cells mentioned above would not have to rely upon stromal cells to produce reduced cysteine if they were more capable of oxidized cystine uptake. To more effectively acquire metabolites, cancer cells can modulate nutrient uptake using a variety of mechanisms; here we examine some of the adaptations that tumors utilize to better obtain nutrients and therefore increase the accessibility of metabolites from the environment.

**Cell surface transporters:** Most nutrients are transported into cells through transmembrane proteins, and transport can be either equilibrative or coupled to an energy consuming process to concentrate the nutrient in cells (Glatz et al. 2010; Hediger et al. 2013; Szablewski 2013; Perez-Escuredo et al. 2016; Young 2016; Inoue 2017). Many nutrient transport proteins are upregulated in cancer, and there has been a renewed interest in understanding nutrient transport phenomena in cancer (Nicklin et al. 2009; Cesar-Razquin et al. 2015; Krall et al. 2016; Broer A et al. 2018; Cha et al. 2018; Ladanyi et al. 2018; Tajan et al. 2018; Todenhofer et al. 2018). One of the most well-known cancer phenotypes is the avid uptake of glucose, a phenomenon that is at least partially driven by increased expression of GLUT family glucose transporters (Szablewski 2013). This increased capacity for glucose transport may increase glucose accessibility to tumors.

In some cases, transporter expression has less predictable effects on nutrient uptake, and therefore availability. The uptake of amino acids occurs through a series of transmembrane transporters with overlapping amino acid specificities (Hediger et al. 2013; Kandasamy et al. 2018). Many of these transporters are obligate amino acid exchangers, which take up one amino acid and excrete a second. These amino acid exchangers are unable to facilitate net uptake of amino acids, but are instead able to shift the relative ratios of various intracellular amino acids. Multiple studies have shown that knocking down expression of amino acid exchangers such as ASCT2 and LAT1 can hinder cancer growth (Nicklin et al. 2009; van Geldermalsen et al. 2016; Cormerais et al. 2018), suggesting that the redistribution of
intracellular and extracellular amino acids can affect both growth signaling and tumor proliferation. However, the specific effects of increased expression of amino acid exchangers on nutrient accessibility are difficult to predict due to the complex and redundant interactions between amino acid transporters. Further, amino acid transporter activity will be affected by the intracellular and extracellular levels of multiple amino acids. Many studies of amino acid exchange involve non-physiological conditions wherein cells are loaded with high levels of an amino acid of interest and then efflux of that amino acid and uptake of others are observed. Thus, further work to understand the functions of each transporter when physiological concentrations of amino acids are present is warranted.

**Nutrient uptake from extracellular polymers and macromolecules:** Not all nutrient acquisition is mediated by the uptake of free metabolites through cell-surface transporters; instead, some metabolites are scavenged from extracellular polymers. One such nutrient is glutathione, a tripeptide that is present at ~10 μM in circulation (Pastore et al. 1998) but is much more abundant in the interstitial fluid of some tumors (Sullivan, Danai, et al. 2019). Glutathione contains the amino acids cysteine, glutamate, and glycine, and can be a source of these amino acids (Orlowski and Meister 1970); however, tumor cells must first degrade glutathione into its amino acid components for uptake through cell-surface transporters. This process requires the expression of γ-glutamyl transferases (GGTs), extracellular membrane proteins that degrade glutathione in the environment. GGT expression is upregulated in some tumors (Hanigan et al. 1999) and downregulated in others (Priolo et al. 2018), suggesting that tumors may differ in their ability to degrade and utilize glutathione as a source of amino acids. Recent work has suggested that glutathione breakdown may serve additional functions (Boysen 2017), but the ability of cells to express GGT and utilize extracellular glutathione as a nutrient source likely plays a role in determining the accessibility of certain amino acids to tumors.

Some cancer cells are able to take up larger macromolecules. For instance, certain tumors are able to consume whole protein from the environment through integrin-mediated scavenging (Finicle et al. 2018), receptor-mediated endocytosis (Merlot et al. 2014; Finicle et al. 2018) or by non-specific uptake involving macropinocytosis (Recouvreux and Commissso 2017; Finicle et al. 2018). The ability to effectively utilize extracellular protein as an amino acid source can increase the effective accessibility of amino acids for cells within tumors (Finicle et al. 2018). Nutrient scavenging can also be used to take up molecules other than protein to support cellular metabolic processes (Kim et al. 2018). Beyond taking up macromolecules from the environment, some cells can even invade and consume neighboring cells through the process of entosis, allowing for replenishment of nutrients (Overholtzer et al. 2007; Krajcovic et al. 2013; Hamann et al. 2017). Though this process is likely a response to low nutrient levels rather than an active strategy of obtaining nutrients under basal conditions, it provides another path for cancer cells to increase nutrient accessibility.

**Nutrient recycling**—In addition to altered nutrient uptake, some tumors are able to modulate metabolite accessibility by breaking down macromolecules into their constituent parts through the process of autophagy (Kimmelman and White 2017; Wyant et al. 2017; An
and Harper 2018). Autophagy can alter intracellular metabolite levels in response to starvation (Guo et al. 2016), but recycling of nutrients in this way cannot provide a net source of new metabolites for tumor cells. Recycling processes do not lead to net metabolite consumption, and are therefore unable to directly fuel cell growth; however, nutrient recycling can be important as a mechanism to alter nutrient accessibility to allow tumors to preserve levels of critical nutrients during transient periods of deprivation, and thus can affect cancer cell survival. This effect on nutrient availability may explain, in part, why impairment of autophagy can hinder tumor growth (Kimmelman and White 2017).

**Altered nutrient biosynthesis**—For those metabolites that can be produced by tumors, *de novo* synthesis represents an important method to modulate nutrient availability. The synthesis of many classes of metabolites, including amino acids (Liu W et al. 2012; Mattaini et al. 2016) and lipids (Long et al. 2018), is upregulated in tumors and may represent a method for tumors to bypass low environmental nutrient accessibility in some tissue contexts. Often, the increased rate of *de novo* metabolite synthesis is necessary to maintain tumor proliferation, suggesting that the improved nutrient availability resulting from increased biosynthesis is required to meet the nutrient demands of the cell. For instance, many tumors upregulate the enzymes of the serine synthesis pathway, which converts the glycolytic intermediate 3-phosphoglycerate into serine through a three-step process (Adams 2007; Locasale et al. 2011; Possemato et al. 2011; Nilsson et al. 2012; DeNicola et al. 2015; Ben-Sahra et al. 2016; Samanta et al. 2016). The altered availability of nutrients due to upregulation of serine synthesis can promote tumor growth (Possemato et al. 2011; DeNicola et al. 2015; Pacold et al. 2016) and at least in some cases, low availability of serine can drive this effect (Sullivan, Mattaini, et al. 2019). However, biosynthesis of one nutrient inevitably generates a metabolic cost elsewhere. For instance, for each molecule of serine synthesized by a cancer cell, the cell must consume $\frac{1}{2}$ glucose, 2 NAD$^+$, and convert 1 glutamate into 1 $\alpha$-ketoglutarate. Thus, altered nutrient biosynthesis can affect the allocation of metabolic resources to other pathways, not just the end product of a biosynthetic pathway. As a result, variability in biosynthetic rates can be an important determinant of nutrient availability for tumors.

**Conclusions**

Restricting tumor growth by targeting metabolic pathways or nutrients that are limiting for proliferation remains an attractive therapeutic strategy. However, to successfully target metabolism in this fashion, we must continue to develop a better understanding of what is limiting for tumor growth and the factors that determine these limitations. Both the demand for a metabolite and its accessibility to cancer cells within a tumor will define what is limiting, and each of these terms is determined by a complex mix of tumor-intrinsic and tumor-extrinsic factors that must be considered when studying cancer metabolism. Critically, these variables often represent factors that are unique to specific tumor types. Thus, the altered demand and accessibility of nutrients in tumors may render them specifically vulnerable to inhibition of certain metabolic pathways or deprivation of particular nutrients. Better understanding the complex interplay between these factors will be essential to turn these unique characteristics of cancers into specific, effective therapies.
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Figure 1.
Nutrient limitation is determined by the combined effects of demand and accessibility. Tumor survival and proliferation is influenced by the intracellular concentrations of many metabolites. This intracellular concentration is dictated by the rate of consumption of the metabolite (demand) as well as the rate of metabolite acquisition (accessibility). Color version of this figure is available online.
Figure 2.
Metabolite demand of cancer cells is determined by several cell-intrinsic factors. These variables include the presence of specific tumor-promoting mutations, chromosomal abnormalities, phenotypic states, and the tissue of origin of the tumor. Color version of this figure is available online.
Figure 3.
Nutrient accessibility to cells within tumors is driven by both cell-extrinsic and cell-intrinsic variables. Circulating metabolite levels and local microenvironmental nutrient levels determine nutrient accessibility to cells within the tumor, and cell surface transport, scavenging, recycling, and de novo metabolite synthesis influence the intracellular levels of metabolites that can be used by the cells.
Color version of this figure is available online.