

Review

The Molecular Link from Diet to Cancer Cell Metabolism

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Malignant cells remodel their metabolism to meet the demands of uncontrolled cell proliferation. These demands lead to differential requirements in energy, biosynthetic precursors, and signaling intermediates. Both genetic programs arising from oncogenic events and transcriptional programs and epigenomic events are important in providing the necessary metabolic network activity. Accumulating evidence has established that environmental factors play a major role in shaping cancer cell metabolism. For metabolism, diet and nutrition are the major environmental aspects and have emerged as key components in determining cancer cell metabolism. In this review, we discuss these emerging concepts in cancer metabolism and how diet and nutrition influence cancer cell metabolism.

Cancer cells exhibit metabolic alterations to satisfy the biosynthetic, bioenergetic, and signaling demands of uncontrolled proliferation. Altered metabolism at the molecular level has been described for nearly 100 years, since Otto Warburg and colleagues reported that malignant cells took up more glucose than their normal tissue counterparts and preferentially fermented glucose to make lactate in lieu of the more energetically efficient oxidation to CO₂. It is now widely appreciated that alterations in the uptake and metabolism of carbohydrates, lipids, and amino acids occur in tumors. The particular nutrients that are more avidly taken up by cancer cells are highly variable, with subsets of cancers exhibiting altered glucose metabolism, altered one-carbon metabolism, and increased reliance on amino acid metabolism, along with many other pathways. These observations are used clinically as imaging modalities and are the subjects of ongoing drug development efforts (Stuani et al., 2019; Vander Heiden and DeBerardinis, 2017). These concepts have been reviewed extensively over the years (Weinberg and Chandel, 2015; Wolpaw and Dang, 2018).

Cancer metabolism, as with all processes in life, comprises both genetic and environmental components. Nearly all oncogene and tumor suppressor genes have the capacity to alter metabolism in some form (Vander Heiden and DeBerardinis, 2017). Mutations that engage signaling pathways and transcriptional programs hard-wire some elements of the metabolic network by altering gene expression and activity through the placement of post-translational modifications onto metabolic enzymes and transporters, for example. These cancer-associated processes are also engaged by environmental factors specific to the spatial environment within the tissue of origin, such as the presence of growth factors and cytokines, cell-cell contacts. Beyond these factors that shape the activity of the internal cellular metabolic network, the availability of nutrients, which is completely shaped by the environment, plays a dominant role in defining cancer cell metabolism (Palm and Thompson, 2017; Zhu and Thompson, 2019). Nutrient availability that any malig-

nant cell might experience comes from the metabolites released from surrounding cells and metabolite composition of the plasma in the vasculature.

Plasma metabolite levels are set by a conglomeration of physiological processes involving interactions with the gut, liver, muscle, pancreas, and other tissues. Nutrient availability in the plasma begins with dietary intake, and concentrations of metabolites vary dramatically on the basis of their intake from the diet (Mentch et al., 2015). Certain diets are known to be associated with some aspects of health. For example, the Mediterranean diet has been associated with longer lifespans. Conversely, the Western diet is associated with obesity, cancer, and coronary heart disease. Interestingly, plant-based diets have long been investigated as cancer therapy (Gerson, 1978). Although strong epidemiological evidence linking these dietary patterns to disease exists, an understanding of the molecular mechanisms that underlie these effects is not well developed. Even less understood is how diet shapes metabolic pathways in health, let alone cancer progression and treatment (Goncalves et al., 2019a; Kanarek et al., 2020; Lien and Vander Heiden, 2019). Ongoing research into central carbon metabolism, that processes carbohydrates, lipids, and amino acids, provides insights into potential opportunities to modulate cancer cell metabolism. In this review, we discuss emerging findings that provide a molecular link from diet to cancer and present considerations for therapeutic strategies to target these mechanisms.

Mechanistic Principles that Link Diet to Cellular Cancer Metabolism

As mentioned, cancer cell metabolism is highly influenced by environmental factors, including tumor acidity, stromal and immune cell populations, and mechanical properties of tumor architecture. These features have been reviewed elsewhere (Bi et al., 2020; Wolpaw and Dang, 2018). Of particular interest, the nutrients available in the microenvironmental milieu that surrounds the tumor are responsible for defining much of tumor cell

metabolism (Chen et al., 2019; Tasdogan et al., 2020). Indeed, although tumoral metabolism is highly heterogeneous and driven by anatomical location, genetic profiles, and other factors, some tumor types have been shown to develop metabolic dependencies on certain nutrients, such as glutamine and cysteine. The availability of nutrients is dictated by the flow of plasma nutrients from systemic circulation to tumor cells (Muir and Vander Heiden, 2018). As such, the determinants of plasma nutrient availability are of particular interest, as it is a major point of control over tumor metabolism that is also amenable to both pharmacological and lifestyle and environmental interventions.

Nutrient availability exerts control over cellular metabolism through multiple mechanisms. The cellular uptake of nutrients from the surrounding microenvironment is one such process, which is regulated tightly by the kinetic properties of active transporters, including their Michaelis constants (Nelson and Cox, 2000). Physiologically, cancer cells encounter concentrations of nutrients that are at or above those found in corresponding normal tissues. These increases in nutrient availability influence the rate of nutrient uptake, which then propagates to changes in metabolic flux through the metabolic network and downstream functions (Palm and Thompson, 2017). This paradigm is best illustrated by the ability of the liver to sense high glucose levels and respond with increased glycogen synthesis. This switch is accomplished, in part, via the high K_m of hepatic glucose transport (~5 mM). When in a fasting state, glucose concentrations are low (~3 mM), allowing glucose to mostly bypass hepatic uptake and reenter circulation. However, in a fed state, plasma glucose concentrations increase (~8 mM), leading to a proportional increase in glucose uptake (Mueckler and Thorens, 2013). This 3-fold increase in glucose uptake from baseline prompts glycogen synthesis and thus allows the liver to accomplish its key glucose homeostatic function.

The plasma metabolome reflects dietary intake in the context of individual metabolic heterogeneity, which includes factors as such liver function, gut microbiome composition, and muscle and adipose metabolism (Zeevi et al., 2015). An emerging, but still undeveloped, field of research has considered the application of metabolite profiling in conjunction with dietary tracking to predict circulating plasma alterations that occur as a result of nutrient intake. Although overall dietary patterns are reproducibly reflected in the plasma metabolome, further work is needed to better define more granular features of diet, including individual foods and their effects on metabolite concentrations (Wittenbecher et al., 2015).

The clinical value of measuring dietary patterns and metabolic outcomes is evidenced by the established links between certain diets and dysregulations of whole-body metabolism. The constellation of chronic conditions associated with metabolic syndrome—obesity, insulin resistance, and hyperglycemia—have also all been associated with higher cancer risk and poorer patient prognosis (Perry and Shulman, 2020). The link from obesity to cancer has been attributed to a number of mechanisms, including endoplasmic reticulum (ER) stress, inflammation, hormonal signaling, and possibly altered metabolism due to changes in plasma metabolite levels (Iyengar et al., 2016; Ulrich et al., 2018). Hyperglycemia is also associated with greater cancer risk and progression. This protumorigenic effect may be due to both systemic effects of insulin/insulin-related growth

factor-1 (IGF-1), other growth factors, and inflammatory signaling and direct uptake of glucose by tumor cells to drive epigenetic and biosynthetic changes (Goncalves et al., 2018). Thus, the role of diet-mediated changes to systemic metabolism and how they may affect tumor metabolism (Figure 1) warrants further study.

Macronutrient Metabolism and Molecular Mechanisms of Cancer

Calorie Restriction

Calorie restriction (Figure 1) without malnutrition (CR) has been shown to extend lifespan and delay the onset of age-related diseases, including cancer. This phenomenon has been widely studied in rodents, and the anti-cancer and longevity-promoting effects of CR appear to be conserved across species ranging from worms to non-human primates (Fontana et al., 2010; Mattison et al., 2017). Numerous animal studies have shown that CR can prevent many cancers and restrict progression and metastasis (Lv et al., 2014). These positive effects have been shown in cancers from diverse tissues including mammary, lung, prostate, brain, bladder, pancreatic, hepatic, skin, colorectal, and ovarian (Castejón et al., 2020; Lv et al., 2014). The molecular mechanisms believed to underlie these effects have been attributed largely to reduced circulating levels of several hormones, such as growth factors and cytokines. Particularly, CR has been associated with lower levels of circulating IGF-1, which is known to engage signaling networks involving RAS/MAPK and PI3K/AKT/mTOR, which are common dysregulated pathways in cancers (Goncalves et al., 2018). Thus, CR appears to exert a host of effects on signaling pathways that could have anti-cancer activity. In addition, CR has also been shown to have antiangiogenic and proapoptotic effects on tumors in mice, as well as systemic anti-inflammatory effects (O'Flanagan et al., 2017). The effects on metabolism are less understood but have been the subject of preliminary studies. CR slows basal metabolic rate, an effect that has been shown in humans (Redman et al., 2018). This is theorized to slow aging and protect against age-related disease because of a decrease in the production of mitochondrial reactive oxygen species and associated cellular oxidative damage (Sohal and Allen, 1985). Compared with *ad libitum* (AL) feeding, food intake in CR mice has been also shown to trigger an initial increase in fatty acid (FA) synthesis, followed by a compensatory increase in FA oxidation (Bruss et al., 2010). This cyclical pattern of adipose tissue metabolism reflects dynamic changes in expression of FA synthesis enzymes such as FA synthase (FAS) and acetyl-CoA carboxylase (ACC1). In addition, CR has been linked to decreased glycolysis and alterations in FA membrane composition, with decreased levels of polyunsaturated FAs (PUFAs) and increased monounsaturated FAs (MUFAs) (Jové et al., 2014). Both increased FA oxidation and decreased membrane polyunsaturation are thought to help protect cells against oxidative damage (Weinberg and Chandel, 2015). CR has also been shown to alter other metabolic pathways, including the carnitine shuttle pathway, sphingosine metabolism, and methionine metabolism (Green et al., 2017). In the future, targeting metabolic pathways to assess the extent that altered metabolism caused by CR can exert anti-cancer effects will be interesting.

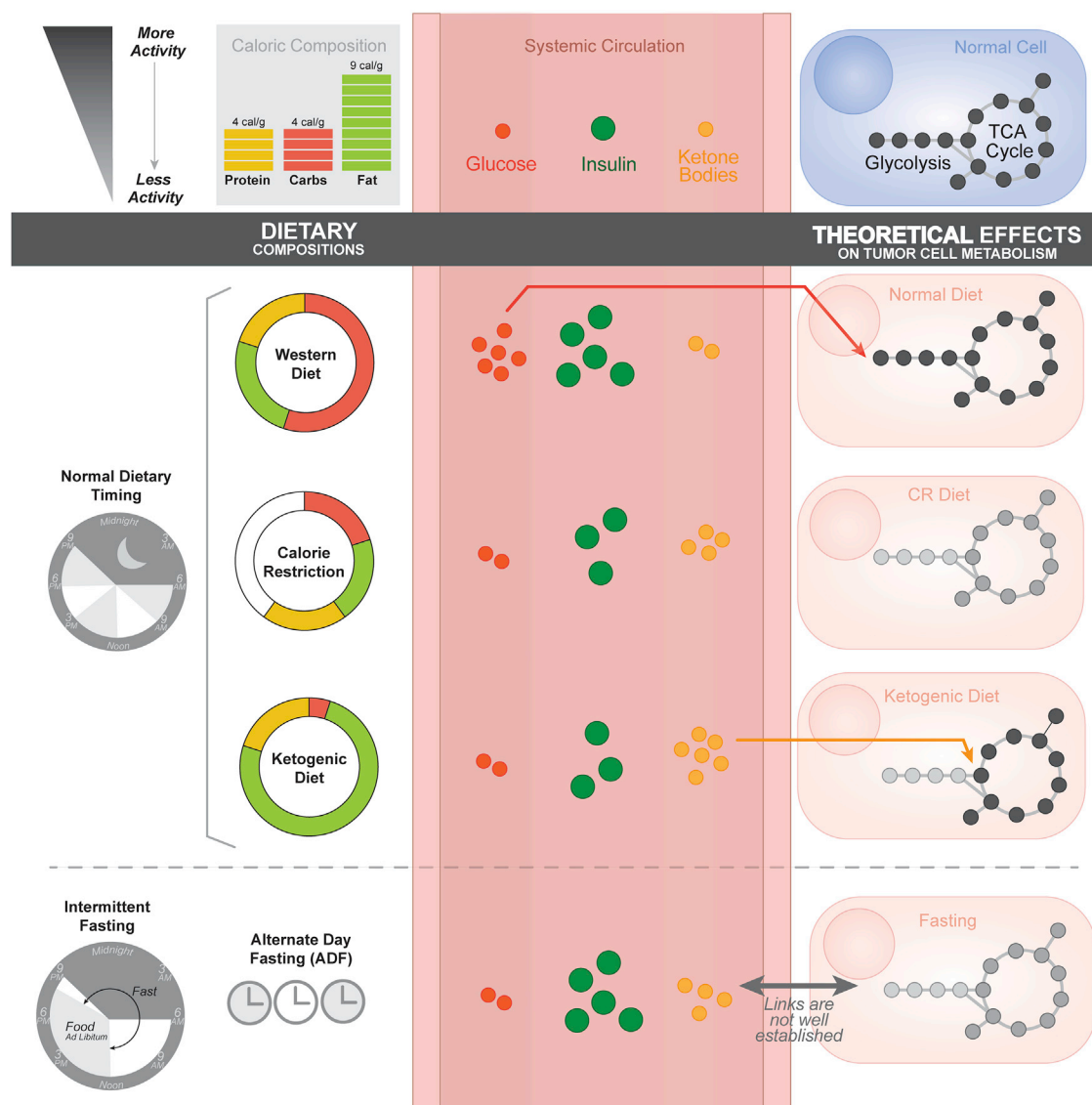


Figure 1. Dietary Compositions Affect Circulating Metabolic Factors and Nutrient Availability, Which, in Turn, Are Thought to Have Effects on Tumor Cell Metabolism

Dietary timing as well as caloric compositions are known to affect endocrine secretions of insulin, which thereby affect cellular uptake of glucose. Limitations of glucose and an abundance of ketone bodies during the ketosis induced by the ketogenic diet have been linked to reduced glycolysis and enhanced oxidative processing. These suggest that, although these mechanisms are not well understood, diets may have important roles in driving cancer cell metabolism.

In addition to the demonstrated effects metabolic rate, human studies have shown that CR is capable of altering certain molecular factors associated with cancer prevention from animal studies (Most et al., 2017). Results from the CALERIE-2 (Comprehensive Assessment of Long-Term Effects of Reducing Intake of Energy) trial showed that an approximate 15% reduction in calories in non-obese adults over 2 years reduces thyroid hormone activity and reactive oxygen species production (Redman et al., 2018). Similar results along with reductions in fasting insulin concentrations were obtained in a population of mostly overweight but non-obese participants achieving approximately 18% reduction in caloric intake over 6 months (Heilbronn et al.,

2006; Most et al., 2017). However, these studies failed to demonstrate a reduction in levels of serum IGF-1. An observational study of members of the Calorie Restriction Society, a group of individuals who have been voluntarily restricting caloric intake while maintaining adequate nutrition, found that compared with matched controls, IGF-1 levels were reduced in members only if protein intake was also reduced (Most et al., 2017). Currently, clinical trials are ongoing to more directly assess the impact of CR on cancer prevention and treatment (Castejón et al., 2020).

However, caution must be taken before universally applying CR as an anti-cancer strategy, as much remains to be understood about whether CR imposes differential effects on cancer

on the basis of underlying metabolic dependencies, tumor location and microenvironment, mutational status, and/or metastasis versus primary tumors (García-Jiménez and Goding, 2019; Kaiaany and Sabatini, 2009).

Fasting

Recently, fasting regimens such as alternate-day fasting and time-restricted feeding have been shown to have health-promoting effects (de Cabo and Mattson, 2019; Longo and Mattson, 2014; Mitchell et al., 2019). Fasting (Figure 1), defined by periods of caloric deprivation ranging from hours to days, is an attractive alternative to CR, as certain fasting regimens are easier to adhere to and may be better tolerated by cancer patients who are at risk for undesired weight loss and cachexia (Safdie et al., 2009). Interestingly, short-term fasts dramatically alter serum IGF-1 levels in humans, whereas long-term CR may not. Studies in yeast and mammalian cells have shown that periods of nutrient restriction protect non-oncogene-expressing yeast and normal cells against oxidative stress and chemotherapy, whereas nutrient restriction offers no protection or sensitizes oncogene-expressing yeast and cancer cells to these conditions (Lee et al., 2012; Raffaghello et al., 2008). In mice, 24–60 h of fasting protected against extremely high doses of chemotherapy (Lee et al., 2012; Raffaghello et al., 2008) and radiotoxicity (de la Cruz Bonilla et al., 2019) and increased the effectiveness of chemotherapies in mice grafted with pancreatic cancer, melanoma, breast cancer, glioma, and neuroblastoma cells (D'Aronzo et al., 2015; Lee et al., 2012), which in some cases resulted in long-term cancer-free survival (Lee et al., 2012). Mechanistically, fasting is thought to be protective toward non-neoplastic cells because hormonal and metabolic changes during fasting direct normal cells toward a stress-resistant state characterized by a switch from growth processes to maintenance and repair (Di Biase et al., 2017; Lee et al., 2012; Nencioni et al., 2018). Cancer cells are unable to adopt this stress-resistant state and therefore not protected or sensitized to stress. Fasting and “fasting-mimicking diets” may also improve cancer outcomes by enhancing anti-cancer immune function through the promotion of T cell-mediated tumor cytotoxicity (Di Biase et al., 2016).

The effects of fasting and dietary timing (Figure 1) on human cancer risk and progression remain understudied (Marinac et al., 2016; Yokoyama et al., 2016). However, measures associated with cancer have been shown to be affected by fasting in humans. A controlled trial of alternate-day fasting, a dietary regimen in which food is consumed AL every other day and followed by a day of complete CR, yielded reductions in plasma methionine and thyroid hormone T3 levels (Stekovic et al., 2019). Another recent study in humans has demonstrated significant changes in blood metabolite profiles after 58 h of fasting (Teruya et al., 2019). These changes reflect alterations in antioxidant defense mechanisms, mitochondrial activity, and pentose phosphate pathway rewiring, among other changes to metabolism that are implicated in cancers. In cancer patients, 5–56 h of fasting prior to and/or following chemotherapy was well tolerated and reduced side effects of chemotherapy, consistent with previously discussed results in yeast, mice, and mammalian cells (Safdie et al., 2009). As such, fasting appears to be an intriguing way to influence cancer cell metabolism that may synergize with chemotherapy and radiation.

Macronutrient Balance

Carbohydrate and Fat Intake. Individual macronutrient intake may play as large a role as caloric intake in dictating longevity, health, and disease. Diets high in saturated fats and carbohydrates, such as the Western diet, are linked to poorer health outcomes. The plasma metabolite signature reflects this burden of increased central carbon metabolism, with high levels of short-chain acylcarnitines and circulating amino acids (Bouchard-Mercier et al., 2013; Douris et al., 2015). Recent work has focused on how diets low in carbohydrates or protein influence these factors and the extent of their benefits in preventing or treating cancer. The ketogenic diet (KD) is a type of low-carbohydrate diet that has been most extensively studied in relation to cancer. The classical KD is used to treat epilepsy and is defined as a “high-fat, moderate-protein, low-carbohydrate diet,” with a specified 4:1 or 3:1 weight ratio of fat to combined protein and carbohydrates (Huffman and Kossoff, 2006). KDs result in lower blood glucose levels, leading to ketosis involving reduced glycolysis and increased β -oxidation (Puchalska and Crawford, 2017). The production of ketone bodies from FAs in the liver provides energy-producing substrates for the brain and other organs. This causes a number of effects on central carbon metabolism, including altered glucose and central carbon metabolism, which tumors are known to require (Allen et al., 2014; Goncalves et al., 2019b; Liberti and Locasale, 2016). KDs have also been hypothesized to work through mechanisms similar to those postulated in CR, including reducing anabolic hormones such as IGF-1 and insulin and increasing oxidative stress in tumors (Allen et al., 2014; Xia et al., 2017). Interestingly, a recent study showed that the KD synergizes with PI3K inhibitors, likely through suppression of insulin production (Hopkins et al., 2018).

Currently there is no rigorous evidence that low-carbohydrate diets and KDs decrease cancer incidence or improve outcomes in humans (Erickson et al., 2017), but much remains to be studied. Mouse studies on KDs as interventions in xenograft models have shown mixed results, with some reports of reduced tumor growth (Caso et al., 2013; Klement et al., 2016), others showing effects on tumor growth in combination with chemotherapy or radiotherapy (Allen et al., 2013), and others reporting no benefit of a KD (Maurer et al., 2011). It should be noted that these studies have considerable differences in the macronutrient compositions of their control diets and KDs, and in most of these studies, protein intake was lower in KD groups. Because protein intake has been shown to influence cancer, this is a major confounding factor. However, two of these studies kept protein intake consistent between groups and still saw a beneficial effect of KD and low-carbohydrate diets in prostate cancer xenograft models (Caso et al., 2013), suggesting that low-carbohydrate diets or KDs could be beneficial in some cancer settings. It is known that tumors can vary widely as to their dependence on glucose metabolism (Liberti et al., 2017). However, it is unknown whether a tumor's preference for glucose metabolism predicts its responsiveness to diets that alter blood glucose levels.

Protein Intake. Although protein intake has a strong effect on health, less work has been done to assess how dietary protein affects cancer. One study found that middle-aged U.S. men and women who reported moderate (10%–19% calories from protein) or high (20% or more calories from protein) protein

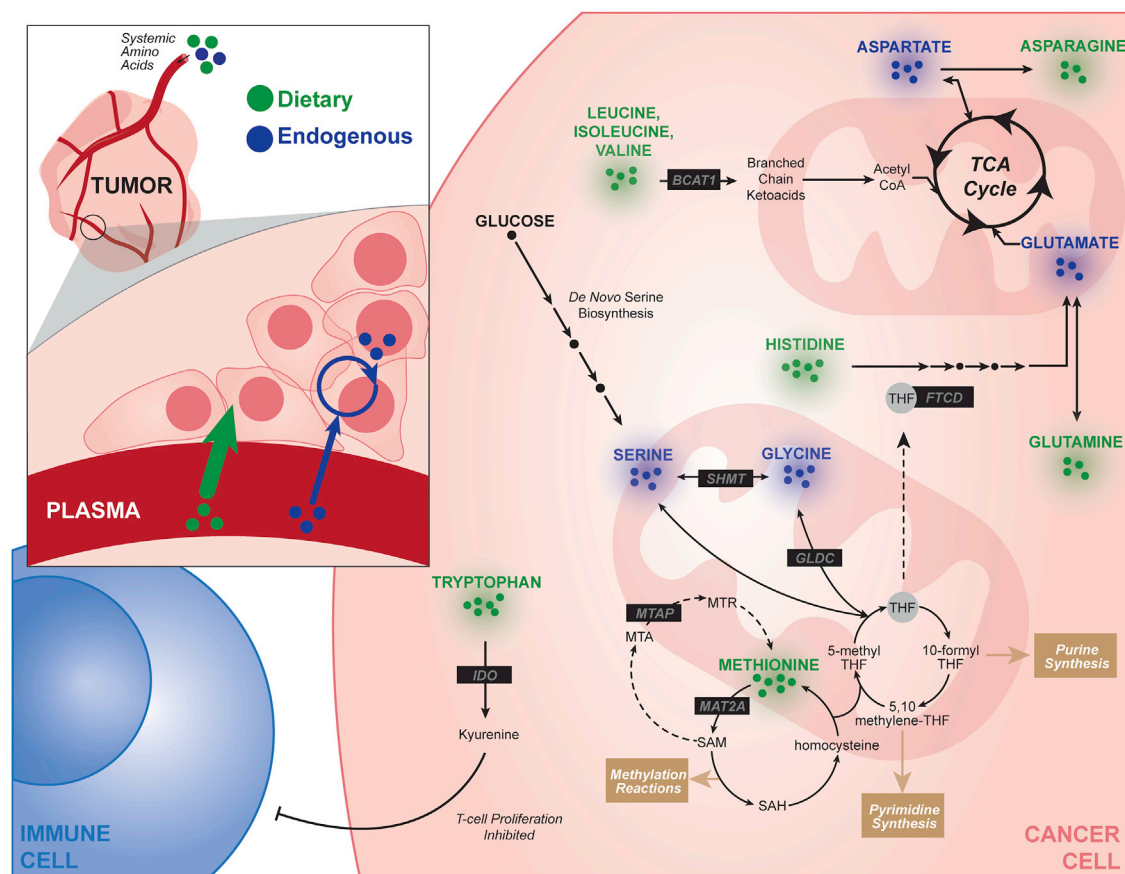


Figure 2. Circulating Amino Acids Are Metabolized in Cancer Cells to Provide Unique Biosynthetic and Energetic Requirements of the Tumor MTAP, S-methyl-5'-thioadenosine phosphorylase; MAT2A, methionine adenosyltransferase 2A; MTA, 5'-methylthioadenosine; THF, tetrahydrofolate; BCAT1, branched-chain amino acid transaminase 1; FTCD, formimidoyltransferase cyclodeaminase.

intake had a significantly increased risk for cancer mortality compared with those reporting low protein intake, but the trend was reversed for those older than 65 years (Levine et al., 2014). Interestingly, the increased cancer risk among middle-aged subjects was somewhat diminished if their dietary protein came from plant rather than animal sources, which have markedly different amino acid content. This study also found that mice consuming a low-protein (4% calories from protein) diet had decreased tumor incidence and growth of implanted breast and melanoma cells compared with those consuming a high-protein (18% calories from protein) diet. Both human and mice in low-protein groups had lower IGF-1 levels, which have been previously reported in humans with decreased protein intake (Fontana et al., 2008). Another study showed that mice consuming a low-carbohydrate, high-protein (58% calories from protein) diet had slower growth of implanted squamous cell carcinoma and colorectal carcinoma tumors and decreased incidence of tumors in a spontaneous breast cancer model compared with mice consuming a Western diet (Ho et al., 2011). Mice consuming the low-carbohydrate, high-protein diet did not show decreased levels of IGF-1 but did have lower blood glucose and insulin levels.

Different studies give contrasting views on whether protein or carbohydrate restriction is more beneficial for cancer treatment

and prevention, which could be explained in several ways. It may be that different cancer types respond differently to macronutrient depletion, as shown in Figure 1, with some extremely glycolytic cancers being more affected by carbohydrate-restricted diets than protein-restricted ones and cancers dependent on IGF-1 signaling responding best to protein restriction. Another possible explanation is that restricting any macronutrient in the diet is beneficial compared with a diet replete with all three macronutrients, as depleting at least one macronutrient triggers some of the same starvation responses that are seen in CR and thought to be anti-cancer. It is also unclear whether low-protein diets may reduce cancer cell growth through the deprivation of one or more amino acids, as cancers often show increased dependence on particular amino acids (discussed more below). Further research is needed to answer these questions and better determine how the macronutrient compositions of diets affect cancer.

Dietary Amino Acid Balance in Cancer

The increased metabolic demands of cancerous proliferation require altered amino acid metabolism, as illustrated in Figure 2. As such, tumor cells adapt to uptake and metabolize microenvironmental nutrients to meet these demands. Amino acids serve

as both proteinogenic precursors and as metabolic intermediates and are taken up in tumors. As metabolites, they serve as catabolic substrates for the TCA cycle, their oxidation and reduction maintains cellular redox balance, and they serve as signaling intermediates that propagate nutrient status to growth signaling such as mTOR and modifiers of chromatin and nucleic acids (Liu and Sabatini, 2020; Reid et al., 2017). They also participate in all aspects of anabolic metabolism, some of which are included in Figure 2.

Amino Acid Metabolism in Cancer

Methionine Metabolism. Methionine is a sulfur-containing amino acid involved in redox homeostasis, chromatin and nucleic acid methylation, polyamine synthesis, and other metabolic processes. As an essential amino acid, dietary methionine is converted to S-adenosyl-methionine (SAM), which serves as a universal methyl group donor for methylation reactions, and homocysteine, which interfaces with folate cycle and transsulfuration pathway. Methylthioadenosine (MTA) is also metabolized to methionine via activity of MTA phosphorylase (MTAP) as a part of the methionine salvage pathway. Altered methionine metabolism is implicated in tumor biology (Sanderson et al., 2019a). Methionine may provide a useful clinical staging tool, with L-[methyl- ^{11}C] methionine (MET) uptake of considerable prognostic utility (Lückerath et al., 2015). Elevated protein expression and activity have been noted for enzymes involved in methionine metabolism, including methionine adenosyltransferase 2A (MAT2A) and methyltransferase nicotinamide N-methyltransferase (NNMT) in tumor cells (Eckert et al., 2019; Ulanovskaya et al., 2013; Wang et al., 2019).

Targeting of methionine metabolism in cancer has yielded results, with administration of recombinant methioninase (rME-Tase) showing success in preclinical models (Hoffman et al., 2019). Another avenue of methionine targeting of particular interest is dietary methionine restriction (MR), an intervention that has been shown to extend lifespan (Bárcena et al., 2018; Lee et al., 2014). The restriction of methionine availability can drive potent reductions in methionine metabolism, as illustrated by a recent study that showed that MTAP-deleted cells subjected to MR abrogated MTA accumulation to levels seen in MTAP-expressing cells (Sanderson et al., 2019b). In cancer, MR has produced therapeutic responses in preclinical models ranging from patient-derived xenografts to anatomically restricted autochthonous models with genetically defined driver mutations. Synergies with both chemotherapy and radiation have been observed. In each of these cases, the mechanisms underlying MR appear to be cell autonomous and coupled to altered demands for nucleotide biosynthesis and redox metabolism that result from alterations in methionine metabolism imposed by MR. Defining a clinically feasible regimen of dietary MR has been challenging, as methionine depletion is associated with toxicities. Recently, it has been demonstrated the reduced methionine levels can be well tolerated over a 3 week period with no significant side effects in healthy humans (Gao et al., 2019). Together with observed benefits as an antineoplastic agent, MR presents an enticing opportunity to selectively target a metabolic vulnerability of cancer through a dietary intervention.

Cysteine Metabolism. Cysteine, which can be synthesized from methionine via the transsulfuration pathway or taken up in

its oxidized form cystine via the system x_c^- amino acid antiporter, is limiting for glutathione production and therefore critical for cellular redox homeostasis (Zhu et al., 2019). Certain cancers have been shown to upregulate the system x_c^- transporter under oxidative stress (Polewski et al., 2016), and intracellular cysteine depletion can lead to an oxidative, iron-dependent form of non-apoptotic cell death termed ferroptosis (Dixon et al., 2012). Cancer cells often have higher basal levels of reactive oxygen species generation and can display increased iron uptake, so it has been proposed that pharmacological induction of ferroptosis could be a selective strategy to treat cancer (Hassannia et al., 2019). Although interesting, it remains for future study to investigate whether dietary strategies such as cysteine/cystine limitation, alterations in antioxidant consumption, or iron supplementation could influence tumor responsiveness to ferroptosis and redox processes (Piskounova et al., 2015; Sayin et al., 2014).

Branched-Chain Amino Acids (BCAAs). Leucine, isoleucine, and valine make up the class of BCAAs, which are known to function as both metabolic intermediates and in nutrient-sensing signaling pathways implicated in cancer. BCAAs are catabolized by branched-chain aminotransferase 1 (BCAT1) in a number of tissues (Neinast et al., 2019). Using α -ketoglutarate as a cofactor, BCAT1 catalyzes the conversion of BCAAs to glutamate and their corresponding branched-chain ketoacids (BCKAs). BCKAs subsequently undergo decarboxylation in the mitochondria to form acyl-CoA esters, which can be used to replenish the TCA cycle.

This pathway provides an alternative to glucose utilization in the TCA cycle, and accordingly, BCAT1 overexpression has been reported in many cancer types, including glioblastomas (Tönjes et al., 2013), breast cancers, and several hematological malignancies (Raffel et al., 2017). In human and mouse models of chronic myeloid leukemia (CML), aberrant metabolic activity through BCAT1 was shown to be required for neoplastic growth. However, the mechanisms that dictate BCAA metabolism appear to be highly variable across tumor types. A study of mutant *Kras*-driven pancreatic ductal adenocarcinoma (PDAC) and non-small cell lung cancer (NSCLC) mouse models showed significant differences in BCAA utilization, with BCAA-derived nitrogen supporting nonessential amino acid and DNA synthesis in NSCLC tumors (Mayers et al., 2016). As such, both genetic and microenvironmental contexts shape BCAA metabolism in different cancers and require further characterization.

These observations suggest that restricting BCAA availability through dietary manipulation is of interest (Sivanand and Vander Heiden, 2020). Although this remains to be characterized in cancer models, studies in mice have demonstrated that dietary valine serves a crucial role in maintaining hematopoietic stem cells (HSCs) in the bone marrow niche, a requirement that may be recapitulated in cancer stem cells (CSCs), which give rise to hematological malignancies (Taya et al., 2016). BCAAs have been largely studied in the context of obesity and insulin resistance, and elevated levels have been associated with systemic metabolic disease states. Circulating BCAA levels in the plasma have been linked to skeletal muscle breakdown as a result of cancer-associated cachexia, a condition of muscle wasting observed in patients with advanced disease. Exogenous supplementation of BCAAs has shown limited benefits in alleviating

cachectic muscle loss. Interestingly, a recent study has shown that this systemic elevation of BCAAs occurs prior to development of PDAC in human and mouse models, suggesting a model whereby liberated tissue BCAAs may function as nutrient sources for neoplastic cells (Mayers et al., 2014).

Tryptophan. The tumor microenvironment includes tumor cells, extracellular matrix, as well as the immune and stromal cells. Although the complex interplay between different factors in this milieu is very complex, tryptophan catabolism has been implicated as a key process that drives the suppression of anti-tumor immune cell activity. More specifically, the metabolic processing of tryptophan to its immune modulatory metabolite, kynurenine, occurs via the enzymatic activity of indoleamine-2,3-dioxygenase (IDO) in tumor cells (Uyttenhove et al., 2003). This catabolic process is replicated by tryptophan-2,3-dioxygenase (TDO) in the liver and brain and affects systemic tryptophan levels. Although IDO has been widely implicated in cancer, TDO has been shown to be overexpressed in malignant gliomas as well, providing evidence for the tumor-promoting role of tryptophan metabolism. The mechanisms that underlie these observations are poorly understood but may involve the engagement of aryl hydrocarbon receptors (Opitz et al., 2011). Such a coordinated response modulated via tryptophan metabolism may allow tumors to alter their interaction with the immune system and has drawn significant interest as a possible target for dietary intervention or drug development (Platten et al., 2019).

Serine and Glycine. The intersection of folate and methionine cycles forms the core cellular processing for one-carbon units, molecular building blocks required for the biosynthesis of lipids, nucleotides, and proteins as well as a major component of redox maintenance (Locasale, 2013; Yang et al., 2016). This one-carbon metabolism network integrates nutritional status via inputs of various amino acids, including serine and glycine, to generate functional outputs, as shown in Figure 2. Accordingly, restriction of serine and derived glycine in the diet has been shown to attenuate tumor growth in a number of xenograft and autochthonous murine models (Labuschagne et al., 2014; LeBoeuf et al., 2020; Maddocks et al., 2017; Sullivan et al., 2019). Although serine and glycine can both be synthesized *de novo* from glycolysis, increased levels of both serine uptake and biosynthesis suggest that one-carbon metabolism is often altered in cancer. The uses are multifaceted, including nucleotide synthesis, sphingolipid synthesis, mitochondrial function, methylation metabolism, and redox maintenance (Gao et al., 2018; Reid et al., 2018).

Arginine, Histidine, Aspartate, and Asparagine. Tumors often exhibit specific auxotrophy for other individual amino acids as well. The dependence of cancer cells on exogenous uptake of these nutrients appear to be cancer-specific metabolic vulnerabilities whose targeting may synergize with pharmacological therapies in the future.

In the case of asparagine, intracellular concentrations have been shown to regulate the uptake of other amino acids, including serine, arginine, and histidine, through its function as an exchange factor (Krall et al., 2016). Indeed, possibly through mTORC1 pathway activation and also effects on nucleotide synthesis, the maintenance of intracellular asparagine serves as an important regulator of cell proliferation seen in cancer (Pavlova et al., 2018; Zhang et al., 2014). Because cancer cells often

exhibit asparagine auxotrophy, asparaginase administration reducing exogenous asparagine bioavailability has shown some success in limiting tumor proliferation and metastatic potential (Hettmer et al., 2015; Knott et al., 2018). Cancer cells are known to import arginine to be used in myriad roles, including regulation of cell proliferation, protein modification, and immune modulation (Qiu et al., 2015). Abnormal expression and function of the enzymes involved in arginine catabolism, particularly argininosuccinate synthase (ASS), have been described in a number of cancers. Interventions targeting arginine auxotrophy and altered metabolism have shown success in preclinical xenograft models; however, further studies are needed to determine if these effects may extend further.

The amino acid histidine has also been implicated in modulating the efficacy and toxicity of methotrexate treatment, an antimetabolite therapy that is known to disrupt the generation of THF from dihydrofolate (DHF) as a part of the folate cycle. Given that THF is a crucial cofactor for the function of a number of enzymes involved cell proliferation, methotrexate can reduce tumor growth. The pool of available THF can be further reduced by increases in histidine metabolism, which is performed via THF-dependent formimidoyltransferase cyclodeaminase (FTCD) activity. In fact, histidine-rich diets have been shown to boost the effectiveness of methotrexate treatment and lower the toxicity noted in murine cancer models (Kanarek et al., 2018).

Microbiota, Diet, and Cancer

A discussion of diet remains incomplete without considering the gut microbiome, a consortium of trillions of microbes that contribute in meaningful but poorly understood ways to host metabolism. The microbial composition of the gut microbiome has likely undergone significant adaptations as human diets have evolved over both short- and long-term timescales, with the Western diet, high in fats and carbohydrates, associated with the evolution of greater populations of polysaccharide-degrading microbiota to extract calories and provide needed food-derived energy and CR associated with increased probiotic microbes and suppressed proinflammatory strains (Turnbaugh et al., 2009; Zheng et al., 2018). The shifts in the species of microflora that colonize the gut are associated with metabolic phenotypes in the individual host (Perry et al., 2016; Turnbaugh et al., 2009).

Although the role of the microbiome in cancer is not yet well defined, diet-driven changes in gut microbiota are relevant in shaping tumor development, progression, and therapy. Microbial imbalance, or dysbiosis, between colorectal cancer (CRC) tissue and adjacent mucosa has been described in the literature, with neoplastic enrichment of specific microbes such as *Fusobacterium nucleatum* (Fn), *Escherichia coli*, and *Bacteroides fragilis* (Collins et al., 2011; Iida et al., 2013; Nakatsu et al., 2015). In addition, recent evidence has demonstrated co-migration of commensal microbiota within CRC metastases (Bullman et al., 2017) and microbial influence in modulating antitumor immune activation and therapy response (Jin et al., 2019; Routy et al., 2018; Viaud et al., 2013). Furthermore, recent emerging data are suggesting that many elements of cancer can be predicted by microbiome composition with signatures present in

peripheral blood in the form of cell-free DNA (Poore et al., 2020). Mechanisms that link cross-talk from microbes to tumor cells are also emerging, such as a recent study of NAD⁺ metabolism showing that tumor cells can satisfy requirements of NAD synthesis from the provision of nutrients derived from microbial sources (Shats et al., 2020). Given the microbiome is known to exert control over a multitude of cellular and whole-body functions, it is interesting to speculate that additional links between diet and tumor behavior exist (Cani, 2018).

Concluding Remarks

Our molecular understanding of diet and nutrition is still in its infancy, a lack of understanding that extends to human health as well. It is highly debated both in popular culture and among scientists as to what constitutes a healthy diet. The answer ranges from low-carbohydrate KDs to diets high in carbohydrates but low in saturated fat, such as typical plant-based diets. Even less understood is how these diets affect metabolism at the cellular level. Although studies that have used metabolomics technology and stable isotope tracing are emerging and have led to new developments on fundamental questions in diet, much remains to be understood. Indeed, better controlled dietary intake studies with varied populations are necessary to understand the breadth of inter-patient variability in normal metabolism. Without understanding this and the effect of diet, an understanding of tumor metabolism is difficult to develop.

Nevertheless, there are a few intriguing examples of specific diets being able to target specific aspects of tumor metabolism with profound consequences that can be molecularly interpreted. These effects can occur both systemically, as appears to be the case in the insulin-lowering antitumor effects of the KD, or cell autonomously, which appears to be the case for restriction of serine/glycine or methionine. By affecting whole-body nutrient uptake, the modulation of diet can have profound influences on tumor cell metabolism. This can occur alone or in combination with therapies that may interact with the diet modality in question. These observations, although promising as potential future therapeutic targets, require a deeper mechanistic understanding, which we expect to develop in the coming years.

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DECLARATION OF INTERESTS

J.W.L. advises Nanocare Technologies, Raphael Pharmaceuticals, and Restoration Foodworks.

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