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Review

Lipid Metabolism at the Nexus of Diet and Tumor Microenvironment

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Obesity is a leading contributing factor to cancer development worldwide. Epidemiological evidence suggests that diet affects cancer risk and also substantially alters therapeutic outcome. Therefore, studying the impact of diet in the development and treatment of cancer should be a clinical priority. In this Review, we set out the evidence supporting the role of lipid metabolism in shaping the tumor microenvironment (TME) and cancer cell phenotype. We will discuss how dietary lipids can impact phenotype thereby affecting disease trajectory and treatment response. Finally, we will posit potential strategies on how this knowledge can be exploited to increase treatment efficacy and patient survival.

Highlights

Obesity and excess caloric intake promotes cancer aggressiveness, reduces response to chemotherapy and increases the likelihood of re-occurrence, yet little is known about how to better target tumors in these patients.

Altered metabolism is a common feature of human cancers. Distinct metabolic phenotypes are often caused by a combination of tissue specific contexts and distinct genomic alterations of the tumor.

Lipid metabolism represents a therapeutic opportunity in many tumor types. To translate these therapies into the clinic it is necessary to establish robust genomic, histological and biometric biomarkers for modulators of lipid metabolism.

Utilizing diet as a modality to increase therapy efficacy could have significant effect in some tumors.

Obesity and the Tumor Microenvironment

Excess caloric intake leads to obesity and is a major risk factor for diabetes, cardiovascular disease, stroke, and incidence of cancer worldwide. Indeed, high body fat is associated with an increased likelihood of developing multiple hematological malignancies, and breast, esophageal, renal, colon, pancreatic, and endometrial cancers [1]. Prospective analysis of 900 000 cancer-free adults in the US showed that men and women with the highest body mass index (BMI) had a 52% and 62% increased risk, respectively, of dying from cancer than their normal weight counterparts [2]. Increased body weight and fat tissue results in altered hormone levels, such as increased estrogen and insulin, which play major roles in cancer development and can result in systemic metabolic changes; that is, **hyperglycemia** (see Glossary; due to insulin resistance) or elevated levels of circulating lipids. Obesity also promotes tissue inflammation and vascular dysfunction [3]. However, there is limited understanding of the direct impact that diet has on cells within the TME. For example, it is not well known if elevated blood glucose levels promote the proliferation of cancer cells or if increased lipid availability in the TME promotes cancer cells to use these lipids as an energy source or substrates for membrane synthesis.

Epidemiological evidence suggests that diet substantially alters treatment outcome in cancer patients; that is, meta-analyses show that breast cancer recurrence is 30% higher in obese women compared to their normal-weight counterparts [4]. Therefore, a better understanding of the effect of diet, in particular the carbohydrate- and fat-rich western diet, on nutrient availability within the TME and its impact on signaling pathways that determine drug sensitivity is essential for the development of novel anticancer therapies. In this Review, we discuss lipid metabolism within the context of the TME and explore how diet can impact cancer phenotype, disease trajectory, and treatment response.

Lipid Metabolism and Cancer

The synthesis of lipids is a highly coordinated and controlled molecular program regulated by the sterol regulatory element binding proteins (SREBPs), which respond to upstream signaling networks (i.e., PI3K/AKT/mTORC1 pathway) and to the cellular nutrient status (i.e., environment deplete of lipids [5]) to regulate the expression of enzymes involved in cholesterol and fatty acid (FA) synthesis and uptake [6]. Lipids are a highly diverse class of biological molecules, including FAs, triglycerides, sterols, as well as phospholipids and glycolipids – the main structural components of biological membranes.

Aberrant lipid metabolism is found in many human cancers, predominantly but not exclusively to maintain ample production of phospholipids to generate the membranes of cancer cells. De *novo* synthesized lipids are also used by cancer cells to generate energy via fatty acid oxidation (FAO) [7] and are required for post-translational modification of proteins [6] (Figure 1). Altered lipid

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metabolism is also associated with oncogenic events in cancer. In lymphoma, amplification of *MYC* leads to upregulation of *de novo* lipogenesis, suggesting it is required for MYC-dependent transformation and growth [8]. MYC cooperates with SREBPs to regulate lipid synthesis and tumor growth in multiple cancer types [9]. Clear cell renal cell carcinomas (ccRCCs), characterized by functional loss of the von Hippel–Lindau (VHL) tumor suppressor that leads to stabilization of the hypoxia inducible factors (HIFs), show a shift in cellular metabolism where glutamine-derived carbon is almost exclusively used for *de novo* lipogenesis [10]. Indeed, ccRCCs are histologically defined by the presence of large organelles that store glycogen and lipids, thus altered lipid metabolism is central to the tumor phenotype [11].

Cancer mutations converge on deregulated metabolism [12] and oncogenic hotspot mutations are also found in metabolic enzymes. For instance, mutations in *IDH* occur in low-grade gliomas, secondary glioblastomas, and acute myelogenous leukemias (AML) [13,14]. Point mutations in *IDH1* lead to neomorphic activity and production of the oncometabolite 2-hydroxyglutarate (2-HG). Accumulation of 2-HG alters the activity of oxoglutarate-dependent dioxygenases; several of which control the methylation state of DNA and histones [15]. Wild-type isocitrate dehydrogenase (IDH) proteins in cancer can also reductively carboxylate α-ketoglutarate to generate citrate, allowing glutamine-derived carbon atoms to be shuttled into lipid synthesis, particularly when the activity of the tricarboxylic acid (TCA) cycle is impaired, such as under hypoxic conditions or in cells with defective mitochondria [10,16,17]. IDH1 protein expression is also upregulated in primary glioblastomas, with its inhibition resulting in decreased levels of α-ketoglutarate, reduced NADPH production, and lower flux of acetate- and glucose-derived carbon into lipids [18]. These metabolic changes are accompanied by altered histone methylation and differential expression of differentiation markers [15,18], suggesting that alterations in metabolic genes not only impact metabolic pathways but can also affect global gene expression through epigenetic mechanisms.

Specific components of the lipogenic machinery have been shown to play a protumorigenic role in several cancers. For example, fatty acid synthase (FASN), a key downstream target of SREBP responsible for the NADPH-dependent synthesis of palmitate (Figure 1), is upregulated in breast, prostate, ovarian, stomach, and colorectal cancers [19]. Increased FASN expression correlates with established oncogenic events, such as HER2 amplification in breast cancer [20] and PTEN loss in prostate and ovarian cancers [21,22]. Efforts to efficiently block FASN for cancer treatment have been hampered by unexpected toxicity and metabolic compensation via lipid uptake [6]. Thus, lipid metabolism is indispensable for tumor progression and targeting it can be efficacious in cancer, but understanding the conditions and context that imparts sensitivity to inhibition is key to the development of successful treatment strategies.

Environmental Heterogeneity within the TME

Genetic intratumor heterogeneity is central to tumor evolution and drug resistance [23]. However, it is also clear that solid tumors must contain substantial metabolic intratumor heterogeneity, in part as a result of gradients of blood-derived nutrients and oxygen delivered by the tumor vasculature into the TME. Oxygen availability impacts cancer cells, as low oxygen (hypoxia) results in the stabilization and activation of HIF proteins that drive the transcription of distinct sets of target genes allowing metabolic adaptation. The presence of tumor hypoxia by the histological detection of HIFs, or their downstream targets, is associated with a poor clinical outcome in cancer patients, particularly in invasive tumors of a higher grade or more aggressive stage [24–28]. Moreover, cancer cells that reside in hypoxic environments have increased metastatic capacity, stem-like properties and display chemoresistance [29].

Blood oxygen levels are tightly regulated as **hypoxemia** results in organ damage and death. In contrast, levels of circulating nutrients, such as sugars, amino acids, and lipids, can fluctuate significantly due to dietary intake; for example, **postprandial** circulating lipid levels are higher in obese men and women compared to their normal weight counterparts [30,31]. If oxygen is limiting within the TME, due to inadequate vasculature or high proliferative capacity of cancer cells driving demand

Glossary

Auxotrophic: the requirement of extrinsic factors, that cannot be synthesized by an organism, to support its own growth.
Desmoplasia: growth of connective tissue, usually associated with cancer.
High-fat diet (HFD): diet with levels of fat that are above that of what is normally consumed.
Hyperglycemia: when a patient has higher glucose levels in their bloodstream.
Hypoxemia: when there is dangerously low levels of oxygen in arterial blood.
Lipogenesis: metabolic process of making lipids.
Lipotoxicity: accumulation of lipids that results in cell dysfunction and death.
Macropinocytosis: cellular process of nonspecific uptake of extracellular fluid.
Postprandial: time during or after eating a meal.
Preprandial: time before eating a meal.
Tissue dysplasia: abnormal growth and change of a tissue.

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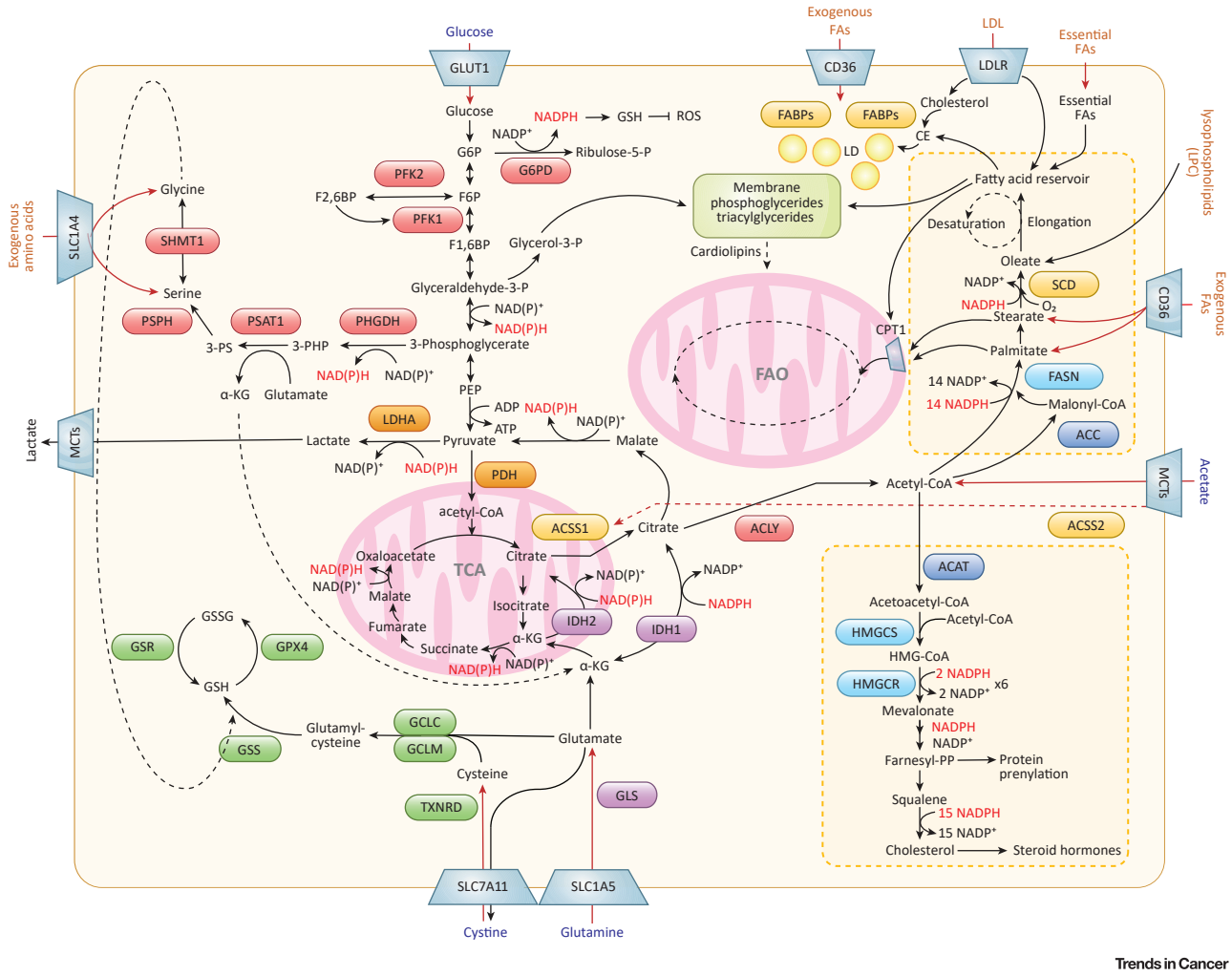

Trends in Cancer

Figure 1. Intrinsic and Extrinsic Lipid Supply in Cancer.

The central pathways that regulate lipid abundance in cancer cells via *de novo* lipogenesis, lipid uptake or lipid degradation via fatty acid oxidation (FAO). *De novo* lipogenesis and cholesterol biosynthesis are highlighted in yellow. Lipid integrity is modulated by compartmentalization of lipids into lipid droplets (LDs) and detoxification of oxidative lipid damage via glutathione peroxidase 4 (GPX4). Abbreviations: ACAT, acetyl-CoA acetyltransferase; ACC, acetyl-CoA carboxylase; ACLY, ATP citrate lyase; ACSS1, acetyl-CoA synthetase; CPT1, carnitine palmitoyltransferase I; FABPs, fatty acid binding proteins; FASN, fatty acid synthase; G6PD, glucose-6-phosphate dehydrogenase; GCLC, glutamate–cysteine ligase catalytic subunit; GCLM, glutamate-cysteine ligase modifier subunit; GLS, glutaminase; GLUT1, glucose transporter 1; GSR, glutathione-disulfide reductase; GSS, glutathione synthetase; HMGCR, hydroxymethylglutaryl-CoA reductase; HMGCS, hydroxymethylglutaryl-CoA synthase; IDH, isocitrate dehydrogenase; LDHA, lactate dehydrogenase A; LDLR, low density lipoprotein receptor; MCTs, monocarboxylase transporters; PDH, pyruvate dehydrogenase; PHGDH, phosphoglycerate dehydrogenase; PFK, phosphofructokinase; PSAT1, phosphoserine aminotransferase 1; PSPH, phosphoserine phosphatase; SHMT1, serine hydroxymethyltransferase 1; SCD, stearoyl-CoA desaturase; SLC1A4, solute carrier family 1 member 4; SLC1A5, solute carrier family 1 member 5; SLC7A11, solute carrier family 7 member 11; TXNRD, thioredoxin reductase.

above that of supply, then metabolite concentrations also form steep gradients in tumors, resulting in regions deplete of blood-derived nutrients. As a consequence, populations of cancer cells distant from the vasculature are under conditions of extreme metabolic stress and could be more sensitive to fluctuations in circulating nutrient concentrations. Unlike oxygen gradients nutrient gradients exhibit diurnal tidal-like fluctuations depending on the frequency of food intake and composition of the diet (Figure 2). Thus, local TME nutrient levels have a substantial impact on tumor phenotype, particularly in individuals whose circulating nutrient levels are consistently in excess and whose

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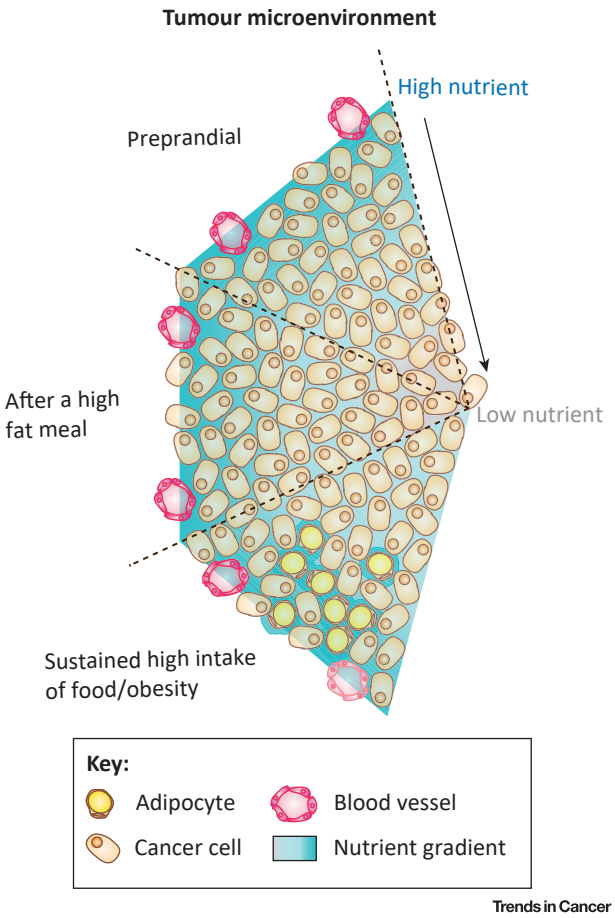

Figure 2. Nutrient Availability and Penetrance in the Tumor Microenvironment.
Diagramatic representation of the tumor microenvironment and nutrient gradients that will exist in patients **preprandial** (before a meal), **postprandial** (after a high-fat meal), or in patients who have a sustained high food intake (green, high nutrient availability; grey, low nutrient availability). In some tumors, metabolic symbiosis with stromal cells (e.g., cancer-associated fibroblasts or adipocytes) further alters local nutrient availability (regional green intensity).

tumors have a genomic architecture that imparts an **auxotrophic** phenotype for specific factors; such as, $KRAS^{v12}$-driven tumors dependent on **macropinocytosis** to scavenge nutrients from their local microenvironment [32].

The cellular response to lipid and oxygen depletion is not necessarily distinct. Indeed, SREBPs are part of an oxygen-sensing pathway in yeast controlling the expression of hypoxia-dependent genes [33]. In mammalian cancer cells, SREBPs and their downstream targets are upregulated in hypoxia and essential for cell survival [34,35]. Furthermore, fatty acid desaturases, which are controlled by SREBP, utilize molecular oxygen as a cofactor for the introduction of double bonds into newly synthesized FAs [36]. Desaturation is indispensable in cancer to avoid **lipotoxicity** under conditions of nutrient stress, be it through dependency on steroyl-CoA desaturase (SCD) or fatty acid desaturase 2 (FADS2) [37,38].

Maintenance of lipid synthesis under hypoxic conditions promotes cancer cell survival but the contribution of glucose-derived carbon to generate citrate and acetyl-CoA via the TCA cycle is compromised, due to the shunting of pyruvate to lactate. Under hypoxia, cancer cells shift the production

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of acetyl-CoA from glucose to glutamine as maintenance of lipid synthesis is essential for cell survival [16,17]. Indeed, HIF1 activation promotes SIAH2-mediated degradation of OGDN2, resulting in a shunt of glutamine-derived carbon into FA synthesis [39]. More recently we and others identified acetyl-CoA synthetase 2 (ACSS2) to be a novel drug target in aggressive breast, brain, prostate, ovary and lung cancers [40–43]. ACSS2 expression is driven by SREBP2 under metabolic stress [40] and extracellular acidification [44] allowing for the conversion of acetate to acetyl-CoA for lipid synthesis.

Lipid metabolism is also important in disease recurrence and metastasis formation. Two distinct murine models of breast cancer (MYC/KRAS and MYC/NEU) showed an upregulation of genes involved in FA metabolism in tumors treated with neoadjuvant therapy, suggesting it is a common feature of residual disease [45]. In ovarian cancer, the primary metastatic site is the adipocyte-rich omentum and adipocytes secrete adipokines coercing cancer cells to selectively metastasize to this tissue. It has been shown that ommental adipocytes release free FAs that are taken up by ovarian cancer cells in a fatty acid binding protein 4 (FABP4)-dependent manner for FAO and energy generation [46].

While enhanced lipid synthesis supports cell growth and proliferation, cancer cells also have to protect their lipid pools from oxidative damage. In ccRCC cells inhibition of glutathione peroxidase 4 (GPX4), which removes lipid peroxides from membrane lipids, results in the induction of ferroptosis [47,48]. Generation of membrane lipids containing long-chain polyunsaturated FAs (PUFAs) promotes cancer cell sensitivity towards ferroptosis induction, as inhibition of acyl-CoA synthetase 4 (ACSL4), which preferentially generates PUFA-containing acyl-CoAs, blocks cell death induction after GPX4 inhibition [49]. Moreover, therapy-resistant cancer cells that have undergone epithelial to mesenchymal transition (EMT) are dependent on GPX4 for their survival [50]. Thus, maintenance of a dynamic reservoir of lipids in cancer cells is essential for tumor growth and disease progression but also causes a selective liability that can be exploited therapeutically.

High-Fat Diets and Cancer

As mentioned previously, SREBPs also control serum-derived lipid uptake through regulating the expression of the low-density lipoprotein receptor (LDLR). In pancreatic cancers and glioblastomas, SREBPs upregulate LDLR expression, resulting in the enhanced uptake and storage of cholesteryl esters (CEs) in lipid droplets in an acetyl-coenzyme acetyltransferase 1 (ACAT1/SOAT1)-dependent manner. This results in a positive feedback loop that maintains high PI3K/AKT/mTOR/SREBP activity and fuels cancer aggressiveness [51,52]. It is likely that cancer cells attempt to fulfill their lipid demand through lipid uptake as long as lipids are readily available within the TME.

Ras-driven tumors, such as lung adenocarcinomas (LUACs) and pancreatic ductal adenocarcinomas (PDACs), harbor recurrent activating hotspot mutations in the oncogene *K-ras*. Ras-transformed cells exhibit an endocytic phenotype in which they take up and catabolize extracellular proteins to fuel cellular bioenergetics and growth [32]. This hard-wired dependency results in enhanced sensitivity towards macropinocytosis inhibitors in *K-ras*-mutant but not wild-type PDAC xenografts [53]. In addition, tumor-associated stromal cells present in the TME can be coerced into supporting specific metabolic phenotypes to aid cancer growth. For example, pancreatic stellate cells (PSCs) undergo transdifferentiation into cancer-associated fibroblasts (CAFs), resulting in metabolic rewiring and excretion of lysophosphatidylcholine into the TME, which is then metabolized to lysophosphatidic acid (LPA) by autotaxin [54]. As LPA is an important lipid mediator, this stromal signaling axis promotes tumor growth and disease progression [54].

While multiple preclinical studies have clearly demonstrated the importance of lipid provision for cancer growth, they are mostly performed under standard conditions where the nutritional aspects of a western diet are not included. It is likely that the metabolic composition of the TME, and heterotypic cellular relationship of cancer and non-cancer cells within it, will be distinct in cancers arising in individuals exposed to different diets and nutritional regimens, such as those consuming a **high-fat diet (HFD)**.

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The impact of different diets on RAS-dependent cancer initiation and development was studied in a mouse model of sporadic cancer. Mice were generated with inducible RasV12 expression that produced a mosaic of transformed epithelial cells in the pancreas and small intestine [55]. Mice previously fed a HFD displayed reduced extrusion of transformed cells from the mosaic tissues, suggesting exogenous lipid supply aided the persistence of transformed cells promoting **tissue dysplasia** [55]. This could be phenocopied *in vitro*, where addition of FAs, particularly palmitate, reduced apical extrusion of epithelial cells from the monolayer in a dose-dependent manner [55]. Moreover, in several mutant KRas preclinical PDAC models, tumor growth and metastasis were increased in mice fed a HFD [56,57]. Obesity-induced inflammation was also shown to promote **desmoplasia** and immune activation of PSCs and reduce vascular perfusion and drug delivery [56]. Enhanced adipocyte infiltration caused by obesity also promoted PDAC growth and metastasis [58] and supplementation with adipose tissue-conditioned medium increased the migratory capacity of cancer cells *in vitro* [58]. In another study, the increased PDAC tumor burden of mice fed a HFD translated into a shorter survival time [59]. In colon cancer, HFD was shown to enhance the number and function of *Lgr5*$^{+}$ intestinal stem cells [60]. Intestinal crypt-derived organoids extracted from mice fed a HFD displayed increased regenerative capacity and were less dependent on niche factors generated by Paneth cells for growth. This phenotype was recapitulated by the addition of palmitate to the culture medium, indicating that this lipid is a central component in the regulation of stem cell function [60]. Therefore, local lipid availability within the TME provided by the diet markedly influences the outcome of oncogene activation and can determine the frequency of tumor formation in different tissues.

Altering nutrient supply and availability in the TME can also influence disease aggressiveness and treatment response. Aggressive ovarian, breast and melanoma cancer cell lines were found to have high expression levels of monoacylglycerol lipase (MAGL), which regulates the release of free FAs from neutral lipid stores [61]. While xenografts expressing shRNAs against MAGL showed a marked reduction in growth, this effect was completely abolished in mice fed an HFD [61]. This is similar to results obtained for SCD and ACAT1, where sensitivity towards target inhibition was only seen under nutrient-deplete conditions [37,51]. Currently, it is highly likely that small molecules that inhibit these promising anticancer targets would initially fail clinical testing and not because they lack target inhibition potency. Effective targeting of these enzymes would require a combination strategy that either diminishes the systemic and, as a consequence, TME lipid availability, or blocks the uptake of local lipids by cancer cells. Future clinical trials have to consider metabolic compensation and at least record nutritional parameters of their participants. We also need to achieve better understanding of the complex relationships between tumor genotype, phenotype, and targeted therapy efficacy and translate this insight into clinical practice.

Complex Synthetic Lethality in Targeting Cancer

Despite the clinical success of PARP inhibitors in BRCA-mutant cancers, identifying other synthetic lethalities that have transitioned to the clinic has so far been limited. This could be due to the TME not imparting sensitivity to the targeted therapy. For instance, HIF2 inhibitors are efficacious in ccRCCs due to the loss of functional VHL resulting in the upregulation of HIF proteins [62]. In other tumor types that have not lost VHL, the efficacy of HIF2 inhibitors is dependent on the presence of tumor hypoxia or other factors elevating HIF2 expression and dependency. This suggests that if tumors alter their vasculature to increase oxygen supply, such as switching to a co-optive rather than a neoangiogenic phenotype [63], HIF expression decreases and drugs targeting HIF2 are no longer efficacious. Indeed, tumors switching to co-option is a mechanism of resistance to antiangiogenic therapy in liver metastases [63]. Thus, complex synthetic lethality marks the TME as being essential for the targeting of cancer-specific dependencies that can be exploited *in vivo* and ultimately in patients (Figure 3).

To date, there are limited studies that have sought to specifically identify novel anticancer targets in obese patients, with the exception of the study by Zaytouni *et al.*, which shows that silencing of arginase 2 (ARG2) in orthotopic PDAC tumors is more efficacious in obese mice [64]. In human PDAC

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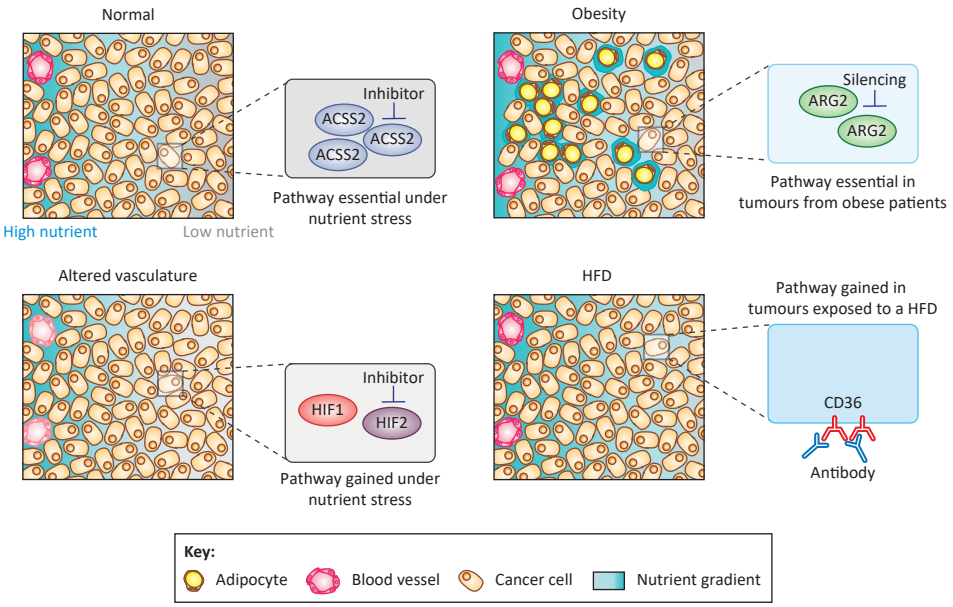

Figure 3. Exploiting the Nutrient Status of Cancer Cells for Cancer Therapy.
Diagramatic representation of the tumor microenvironment and nutrient gradients in patients who have a normal body weight, who consume a high-fat diet (HFD) or who are obese. Also included is the impact of antiangiogenic therapy on intratumoral nutrient gradients (green, high nutrient availability; grey, low nutrient availability). For each environmental condition dictated by nutrient status strategies on how these can be exploited therapeutically are shown. Abbreviations: ACSS2, acetyl-CoA synthetase 2; ARG, arginase; HIF, hypoxia-inducible factor.

samples, higher ARG2 protein expression is correlated with higher BMI [64], suggesting that PDAC tumors in obese patients are also more dependent on ARG2, establishing this enzyme as a novel target in obesity-associated pancreatic cancers (Figure 3). However, tumors with constitutive activation of AKT are also sensitive to ARG2 depletion, despite being unaffected by an HFD [64].

In prostate cancer, expression of the FA receptor CD36, a transmembrane protein that regulates the import of long chain FAs, is associated with poor relapse-free survival [65]. Inactivation of CD36 in a *pten*$^{-/-}$ murine prostate cancer model slowed cancer progression, and treatment with a CD36-targeting antibody reduced tumor growth in patient-derived xenografts (PDXs) [65]. Moreover, metastasis-initiating subpopulations of oral squamous cancer cells, defined by their slow proliferation and high expression of the stem cell marker CD44, have high expression of CD36 and an increased capacity to uptake and metabolize FAs [66]. Mice injected with this subpopulation of cells fed a HFD presented with a higher frequency of lymph node metastases [66]. A similar phenotype could be phenocopied by exposing cancer cells to palmitate prior to implantation. Crucially, mice treated with the monoclonal antibody JC63.1, which blocks the transport activity of CD36, displayed reduced metastasis formation [66]. Together, these studies highlight that extrinsic supply of lipids, particularly the FA palmitate, is essential for metastasis development in a CD36-dependent manner. Thus, this metabolic dependency could be exploited therapeutically and be more efficacious in obese patients (Figure 3).

Dietary Restriction and Cancer

As outlined above, specific genetic alterations that drive cancer development result in complex metabolic alterations that not only affect the metabolic network within cancer cells but can also influence metabolism at the organismal level. Thus, distinct cancers can be considered metabolic diseases under this context, suggesting that aggressiveness and, more importantly, response to therapy could be impacted by dietary modulation or supplementation.

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Lessons on systemic metabolic interventions can be learned from rare genetic disorders like the congenital GLUT1 deficiency syndrome, which is caused by impaired glucose transport across the blood–brain barrier due to mutations in the transporter *SLC2A1*. Children with this disorder develop epilepsy and acquired microcephaly and display developmental delay [67]. To circumvent dependency on glucose metabolism patients were put onto a long-chain triglyceride ketogenic diet. After 5.5 years, 10 of 15 patients were seizure free with no serious adverse effects reported [68], highlighting that dietary modulation can elicit positive and durable responses to disease burden. A similar approach in cancer is needed to be developed in the clinic, particularly for those patients who may be at high risk of disease recurrence and whose tumors have a hard-wired metabolic architecture. Indeed, there is mounting preclinical evidence to suggest that altering specific components of a diet can reduce tumorigenesis. For example, restriction of the amino acid glycine prevents hepatic carcinoma growth while not affecting the formation of preneoplastic foci in mice [69], with a similar outcome being observed in the B16 murine melanoma model [70]. In genetically engineered *Apc*-driven intestinal cancers and *Myc*-driven lymphomas, serine and glycine dietary restriction resulted in increased survival, while only a limited effect was observed in a *K-ras*-driven model of pancreatic cancer, suggesting that tumors with an intrinsic capacity for *de novo* serine synthesis are insensitive to perturbations in extrinsic supply [71]. In $KRAS^{G12A}$ and $NRAS^{Q61K}$ PDXs models, methionine restriction significantly reduced tumor growth and increased the sensitivity to 5-fluorouracil, an inhibitor of pyrimidine nucleotide synthesis. Crucially, the authors show that dietary methionine restriction in a cohort of healthy humans also results in reduced levels of circulating methionine, cysteine and glutathione, comparable to the observations made in the murine models [72].

While these results show that selectively removing specific amino acids from the diet is feasible in reducing nutrient availability in patients, the complexity and flexibility of lipid metabolism may be more challenging. As suggested by multiple preclinical studies, a HFD not only enhances cancer risk but also promotes cancer aggressiveness. Thus, when an obese patient arrives in the clinic, the opportunity to implement long-term dietary intervention to reduce cancer risk has passed and typically they present with a tumor of a higher grade or later stage. Therefore, it is critical to be able to modulate a patient's diet to impede tumor growth in an acute intervention or adjuvant setting to prevent recurrence and increase response to therapy. In a mouse model of melanoma obesity has been shown to increase tumor progression [73]. This effect was particularly potent in BRAF V600E-driven tumor xenografts, as mice fed a HFD reached twice the size of those on a normal diet [74]. Crucially, sensitivity to the chemotherapeutic drug dacarbazine was reinstated by switching HFD mice onto a normal diet or when treated in combination with lipid-lowering agents, such as dehydroacetic acid or orlistat [74,75]. In tumors that are dependent on **lipogenesis** we postulate that the histological scoring of markers of lipid synthesis and uptake, such as FASN and CD36, in tumor tissue could aid patient stratification, particularly when considering altering dietary lipids in cancer patients receiving therapy.

It has been shown that a ketogenic diet, that is, a diet low in carbohydrates and high in fat but with the same caloric intake, improves the efficacy of PI3K inhibitors in a preclinical PDAC model [76]. This was achieved by suppression of a feedback loop, by which PI3K inhibition leads to increased production of insulin, thereby activating the PI3K/AKT signaling pathway despite the presence of the inhibitor. Enhanced production of insulin is reduced by a ketogenic diet, which prevents postprandial surges in blood glucose [76]. A ketogenic diet was also shown to have efficacy in preclinical models of glioblastoma, slowing the growth of PDXs [77]. A combination of a calorie-restricted and ketogenic diet also reduced glioblastoma growth, with a significant enhancement in antitumor effect observed when combined with the glutamine antagonist 6-diazo-5-oxo-L-norleucine [78].

These data show clearly that specific dietary modulations are dependent on the genetic and environmental architecture of tumors. Thus, robust predictive genetic and histological biomarkers are indispensable for patient stratification for targeted therapy. This must be supplemented with detailed information about nutritional status, diet, and lifestyle of individual patients. Without this information, it is not possible to successfully translate any dietary modulation into the era of personalized medicine.

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Concluding Remarks

The development and clinical testing of novel anticancer agents that show promising preclinical efficacy is a challenging process, in which initial patient benefit observed in small trials is often not reproducible in larger trials [79]. This lack of reproducibility could be explained in part by the differences between preclinical models in the laboratory and tumors in patients. Understanding how the genetic architecture of tumors cooperates with the cellular and metabolic composition of the TME to determine phenotype is crucial to discovering these novel vulnerabilities. In particular, successful therapeutic strategies have to take into account the complex relationships between different cell populations within the TME that are subject to dynamic changes in nutrient supply, particularly in response to therapy. Furthermore, we need to apply the full repertoire of the clinical toolkit, such as robust genetic, histological, or biometric imaging biomarkers, allowing patient stratification and temporal monitoring of treatment response. Indeed, the lack of viable biomarkers for targeted therapies that could be more efficacious in patients with a higher BMI or in patients that follow specific dietary regimens is amongst the biggest challenges we face in translating preclinical findings on metabolic vulnerabilities into clinical effect (see Outstanding Questions). Embracing this environmental heterogeneity with scientific rigor is the only route to clinical progress and the ultimate goal of improving cancer therapy and patient outcome.

Outstanding Questions

Are histological and genomic biomarkers for specific dietary regimes robust?

Are there available therapies – not used as first line treatment – that might be more effective in overweight patients?

Is there epidemiological evidence that suggest acute dietary change in cancer patients can improve response to therapy?

Is patient compliance for specific dietary modulations (e.g., ketogenic diet) an issue that could affect treatment response?

Are there chemical mimetics of dietary regimes that could be used instead to circumvent compliance issues and increase treatment efficacy?

Should population-specific effects be considered when prescribing dietary modulation to cancer patients?

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