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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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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 (Humpton 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 of 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 W 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 Commisso 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 ½ glucose, 2 $NAD^+$, and convert 1 glutamate into 1 α-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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## References

Adams CM. 2007 Role of the transcription factor ATF4 in the anabolic actions of insulin and the anti-anabolic actions of glucocorticoids. J Biol Chem. 282(23):16744–16753. [PubMed: 17430894]

An H, Harper JW. 2018 Systematic analysis of ribophagy in human cells reveals bystander flux during selective autophagy. Nat Cell Biol. 20(2):135–143. [PubMed: 29230017]

Appel LJ, Sacks FM, Carey VJ, Obarzanek E, Swain JF, Miller ER 3rd, Conlin PR, Erlinger TP, Rosner BA, Laranjo NM et al. 2005 Effects of protein, monounsaturated fat, and carbohydrate intake on blood pressure and serum lipids: results of the OmniHeart randomized trial. JAMA. 294(19):2455–2464. [PubMed: 16287956]

Arroyo JD, Jourdain AA, Calvo SE, Ballarano CA, Doench JG, Root DE, Mootha VK. 2016 A Genome-wide CRISPR Death Screen Identifies Genes Essential for Oxidative Phosphorylation. Cell Metab. 24(6):875–885. [PubMed: 27667664]

Ashkavand Z, O'Flanagan C, Hennig M, Du X, Hursting SD, Krupenko SA. 2017 Metabolic Reprogramming by Folate Restriction Leads to a Less Aggressive Cancer Phenotype. Mol Cancer Res. 15(2):189–200. [PubMed: 28108628]

Bardeesy N, Cheng KH, Berger JH, Chu GC, Pahler J, Olson P, Hezel AF, Horner J, Lauwers GY, Hanahan D et al. 2006 Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. Genes Dev. 20(22):3130–3146. [PubMed: 17114584]

Barker GA, Ellory JC. 1990 The Identification of Neutral Amino-Acid-Transport Systems. Exp Physiol. 75(1):3–26. English. [PubMed: 2178639]

Batlle E, Clevers H. 2017 Cancer stem cells revisited. Nat Med. 23(10):1124–1134. [PubMed: 28985214]

Ben-Sahra I, Hoxhaj G, Ricoult SJH, Asara JM, Manning BD. 2016 mTORC1 induces purine synthesis through control of the mitochondrial tetrahydrofolate cycle. Science. 351(6274):728–733. English. [PubMed: 26912861]

Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E, Vousden KH. 2006 TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 126(1):107–120. [PubMed: 16839880]

Beroukhim R, Mermel CH, Porter D, Wei G, Raychaudhuri S, Donovan J, Barretina J, Boehm JS, Dobson J, Urashima M et al. 2010 The landscape of somatic copy-number alteration across human cancers. Nature. 463(7283):899–905. [PubMed: 20164920]

Birsoy K, Possemato R, Lorbeer FK, Bayraktar EC, Thiru P, Yucel B, Wang T, Chen WW, Clish CB, Sabatini DM. 2014 Metabolic determinants of cancer cell sensitivity to glucose limitation and biguanides. Nature. 508(7494):108–112. [PubMed: 24670634]

Boots-Sprenger SH, Sijben A, Rijntjes J, Tops BB, Idema AJ, Rivera AL, Bleeker FE, Gijtenbeek AM, Diefes K, Heathcock L et al. 2013 Significance of complete 1p/19q co-deletion, IDH1 mutation and MGMT promoter methylation in gliomas: use with caution. Mod Pathol. 26(7):922–929. [PubMed: 23429602]

Boysen G 2017 The Glutathione Conundrum: Stoichiometric Disconnect between Its Formation and Oxidative Stress. Chem Res Toxicol. 30(5):1113–1116. [PubMed: 28426193]

Brabletz T, Kalluri R, Nieto MA, Weinberg RA. 2018 EMT in cancer. Nat Rev Cancer. 18(2):128–134. [PubMed: 29326430]

Branzoli F, Pontoizeau C, Tchara L, Di Stefano AL, Kamoun A, Deelchand DK, Valabregue R, Lehericy S, Sanson M, Ottolenghi C et al. 2019 Cystathionine as a marker for 1p/19q codeleted gliomas by in vivo magnetic resonance spectroscopy. Neuro Oncol.

Broer A, Fairweather S, Broer S. 2018 Disruption of Amino Acid Homeostasis by Novel ASCT2 Inhibitors Involves Multiple Targets. Front Pharmacol. 9:785. [PubMed: 30072900]

Broer S, Broer A. 2017 Amino acid homeostasis and signalling in mammalian cells and organisms. Biochem J. 474(12):1935–1963. [PubMed: 28546457]

Brown R, Curry E, Magnani L, Wilhelm-Benartzi CS, Borley J. 2014 Poised epigenetic states and acquired drug resistance in cancer. Nat Rev Cancer. 14(11):747–753. [PubMed: 25253389]

Bryant KL, Mancias JD, Kimmelman AC, Der CJ. 2014 KRAS: feeding pancreatic cancer proliferation. Trends Biochem Sci. 39(2):91–100. [PubMed: 24388967]

Cai Y, Crowther J, Pastor T, Abbasi Asbagh L, Baietti MF, De Troyer M, Vazquez I, Talebi A, Renzi F, Dehairs J et al. 2016 Loss of Chromosome 8p Governs Tumor Progression and Drug Response by Altering Lipid Metabolism. Cancer Cell. 29(5):751–766. [PubMed: 27165746]

Cairns RA, Harris IS, Mak TW. 2011 Regulation of cancer cell metabolism. Nat Rev Cancer. 11(2): 85–95. [PubMed: 21258394]

Carrera CJ, Eddy RL, Shows TB, Carson DA. 1984 Assignment of the gene for methylthioadenosine phosphorylase to human chromosome 9 by mouse-human somatic cell hybridization. Proc Natl Acad Sci U S A. 81(9):2665–2668. [PubMed: 6425836]

Cesar-Razquin A, Snijder B, Frappier-Brinton T, Isserlin R, Gyimesi G, Bai X, Reithmeier RA, Hepworth D, Hediger MA, Edwards AM et al. 2015 A Call for Systematic Research on Solute Carriers. Cell. 162(3):478–487. [PubMed: 26232220]

Cha YJ, Kim ES, Koo JS. 2018 Amino Acid Transporters and Glutamine Metabolism in Breast Cancer. Int J Mol Sci. 19(3).

Ciriello G, Miller ML, Aksoy BA, Senbabaoglu Y, Schultz N, Sander C. 2013 Emerging landscape of oncogenic signatures across human cancers. Nat Genet. 45(10):1127–1133. [PubMed: 24071851]

Cormerais Y, Massard PA, Vucetic M, Giuliano S, Tambutte E, Durivault J, Vial V, Endou H, Wempe MF, Parks SK et al. 2018 The glutamine transporter ASCT2 (SLC1A5) promotes tumor growth independently of the amino acid transporter LAT1 (SLC7A5). J Biol Chem. 293(8):2877–2887. [PubMed: 29326164]

Dallmann R, Viola AU, Tarokh L, Cajochen C, Brown SA. 2012 The human circadian metabolome. Proc Natl Acad Sci U S A. 109(7):2625–2629. [PubMed: 22308371]

Dang CV, Le A, Gao P. 2009 MYC-induced cancer cell energy metabolism and therapeutic opportunities. Clin Cancer Res. 15(21):6479–6483. [PubMed: 19861459]

DeNicola GM, Chen PH, Mullarky E, Sudderth JA, Hu Z, Wu D, Tang H, Xie Y, Asara JM, Huffman KE et al. 2015 NRF2 regulates serine biosynthesis in non-small cell lung cancer. Nat Genet. 47(12):1475–1481. [PubMed: 26482881]

Dey P, Baddour J, Muller F, Wu CC, Wang H, Liao WT, Lan Z, Chen A, Gutschner T, Kang Y et al. 2017 Genomic deletion of malic enzyme 2 confers collateral lethality in pancreatic cancer. Nature. 542(7639):119–123. [PubMed: 28099419]

Duro D, Bernard O, Della Valle V, Berger R, Larsen CJ. 1995 A new type of p16INK4/MTS1 gene transcript expressed in B-cell malignancies. Oncogene. 11(1):21–29. [PubMed: 7624129]

Farber S, Cutler EC, Hawkins JW, Harrison JH, Peirce EC 2nd, Lenz GG. 1947 The Action of Pteroylglutamic Conjugates on Man. Science. 106(2764):619–621. [PubMed: 17831847]

Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA. 1948 Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteryl-glutamic acid (aminopterin). New England Journal of Medicine. 238(23):787–793. [PubMed: 18860765]

Fendt SM. 2017 Is There a Therapeutic Window for Metabolism-Based Cancer Therapies? Front Endocrinol (Lausanne). 8:150. [PubMed: 28725214]

Finicle BT, Jayashankar V, Edinger AL. 2018 Nutrient scavenging in cancer. Nat Rev Cancer. 18(10): 619–633. [PubMed: 30097614]

Fitzpatrick TB, Basset GJ, Borel P, Carrari F, DellaPenna D, Fraser PD, Hellmann H, Osorio S, Rothan C, Valpuesta V et al. 2012 Vitamin deficiencies in humans: can plant science help? Plant Cell. 24(2):395–414. [PubMed: 22374394]

Friedberg F, Greenberg DM. 1947 Endocrine regulation of amino acid levels in blood and tissues. J Biol Chem. 168(2):405–409. [PubMed: 20238597]

Fujisaka S, Avila-Pacheco J, Soto M, Kostic A, Dreyfuss JM, Pan H, Ussar S, Altindis E, Li N, Bry L et al. 2018 Diet, Genetics, and the Gut Microbiome Drive Dynamic Changes in Plasma Metabolites. Cell Rep. 22(11):3072–3086. [PubMed: 29539432]

Fukumura D, Duda DG, Munn LL, Jain RK. 2010 Tumor microvasculature and microenvironment: novel insights through intravital imaging in pre-clinical models. Microcirculation. 17(3):206–225. [PubMed: 20374484]

Gaude E, Frezza C. 2016 Tissue-specific and convergent metabolic transformation of cancer correlates with metastatic potential and patient survival. Nat Commun. 7:13041. [PubMed: 27721378]

Glatz JF, Luiken JJ, Bonen A. 2010 Membrane fatty acid transporters as regulators of lipid metabolism: implications for metabolic disease. Physiol Rev. 90(1):367–417. [PubMed: 20086080]

Guo JY, Teng X, Laddha SV, Ma S, Van Nostrand SC, Yang Y, Khor S, Chan CS, Rabinowitz JD, White E. 2016 Autophagy provides metabolic substrates to maintain energy charge and nucleotide pools in Ras-driven lung cancer cells. Genes Dev. 30(15):1704–1717. [PubMed: 27516533]

Hahn SA, Schutte M, Hoque ATMS, Moskaluk CA, daCosta LT, Rozenblum E, Weinstein CL, Fischer A, Yeo CJ, Hruban RH et al. 1996 DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science. 271(5247):350–353. English. [PubMed: 8553070]

Hamann JC, Surcel A, Chen R, Teragawa C, Albeck JG, Robinson DN, Overholtzer M. 2017 Entosis Is Induced by Glucose Starvation. Cell Rep. 20(1):201–210. [PubMed: 28683313]

Han HS, Kang G, Kim JS, Choi BH, Koo SH. 2016 Regulation of glucose metabolism from a liver-centric perspective. Exp Mol Med. 48:e218. [PubMed: 26964834]

Hanahan D, Weinberg RA. 2011 Hallmarks of cancer: the next generation. Cell. 144(5):646–674. [PubMed: 21376230]

Hangauer MJ, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, Galeas J, Dhruv HD, Berens ME, Schreiber SL et al. 2017 Drug-tolerant persister cancer cells are vulnerable to GPX4 inhibition. Nature. 551(7679):247–250. [PubMed: 29088702]

Hanigan MH, Gallagher BC, Townsend DM, Gabarra V. 1999 Gamma-glutamyl transpeptidase accelerates tumor growth and increases the resistance of tumors to cisplatin in vivo. Carcinogenesis. 20(4):553–559. [PubMed: 10223181]

Hansen MF, Jensen SO, Fuchtbauer EM, Martensen PM. 2017 High folic acid diet enhances tumour growth in PyMT-induced breast cancer. Br J Cancer. 116(6):752–761. [PubMed: 28152548]

He CH, Gong P, Hu B, Stewart D, Choi ME, Choi AM, Alam J. 2001 Identification of activating transcription factor 4 (ATF4) as an Nrf2-interacting protein. Implication for heme oxygenase-1 gene regulation. J Biol Chem. 276(24):20858–20865. [PubMed: 11274184]

Hediger MA, Clemencon B, Burrier RE, Bruford EA. 2013 The ABCs of membrane transporters in health and disease (SLC series): introduction. Mol Aspects Med. 34(2–3):95–107. [PubMed: 23506860]

Hopkins BD, Pauli C, Du X, Wang DG, Li X, Wu D, Amadiume SC, Goncalves MD, Hodakoski C, Lundquist MR et al. 2018 Suppression of insulin feedback enhances the efficacy of PI3K inhibitors. Nature. 560(7719):499–503. [PubMed: 30051890]

Hsu RY. 1982 Pigeon liver malic enzyme. Mol Cell Biochem. 43(1):3–26. [PubMed: 7078548]

Hu J, Locasale JW, Bielas JH, O'Sullivan J, Sheahan K, Cantley LC, Vander Heiden MG, Vitkup D. 2013 Heterogeneity of tumor-induced gene expression changes in the human metabolic network. Nat Biotechnol. 31(6):522–529. [PubMed: 23604282]

Humpton TJ, Hock AK, Maddocks ODK, Vousden KH. 2018 p53-mediated adaptation to serine starvation is retained by a common tumour-derived mutant. Cancer Metab. 6:18. [PubMed: 30524726]

Hwang S, Gustafsson HT, O'Sullivan C, Bisceglia G, Huang X, Klose C, Schevchenko A, Dickson RC, Cavaliere P, Dephoure N et al. 2017 Serine-Dependent Sphingolipid Synthesis Is a Metabolic Liability of Aneuploid Cells. Cell Rep. 21(13):3807–3818. [PubMed: 29281829]

Inoue K 2017 Molecular Basis of Nucleobase Transport Systems in Mammals. Biol Pharm Bull. 40(8): 1130–1138. [PubMed: 28768993]

Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, Oyake T, Hayashi N, Satoh K, Hatayama I et al. 1997 An Nrf2 small Maf heterodimer mediates the induction of phase II detoxifying enzyme

genes through antioxidant response elements. Biochemical and Biophysical Research Communications. 236(2):313–322. English. [PubMed: 9240432]

Itoh K, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD, Yamamoto M. 1999 Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Gene Dev. 13(1):76–86. English. [PubMed: 9887101]

Ji X, Qian J, Rahman SMJ, Siska PJ, Zou Y, Harris BK, Hoeksema MD, Trenary IA, Heidi C, Eisenberg R et al. 2018 xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression. Oncogene. 37(36):5007–5019. [PubMed: 29789716]

Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. 2015 Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 520(7545):57–62. [PubMed: 25799988]

Jiang P, Du W, Mancuso A, Wellen KE, Yang X. 2013 Reciprocal regulation of p53 and malic enzymes modulates metabolism and senescence. Nature. 493(7434):689–693. [PubMed: 23334421]

Kandasamy P, Gyimesi G, Kanai Y, Hediger MA. 2018 Amino acid transporters revisited: New views in health and disease. Trends Biochem Sci. 43(10):752–789. [PubMed: 30177408]

Kansanen E, Kuosmanen SM, Leinonen H, Levonen AL. 2013 The Keap1-Nrf2 pathway: Mechanisms of activation and dysregulation in cancer. Redox Biol. 1:45–49. [PubMed: 24024136]

Kastenhuber ER, Lowe SW. 2017 Putting p53 in Context. Cell. 170(6):1062–1078. [PubMed: 28886379]

Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. 2010 Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 152(2):93–100. [PubMed: 20083828]

Kim SM, Nguyen TT, Ravi A, Kubiniok P, Finicle BT, Jayashankar V, Malacrida L, Hou J, Robertson J, Gao D et al. 2018 PTEN Deficiency and AMPK Activation Promote Nutrient Scavenging and Anabolism in Prostate Cancer Cells. Cancer Discov. 8(7):866–883. [PubMed: 29572236]

Kimmelman AC, White E. 2017 Autophagy and Tumor Metabolism. Cell Metab. 25(5):1037–1043. [PubMed: 28467923]

Klement RJ. 2017 Beneficial effects of ketogenic diets for cancer patients: a realist review with focus on evidence and confirmation. Med Oncol. 34(8):132. [PubMed: 28653283]

Knouse KA, Wu J, Whittaker CA, Amon A. 2014 Single cell sequencing reveals low levels of aneuploidy across mammalian tissues. Proc Natl Acad Sci U S A. 111(37):13409–13414. [PubMed: 25197050]

Kobayashi A, Kang MI, Okawa H, Ohtsuji M, Zenke Y, Chiba T, Igarashi K, Yamamoto M. 2004 Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. Mol Cell Biol. 24(16):7130–7139. [PubMed: 15282312]

Kory N, Wyant GA, Prakash G, Uit de Bos J, Bottanelli F, Pacold ME, Chan SH, Lewis CA, Wang T, Keys HR et al. 2018 SFXN1 is a mitochondrial serine transporter required for one-carbon metabolism. Science. 362(6416).

Krajcovic M, Krishna S, Akkari L, Joyce JA, Overholtzer M. 2013 mTOR regulates phagosome and entotic vacuole fission. Mol Biol Cell. 24(23):3736–3745. [PubMed: 24088573]

Krall AS, Xu S, Graeber TG, Braas D, Christofk HR. 2016 Asparagine promotes cancer cell proliferation through use as an amino acid exchange factor. Nat Commun. 7:11457. [PubMed: 27126896]

Kruiswijk F, Labuschagne CF, Vousden KH. 2015 p53 in survival, death and metabolic health: a lifeguard with a licence to kill. Nat Rev Mol Cell Biol. 16(7):393–405. [PubMed: 26122615]

Kumar V, Patel S, Tcyganov E, Gabrilovich DI. 2016 The Nature of Myeloid-Derived Suppressor Cells in the Tumor Microenvironment. Trends Immunol. 37(3):208–220. [PubMed: 26858199]

Ladanyi A, Mukherjee A, Kenny HA, Johnson A, Mitra AK, Sundaresan S, Nieman KM, Pascual G, Benitah SA, Montag A et al. 2018 Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. Oncogene. 37(17):2285–2301. [PubMed: 29398710]

Lamm N, Maoz K, Bester AC, Im MM, Shewach DS, Karni R, Kerem B. 2015 Folate levels modulate oncogene-induced replication stress and tumorigenicity. EMBO Mol Med. 7(9):1138–1152. [PubMed: 26197802]

Le Bourgeois T, Strauss L, Aksoylar HI, Daneshmandi S, Seth P, Patsoukis N, Boussiotis VA. 2018 Targeting T Cell Metabolism for Improvement of Cancer Immunotherapy. Front Oncol. 8:237. [PubMed: 30123774]

LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. 2013 Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol. 24(2):160–168. [PubMed: 22940212]

Lee C, Raffaghello L, Brandhorst S, Safdie FM, Bianchi G, Martin-Montalvo A, Pistoia V, Wei M, Hwang S, Merlino A et al. 2012 Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med. 4(124):124ra127.

Li LH, Dong H, Zhao F, Tang J, Chen X, Ding J, Men HT, Luo WX, Du Y, Ge J et al. 2013 The upregulation of dihydropyrimidine dehydrogenase in liver is involved in acquired resistance to 5-fluorouracil. Eur J Cancer. 49(7):1752–1760. [PubMed: 23313143]

Lin Y-H, Satani N, Hammoudi N, Ackroyd JJ, Khadka S, Yan VC, Georgiou DK, Sun Y, Zielinski R, Tran T et al. 2018 Eradication of ENO1-deleted Glioblastoma through Collateral Lethality. bioRxiv. doi: 10.1101/331538.

Liu W, Le A, Hancock C, Lane AN, Dang CV, Fan TW, Phang JM. 2012 Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic responses regulated by oncogenic transcription factor c-MYC. Proc Natl Acad Sci U S A. 109(23):8983–8988. [PubMed: 22615405]

Liu YC, Li F, Handler J, Huang CR, Xiang Y, Neretti N, Sedivy JM, Zeller KI, Dang CV. 2008 Global regulation of nucleotide biosynthetic genes by c-Myc. PLoS One. 3(7):e2722. [PubMed: 18628958]

Locasale JW, Grassian AR, Melman T, Lyssiotis CA, Mattaini KR, Bass AJ, Heffron G, Metallo CM, Muranen T, Sharfi H et al. 2011 Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis. Nat Genet. 43(9):869–874. [PubMed: 21804546]

Long J, Zhang CJ, Zhu N, Du K, Yin YF, Tan X, Liao DF, Qin L. 2018 Lipid metabolism and carcinogenesis, cancer development. Am J Cancer Res. 8(5):778–791. [PubMed: 29888102]

Lu Z, Xie J, Wu G, Shen J, Collins R, Chen W, Kang X, Luo M, Zou Y, Huang LJ et al. 2017 Fasting selectively blocks development of acute lymphoblastic leukemia via leptin-receptor upregulation. Nat Med. 23(1):79–90. [PubMed: 27941793]

Lyssiotis CA, Kimmelman AC. 2017 Metabolic Interactions in the Tumor Microenvironment. Trends Cell Biol. 27(11):863–875. [PubMed: 28734735]

Ma YS, Li YF, Chiriboga DE, Olendzki BC, Hebert JR, Li WJ, Leung K, Hafner AR, Ockene IS. 2006 Association between carbohydrate intake and serum lipids. Journal of the American College of Nutrition. 25(2):155–163. English. [PubMed: 16582033]

Maddocks ODK, Athineos D, Cheung EC, Lee P, Zhang T, van den Broek NJF, Mackay GM, Labuschagne CF, Gay D, Kruiswijk F et al. 2017 Modulating the therapeutic response of tumours to dietary serine and glycine starvation. Nature. 544(7650):372–376. [PubMed: 28425994]

Maddocks ODK, Berkers CR, Mason SM, Zheng L, Blyth K, Gottlieb E, Vousden KH. 2013 Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. Nature. 493(7433):542–546. [PubMed: 23242140]

Mani SA, Guo W, Liao MJ, Eaton EN, Ayyanan A, Zhou AY, Brooks M, Reinhard F, Zhang CC, Shipitsin M et al. 2008 The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell. 133(4):704–715. [PubMed: 18485877]

Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. 2017 The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 7(3):339–348. [PubMed: 29071215]

Mao L, Merlo A, Bedi G, Shapiro GI, Edwards CD, Rollins BJ, Sidransky D. 1995 A novel p16INK4A transcript. Cancer Res. 55(14):2995–2997. [PubMed: 7541708]

Marjon K, Cameron MJ, Quang P, Clasquin MF, Mandley E, Kunii K, McVay M, Choe S, Kernytsky A, Gross S et al. 2016 MTAP Deletions in Cancer Create Vulnerability to Targeting of the MAT2A/PRMT5/RIOK1 Axis. Cell Rep. 15(3):574–587. [PubMed: 27068473]

Masri S, Papagiannakopoulos T, Kinouchi K, Liu Y, Cervantes M, Baldi P, Jacks T, Sassone-Corsi P. 2016 Lung Adenocarcinoma Distally Rewires Hepatic Circadian Homeostasis. Cell. 165(4):896–909. [PubMed: 27153497]

Masri S, Sassone-Corsi P. 2018 The emerging link between cancer, metabolism, and circadian rhythms. Nat Med. 24(12):1795–1803. [PubMed: 30523327]

Mattaini KR, Sullivan MR, Vander Heiden MG. 2016 The importance of serine metabolism in cancer. J Cell Biol. 214(3):249–257. [PubMed: 27458133]

Mavrakis KJ, McDonald ER 3rd, Schlabach MR, Billy E, Hoffman GR, deWeck A, Ruddy DA, Venkatesan K, Yu J, McAllister G et al. 2016 Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. Science. 351(6278):1208–1213. [PubMed: 26912361]

Mayers JR, Torrence ME, Danai LV, Papagiannakopoulos T, Davidson SM, Bauer MR, Lau AN, Ji BW, Dixit PD, Hosios AM et al. 2016 Tissue of origin dictates branched-chain amino acid metabolism in mutant Kras-driven cancers. Science. 353(6304):1161–1165. [PubMed: 27609895]

Mayers JR, Wu C, Clish CB, Kraft P, Torrence ME, Fiske BP, Yuan C, Bao Y, Townsend MK, Tworoger SS et al. 2014 Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. Nat Med. 20(10):1193–1198. [PubMed: 25261994]

Merlot AM, Kalinowski DS, Richardson DR. 2014 Unraveling the mysteries of serum albumin-more than just a serum protein. Front Physiol. 5:299. [PubMed: 25161624]

Morandi A, Taddei ML, Chiarugi P, Giannoni E. 2017 Targeting the Metabolic Reprogramming That Controls Epithelial-to-Mesenchymal Transition in Aggressive Tumors. Front Oncol. 7:40. [PubMed: 28352611]

Moulder JW, Vennesland B, Evans EA. 1945 A study of enzymatic reactions catalyzed by pigeon liver extracts. J Biol Chem. 160:305–325.

Muir A, Danai LV, Gui DY, Waingarten CY, Lewis CA, Vander Heiden MG. 2017 Environmental cystine drives glutamine anaplerosis and sensitizes cancer cells to glutaminase inhibition. Elife. 6.

Muller FL, Aquilanti EA, DePinho RA. 2015 Collateral Lethality: A new therapeutic strategy in oncology. Trends Cancer. 1(3):161–173. [PubMed: 26870836]

Muller FL, Colla S, Aquilanti E, Manzo VE, Genovese G, Lee J, Eisenson D, Narurkar R, Deng P, Nezi L et al. 2012 Passenger deletions generate therapeutic vulnerabilities in cancer. Nature. 488(7411):337–342. [PubMed: 22895339]

Nagarajan A, Malvi P, Wajapeyee N. 2016 Oncogene-directed alterations in cancer cell metabolism. Trends Cancer. 2(7):365–377. [PubMed: 27822561]

Newgard CB, An J, Bain JR, Muehlbauer MJ, Stevens RD, Lien LF, Haqq AM, Shah SH, Arlotto M, Slentz CA et al. 2009 A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 9(4):311–326. [PubMed: 19356713]

Nicklin P, Bergman P, Zhang B, Triantafellow E, Wang H, Nyfeler B, Yang H, Hild M, Kung C, Wilson C et al. 2009 Bidirectional transport of amino acids regulates mTOR and autophagy. Cell. 136(3):521–534. [PubMed: 19203585]

Nikiforov MA, Chandriani S, O'Connell B, Petrenko O, Kotenko I, Beavis A, Sedivy JM, Cole MD. 2002 A Functional Screen for Myc-Responsive Genes Reveals Serine Hydroxymethyltransferase, a Major Source of the One-Carbon Unit for Cell Metabolism. Molecular and Cellular Biology. 22(16):5793–5800. [PubMed: 12138190]

Nilsson LM, Forshell TZ, Rimpi S, Kreutzer C, Pretsch W, Bornkamm GW, Nilsson JA. 2012 Mouse genetics suggests cell-context dependency for Myc-regulated metabolic enzymes during tumorigenesis. PLoS Genet. 8(3):e1002573. [PubMed: 22438825]

Orlowski M, Meister A. 1970 The gamma-glutamyl cycle: a possible transport system for amino acids. Proc Natl Acad Sci U S A. 67(3):1248–1255. [PubMed: 5274454]

Overholtzer M, Mailleux AA, Mouneimne G, Normand G, Schnitt SJ, King RW, Cibas ES, Brugge JS. 2007 A nonapoptotic cell death process, entosis, that occurs by cell-in-cell invasion. Cell. 131(5):966–979. [PubMed: 18045538]

Pacold ME, Brimacombe KR, Chan SH, Rohde JM, Lewis CA, Swier LJ, Possemato R, Chen WW, Sullivan LB, Fiske BP et al. 2016 A PHGDH inhibitor reveals coordination of serine synthesis and one-carbon unit fate. Nat Chem Biol. 12(6):452–458. [PubMed: 27110680]

Pastore A, Massoud R, Motti C, Lo Russo A, Fucci G, Cortese C, Federici G. 1998 Fully automated assay for total homocysteine, cysteine, cysteinylglycine, glutathione, cysteamine, and 2-mercaptopropionylglycine in plasma and urine. Clin Chem. 44(4):825–832. [PubMed: 9554495]

Pegg AE. 2009 Mammalian polyamine metabolism and function. IUBMB Life. 61(9):880–894. [PubMed: 19603518]

Pegg AE, Williams-Ashman HG. 1969a On the role of S-adenosyl-L-methionine in the biosynthesis of spermidine by rat prostate. J Biol Chem. 244(4):682–693. [PubMed: 4889860]

Pegg AE, Williams-Ashman HG. 1969b Phosphate-stimulated breakdown of 5'-methylthioadenosine by rat ventral prostate. Biochem J. 115(2):241–247. [PubMed: 5378381]

Perez-Escuredo J, Van Hee VF, Sboarina M, Falces J, Payen VL, Pellerin L, Sonveaux P. 2016 Monocarboxylate transporters in the brain and in cancer. Biochim Biophys Acta. 1863(10):2481–2497. [PubMed: 26993058]

Possemato R, Marks KM, Shaul YD, Pacold ME, Kim D, Birsoy K, Sethumadhavan S, Woo HK, Jang HG, Jha AK et al. 2011 Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. Nature. 476(7360):346–350. [PubMed: 21760589]

Priolo C, Khabibullin D, Reznik E, Filippakis H, Ogorek B, Kavanagh TR, Nijmeh J, Herbert ZT, Asara JM, Kwiatkowski DJ et al. 2018 Impairment of gamma-glutamyl transferase 1 activity in the metabolic pathogenesis of chromophobe renal cell carcinoma. Proc Natl Acad Sci U S A. 115(27):E6274–E6282. [PubMed: 29891694]

Puzio-Kuter AM. 2011 The Role of p53 in Metabolic Regulation Genes Cancer. 2(4):385–391. [PubMed: 21779507]

Quelle DE, Zindy F, Ashmun RA, Sherr CJ. 1995 Alternative reading frames of the INK4a tumor suppressor gene encode two unrelated proteins capable of inducing cell cycle arrest. Cell. 83(6): 993–1000. [PubMed: 8521522]

Raeini-Sarjaz M, Vanstone CA, Papamandjaris AA, Wykes LJ, Jones PJH. 2001 Comparison of the effect of dietary fat restriction with that of energy restriction on human lipid metabolism. American Journal of Clinical Nutrition. 73(2):262–267. English. [PubMed: 11157322]

Raghunath A, Sundarraj K, Nagarajan R, Arfuso F, Bian J, Kumar AP, Sethi G, Perumal E. 2018 Antioxidant response elements: Discovery, classes, regulation and potential applications. Redox Biol. 17:297–314. [PubMed: 29775961]

Recouvreux MV, Commisso C. 2017 Macropinocytosis: A Metabolic Adaptation to Nutrient Stress in Cancer. Front Endocrinol (Lausanne). 8:261. [PubMed: 29085336]

Romero R, Sayin VI, Davidson SM, Bauer MR, Singh SX, LeBoeuf SE, Karakousi TR, Ellis DC, Bhutkar A, Sanchez-Rivera FJ et al. 2017 Keap1 loss promotes Kras-driven lung cancer and results in dependence on glutaminolysis. Nat Med. 23(11):1362–1368. [PubMed: 28967920]

Samanta D, Park Y, Andrabi SA, Shelton LM, Gilkes DM, Semenza GL. 2016 PHGDH Expression Is Required for Mitochondrial Redox Homeostasis, Breast Cancer Stem Cell Maintenance, and Lung Metastasis. Cancer Res. 76(15):4430–4442. [PubMed: 27280394]

Sanderson SM, Mikhael P, Dai Z, Locasale JW. 2018 Environmental factors shape methionine metabolism in p16/MTAP deleted cells. bioRxiv. doi: 10.1101/313288.

Sansregret L, Swanton C. 2017 The Role of Aneuploidy in Cancer Evolution. Cold Spring Harb Perspect Med. 7(1).

Santana-Codina N, Roeth AA, Zhang Y, Yang A, Mashadova O, Asara JM, Wang X, Bronson RT, Lyssiotis CA, Ying H et al. 2018 Oncogenic KRAS supports pancreatic cancer through regulation of nucleotide synthesis. Nat Commun. 9(1):4945. [PubMed: 30470748]

Sayin VI, LeBoeuf SE, Singh SX, Davidson SM, Biancur D, Guzelhan BS, Alvarez SW, Wu WL, Karakousi TR, Zavitsanou AM et al. 2017 Activation of the NRF2 antioxidant program generates an imbalance in central carbon metabolism in cancer. Elife. 6.

Schofield HK, Zeller J, Espinoza C, Halbrook CJ, Del Vecchio A, Magnuson B, Fabo T, Daylan AEC, Kovalenko I, Lee HJ et al. 2018 Mutant p53R270H drives altered metabolism and increased invasion in pancreatic ductal adenocarcinoma. JCI Insight. 3(2).

Schwartzenberg-Bar-Yoseph F, Armoni M, Karnieli E. 2004 The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. Cancer Res. 64(7):2627–2633. [PubMed: 15059920]

Serrano M, Gomez-Lahoz E, DePinho RA, Beach D, Bar-Sagi D. 1995 Inhibition of ras-induced proliferation and cellular transformation by p16INK4. Science. 267(5195):249–252. [PubMed: 7809631]

Serrano M, Hannon GJ, Beach D. 1993 A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature. 366(6456):704–707. [PubMed: 8259215]

Shaul YD, Freinkman E, Comb WC, Cantor JR, Tam WL, Thiru P, Kim D, Kanarek N, Pacold ME, Chen WW et al. 2014 Dihydropyrimidine accumulation is required for the epithelial-mesenchymal transition. Cell. 158(5):1094–1109. [PubMed: 25171410]

Sheltzer JM. 2013 A transcriptional and metabolic signature of primary aneuploidy is present in chromosomally unstable cancer cells and informs clinical prognosis. Cancer Res. 73(21):6401–6412. [PubMed: 24041940]

Singh A, Misra V, Thimmulappa RK, Lee H, Ames S, Hoque MO, Herman JG, Baylin SB, Sidransky D, Gabrielson E et al. 2006 Dysfunctional KEAP1-NRF2 interaction in non-small-cell lung cancer. PLoS Med. 3(10):e420. [PubMed: 17020408]

Sonveaux P, Vegran F, Schroeder T, Wergin MC, Verrax J, Rabbani ZN, De Saedeleer CJ, Kennedy KM, Diepart C, Jordan BF et al. 2008 Targeting lactate-fueled respiration selectively kills hypoxic tumor cells in mice. J Clin Invest. 118(12):3930–3942. [PubMed: 19033663]

Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, Kremer D, Hwang RF, Witkiewicz AK, Ying H et al. 2016 Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. Nature. 536(7617):479–483. [PubMed: 27509858]

Steinhauser ML, Olenchock BA, O'Keefe J, Lun M, Pierce KA, Lee H, Pantano L, Klibanski A, Shulman GI, Clish CB et al. 2018 The circulating metabolome of human starvation. JCI Insight. 3(16).

Stone S, Jiang P, Dayananth P, Tavtigian SV, Katcher H, Parry D, Peters G, Kamb A. 1995 Complex structure and regulation of the P16 (MTS1) locus. Cancer Res. 55(14):2988–2994. [PubMed: 7606716]

Stott FJ, Bates S, James MC, McConnell BB, Starborg M, Brookes S, Palmero I, Ryan K, Hara E, Vousden KH et al. 1998 The alternative product from the human CDKN2A locus, p14ARF, participates in a regulatory feedback loop with p53 and MDM2. EMBO J. 17(17):5001–5014. [PubMed: 9724636]

Sullivan MR, Danai LV, Lewis CA, Chan SH, Gui DY, Kunchok T, Dennstedt EA, Vander Heiden MG, Muir A. 2019 Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. Elife. 8(e44235).

Sullivan MR, Mattaini KR, Dennstedt EA, Nguyen AA, Sivanand S, Reilly MF, Meeth K, Muir A, Darnell AM, Bosenberg MW et al. 2019 Increased Serine Synthesis Provides an Advantage for Tumors Arising in Tissues Where Serine Levels Are Limiting. Cell Metab. In press.

Sun P, Wang H, He Z, Chen X, Wu Q, Chen W, Sun Z, Weng M, Zhu M, Ma D et al. 2017 Fasting inhibits colorectal cancer growth by reducing M2 polarization of tumor-associated macrophages. Oncotarget. 8(43):74649–74660. [PubMed: 29088814]

Szablewski L 2013 Expression of glucose transporters in cancers. Biochim Biophys Acta. 1835(2): 164–169. [PubMed: 23266512]

Tajan M, Hock AK, Blagih J, Robertson NA, Labuschagne CF, Kruiswijk F, Humpton TJ, Adams PD, Vousden KH. 2018 A Role for p53 in the Adaptation to Glutamine Starvation through the Expression of SLC1A3. Cell Metab. 28(5):721–736 e726. [PubMed: 30122553]

Tang YC, Yuwen H, Wang K, Bruno PM, Bullock K, Deik A, Santaguida S, Trakala M, Pfau SJ, Zhong N et al. 2017 Aneuploid Cell Survival Relies upon Sphingolipid Homeostasis. Cancer Res. 77(19):5272–5286. [PubMed: 28775166]

Tardito S, Oudin A, Ahmed SU, Fack F, Keunen O, Zheng L, Miletic H, Sakariassen PO, Weinstock A, Wagner A et al. 2015 Glutamine synthetase activity fuels nucleotide biosynthesis and supports growth of glutamine-restricted glioblastoma. Nat Cell Biol. 17(12):1556–1568. [PubMed: 26595383]

Taroni F, Gellera C, Di Donato S. 1987 Evidence for two distinct mitochondrial malic enzymes in human skeletal muscle: purification and properties of the NAD(P)+-dependent enzyme. Biochim Biophys Acta. 916(3):446–454. [PubMed: 3689803]

Todenhofer T, Seiler R, Stewart C, Moskalev I, Gao J, Ladhar S, Kamjabi A, Al Nakouzi N, Hayashi T, Choi S et al. 2018 Selective Inhibition of the Lactate Transporter MCT4 Reduces Growth of Invasive Bladder Cancer. Mol Cancer Ther. 17(12):2746–2755. [PubMed: 30262589]

Torrence ME, Manning BD. 2018 Nutrient Sensing in Cancer. Annual Review of Cancer Biology. 2(1): 251–269.

Ulrich CM. 2007 Folate and cancer prevention: a closer look at a complex picture. American Journal of Clinical Nutrition. 86(2):271–273. English. [PubMed: 17684194]

Ussar S, Griffin NW, Bezy O, Fujisaka S, Vienberg S, Softic S, Deng L, Bry L, Gordon JI, Kahn CR. 2015 Interactions between Gut Microbiota, Host Genetics and Diet Modulate the Predisposition to Obesity and Metabolic Syndrome. Cell Metab. 22(3):516–530. [PubMed: 26299453]

van Geldermalsen M, Wang Q, Nagarajah R, Marshall AD, Thoeng A, Gao D, Ritchie W, Feng Y, Bailey CG, Deng N et al. 2016 ASCT2/SLC1A5 controls glutamine uptake and tumour growth in triple-negative basal-like breast cancer. Oncogene. 35(24):3201–3208. [PubMed: 26455325]

Vander Heiden MG, DeBerardinis RJ. 2017 Understanding the Intersections between Metabolism and Cancer Biology. Cell. 168(4):657–669. [PubMed: 28187287]

Venugopal R, Jaiswal AK. 1996 Nrf1 and Nrf2 positively and c-Fos and Fra1 negatively regulate the human antioxidant response element-mediated expression of NAD(P)H:quinone oxidoreductase1 gene. Proc Natl Acad Sci U S A. 93(25):14960–14965. [PubMed: 8962164]

Wang R, Dillon CP, Shi LZ, Milasta S, Carter R, Finkelstein D, McCormick LL, Fitzgerald P, Chi H, Munger J et al. 2011 The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity. 35(6):871–882. [PubMed: 22195744]

Wiig H, Swartz MA. 2012 Interstitial fluid and lymph formation and transport: physiological regulation and roles in inflammation and cancer. Physiol Rev. 92(3):1005–1060. [PubMed: 22811424]

Wilcox G 2005 Insulin and insulin resistance. Clin Biochem Rev. 26(2):19–39. [PubMed: 16278749]

Wolpaw AJ, Dang CV. 2018 MYC-induced metabolic stress and tumorigenesis. Biochim Biophys Acta Rev Cancer. 1870(1):43–50. [PubMed: 29791870]

Wyant GA, Abu-Remaileh M, Wolfson RL, Chen WW, Freinkman E, Danai LV, Vander Heiden MG, Sabatini DM. 2017 mTORC1 Activator SLC38A9 Is Required to Efflux Essential Amino Acids from Lysosomes and Use Protein as a Nutrient. Cell. 171(3):642–654 e612. [PubMed: 29053970]

Yang L, Achreja A, Yeung TL, Mangala LS, Jiang D, Han C, Baddour J, Marini JC, Ni J, Nakahara R et al. 2016 Targeting Stromal Glutamine Synthetase in Tumors Disrupts Tumor Microenvironment-Regulated Cancer Cell Growth. Cell Metab. 24(5):685–700. [PubMed: 27829138]

Young JD. 2016 The SLC28 (CNT) and SLC29 (ENT) nucleoside transporter families: a 30-year collaborative odyssey. Biochem Soc Trans. 44(3):869–876. [PubMed: 27284054]

Yuneva MO, Fan TW, Allen TD, Higashi RM, Ferraris DV, Tsukamoto T, Mates JM, Alonso FJ, Wang C, Seo Y et al. 2012 The metabolic profile of tumors depends on both the responsible genetic lesion and tissue type. Cell Metab. 15(2):157–170. [PubMed: 22326218]

Yuneva MO, Zamboni N, Oefner P, Sachidanandam R, Lazebnik Y. 2007 Deficiency in glutamine but not glucose induces MYC-dependent apoptosis in human cells. J Cell Biol. 178(1):93–105. [PubMed: 17606868]

Zack TI, Schumacher SE, Carter SL, Cherniack AD, Saksena G, Tabak B, Lawrence MS, Zhsng CZ, Wala J, Mermel CH et al. 2013 Pan-cancer patterns of somatic copy number alteration. Nat Genet. 45(10):1134–1140. [PubMed: 24071852]

Zhang H, Chen Z, Savarese TM. 1996 Codeletion of the genes for p16INK4, methylthioadenosine phosphorylase, interferon-α1, interferon-β1, and other 9p21 Markers in Human Malignant Cell Lines. Cancer Genet Cytogenet. 86:22–28. [PubMed: 8616780]

Zhang W, Trachootham D, Liu J, Chen G, Pelicano H, Garcia-Prieto C, Lu W, Burger JA, Croce CM, Plunkett W et al. 2012 Stromal control of cystine metabolism promotes cancer cell survival in chronic lymphocytic leukaemia. Nat Cell Biol. 14(3):276–286. [PubMed: 22344033]

Zhao M, Mishra L, Deng CX. 2018 The role of TGF-beta/SMAD4 signaling in cancer. Int J Biol Sci. 14(2):111–123. [PubMed: 29483830]

Zhu J, Tsai HJ, Gordon MR, Li R. 2018 Cellular Stress Associated with Aneuploidy. Dev Cell. 44(4): 420–431. [PubMed: 29486194]

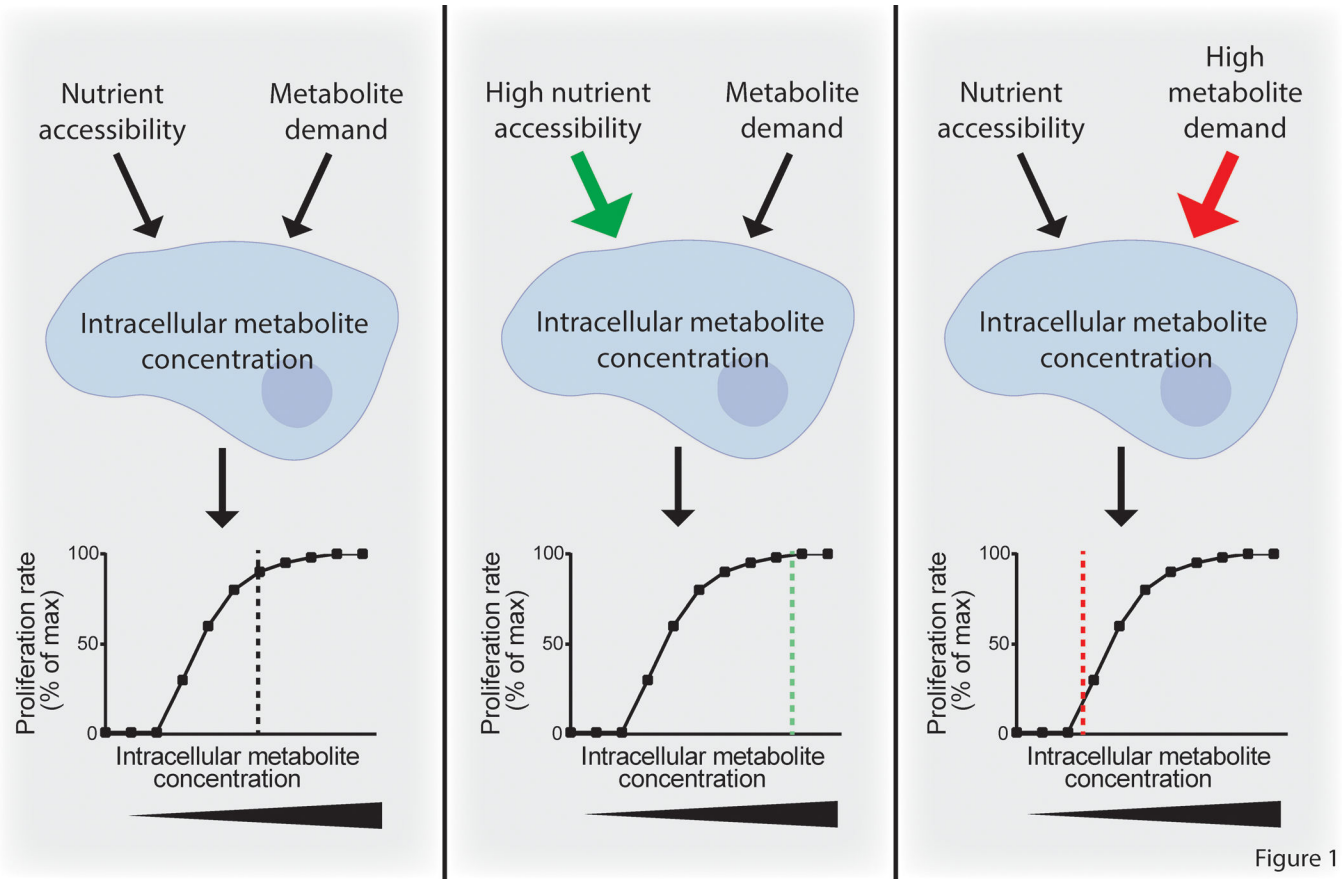


**Figure 1.**

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.

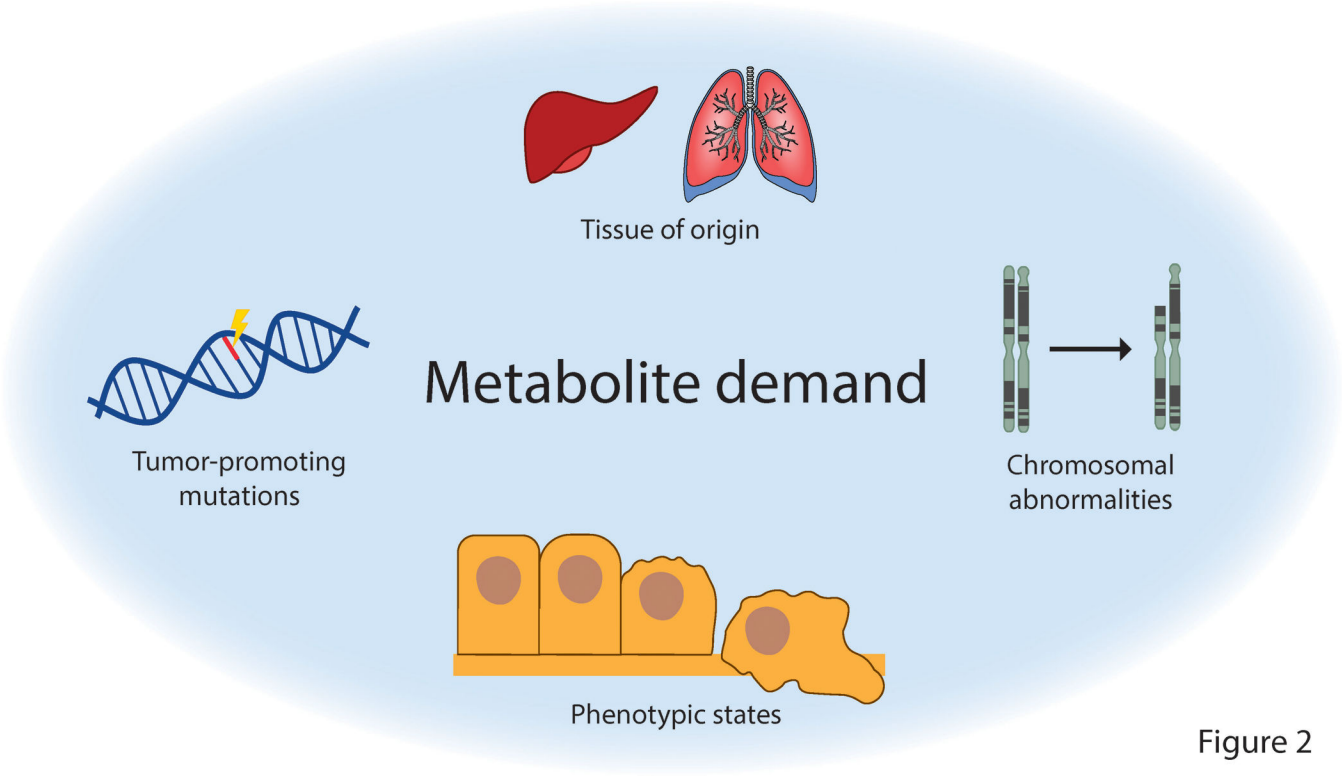


**Figure 2.**

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.

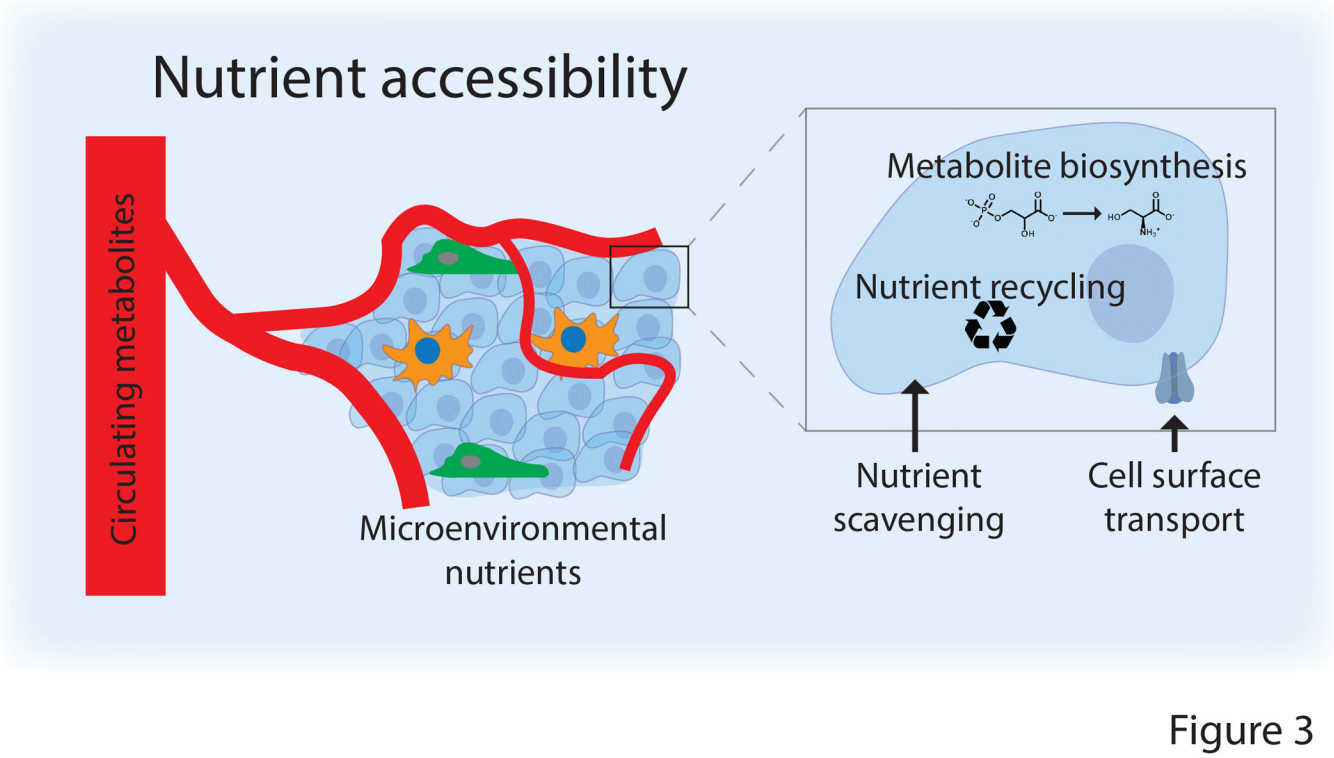


Figure 3

**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.