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Metabolic Co-dependencies in the Tumor Microenvironment

Prasenjit Dey^{1,2}, Alec C. Kimmelman³, Ronald A. DePinho⁴

¹Department of Immunology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

²Tumor Immunology and Immunotherapy program, State University of New York (SUNY) at Buffalo, Buffalo, NY 14260, USA

³Department of Radiation Oncology, Perlmutter Cancer Center, NYU Langone Medical Center, New York, NY 10016, USA

⁴Department of Cancer Biology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract

Metabolic reprogramming enables cancer cell growth, proliferation, and survival. This reprogramming is driven by the combined actions of oncogenic alterations in cancer cells and host cell factors acting on cancer cells in the tumor microenvironment. Cancer cell intrinsic mechanisms activate signal transduction components that either directly enhance metabolic enzyme activity or upregulate transcription factors that in turn increase expression of metabolic regulators. Extrinsic signaling mechanisms involve host-derived factors that further promote and amplify metabolic reprogramming in cancer cells. This review describes intrinsic and extrinsic mechanisms driving cancer metabolism in the tumor microenvironment and how such mechanisms may be targeted therapeutically.

Keywords

metabolic reprogramming; cytokines; extrinsic signaling; intrinsic signaling; metabolic crosstalk

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Correspondence should be addressed to Prasenjit Dey, Elm & Carlton Sts. CGP/BLSC-L5307, Buffalo, New York 14263, prasenjit.dey@roswellpark.org and Ronald A. DePinho, 1515 Holcombe Blvd, Unit 1906, Houston, TX 77030, [832-751-9756](tel:832-751-9756), rdepinho@mdanderson.org.

AUTHOR CONTRIBUTIONS

P.D., A.C.K., and R.A.D. wrote the manuscript.

CONFLICT OF INTEREST DISCLOSURE

P.D. has nothing to disclose. A.C.K. has financial interests in Vescor Therapeutics, LLC. A.C.K. is an inventor with patents pertaining to KRAS-regulated metabolic pathways, redox control pathways in pancreatic cancer, targeting GOT1 as a therapeutic approach, and the autophagic control of iron metabolism. A.C.K. is on the SAB of Rafael/Cornerstone Pharmaceuticals. A.C.K. is a consultant for Deciphera Pharmaceuticals. R.A.D. is a co-founder, advisor, and/or director of Tvardi Therapeutics, Asyilia Therapeutics, Stellanova Therapeutics, Nirogy Therapeutics and Sporos Bioventures. Tvardi and Nirogy are developing STAT3 and MCT inhibitors, respectively.

INTRODUCTION

Metabolic reprogramming, a cancer hallmark, endows cancer cells with growth and proliferative potential in the nutrient-poor tumor microenvironment (TME). Cancer metabolism research stems from Otto Warburg's observation that tumors constitutively consume glucose and generate lactate regardless of the availability of oxygen, whereas normal cells typically utilize oxidative phosphorylation. This "Warburg effect," or aerobic glycolysis, has been documented in many tumor types (1). Although aerobic glycolysis is an inefficient means of generating energy (as ATP), this process provides essential glycolytic intermediates that are channeled into the building blocks needed for cancer cell growth and proliferation (2). Also, glycolysis allows reduction of NAD⁺ to NADH, which is used as a cofactor by many enzymes. Beyond glycolysis, cancer cells use other core metabolic processes such as glutaminolysis and fatty acid oxidation to support their energy demands or anabolic processes, such as protein and nucleotide biosynthesis, one-carbon metabolism, and lipid biosynthesis (3).

A major focus of cancer metabolism research is understanding the process by which oncogenic mutations in cancer cells and host factors in the TME regulate core metabolic functions of anabolism and redox homeostasis. Induction of anabolism and redox resilience provides a survival advantage for cancer cells in the nutrient-deprived and hypoxic conditions of the TME. Although it is well established that anabolism and redox homeostasis are central to cancer growth, clarification is needed as to whether specific mechanisms or factors drive these metabolic adaptations and whether these adaptations can be targeted to inhibit cancer. The study of aberrant oncogenic signaling in cancer cells has provided some answers, as has the elucidation of factors produced by stromal and immune cells and by the endocrine system, which act on the metabolic circuitry of cancer cells.

Mounting evidence suggests that these host signals enable the metabolic adaptability of cancer cells based on the availability of micronutrients and signaling molecules to drive the metabolic nodes in the cancer cells (4-6). For instance, one of the most common signaling pathways activated in cancer, phosphatidylinositol 3-kinase (PI3K), and its downstream effectors—AKT and mTOR—drive many metabolic processes. In cancer, these components are often activated via multiple mechanisms including their direct activation by mutation, indirect activation by upstream oncogene mutations, and extrinsic activation via host-derived factors—with all three mechanisms often occurring together for full pathway activation and optimal metabolic activity in cancer cells (4,7). The extrinsic signals could be in the form of growth factors, cytokines, chemokines, and/or hormones (8,9) acting as signal amplifiers to ramp up the core metabolic functions to proliferate and survive.

This review will cover the intertwined nature of host and cancer cell mechanisms driving cancer cell metabolism. Specifically, we discuss the metabolic co-dependencies of host and cancer cells and review how metabolism and metabolites affect tumor biology, including immunity. The ultimate goal is to identify key metabolic nodes, understand the context in which these nodes might constitute cancer vulnerabilities, and determine how we might convert this knowledge into effective anticancer therapies.

INTRINSIC DRIVERS OF METABOLIC PATHWAYS

Metabolic pathways show high plasticity due to the vast redundancy of biochemical reactions, the presence of myriad enzyme isoforms, the reversibility of metabolic processes, the various anaplerotic (a series of reactions or pathways that replenish tricarboxylic acid [TCA] cycle intermediates) inputs into metabolic cycles (such as glutamine feeding into the TCA cycle), and the availability of multiple fuel sources. All of these features enable cancer cells to adapt to a challenging TME (10). Remarkably, with few exceptions, metabolic enzymes are rarely genetically modified and instead are downstream of, and regulated by, oncogene and tumor suppressor gene mutations (e.g., mutant KRAS or PTEN loss) (11). This section summarizes specific oncogenes and tumor suppressor genes that modulate metabolic pathways for tumor progression (Fig. 1).

PI3K-AKT-mTOR:

The PI3K-AKT signaling pathway is one of the most frequently altered pathways in human cancer (12) which, along with mTOR, controls the uptake and utilization of multiple nutrients, including glucose, amino acids, nucleotides, and lipids (13,14). The PI3K-AKT signaling pathway is downstream of receptor tyrosine kinases (RTKs), G protein-coupled receptors (GPCRs), integrins and cytokine receptors, and is required for normal cell function and growth (15). In normal cells, external growth factors activate PI3K-AKT signaling, whereas cancer cells achieve growth factor independence most often by incurring activating mutations in PI3K subunits such as p110a (PIK3CA) or sustaining inactivating mutations in PTEN, a phosphatase that negatively regulates PI3K-AKT signaling (16). Upon activation, PI3K-AKT can act directly on metabolic enzymes through phosphorylation and indirectly by regulating their expression via activation of downstream transcription factors. Most of the metabolic gene regulations downstream of AKT are mediated by three of its key downstream effectors—mTORC1, the forkhead box O (FOXO) family of transcription factors, and glycogen synthase kinase 3 (GSK3) (17).

MYC is another transcription factor linked to PI3K-AKT and mTOR signaling that fine-tunes the expression of many metabolic genes such as hexokinase II (HK II) and enolase 1 (ENO1) of the glycolytic pathways and induces expression of glucose transporters (18). PI3K-AKT regulates MYC stabilization by inhibiting FOXO and GSK3 function, which in the absence of PI3K-AKT signaling, targets MYC for proteasomal degradation (19,20). However, the regulation of MYC by PI3K-AKT-mTOR can differ across various tumor types, i.e., in multiple tumor types, PI3K inhibition does not translate into decreased MYC levels. In these tumor types, such as pancreatic cancers, oncogenic KRAS regulates MYC via its downstream signaling pathways (21). In pancreatic cancer, MYC can also be stabilized by a feedforward mechanism driven by EGFR and SRC activation of ERK5, which phosphorylates MYC at S62 (MYC function is described in more detail in the MYC section below) (22,23). Thus, the PI3K-AKT-mTOR pathway is integral to the maintenance of core metabolic functions in normal and cancer cells, while aberrant activation is central to tumor progression and maintenance.

KRAS:

Activating mutations in KRAS occur frequently in lung and colon cancers (24) and are present in more than 90% of pancreatic cancers (25). Oncogenic KRAS-mediated reprogramming of cellular metabolism is achieved in part through the transcriptional up-regulation of multiple key glycolysis enzymes, including HK-I/II, phosphofructokinase 1 (PFK1), lactate dehydrogenase A (LDHA), and glucose transporter type 1 (GLUT1) via the KRAS-MEK-ERK pathway (26,27). Oncogenic KRAS also induces expression of (i) monocarboxylate transporter 4 (MCT4), which promotes lactate efflux and maintains intracellular pH in the setting of high glycolysis, (ii) glucosamine-fructose-6-phosphate aminotransferase 1 (GFPT1), which is the rate-limiting enzyme for the hexosamine biosynthesis pathway (HBP), and (iii) ribulose-5-phosphate isomerase (RPIA) and ribulose-5-phosphate-3-epimerase (RPE) of the pentose phosphate pathway (PPP), which enable channeling of glycolysis intermediates through the non-oxidative arm of the PPP to generate ribose-5-phosphate for nucleotide biosynthesis (28,29). Furthermore, oncogenic KRAS regulates glutamine metabolism in pancreatic cancer cells by downregulating the expression of glutamate dehydrogenase 1 (GLUD1) and upregulating expression of the cytosolic aspartate transaminase (GOT1). Ultimately, this pathway leads to the production of pyruvate and reducing equivalents in the form of NADPH, which is required for maintaining the cellular redox state and many anabolic reactions such as cholesterol and fatty acid biosynthesis (30,31).

Other than directly regulating metabolic genes, oncogenic KRAS regulates autocrine and paracrine signaling by upregulating cell surface receptors to receive extrinsic trophic signals, further amplifying cancer cell intrinsic metabolic reprogramming. Specifically, oncogenic KRAS upregulates type I cytokine receptors IL-2 γ , IL-4 α , and IL-13 α 1 in pancreatic cancer cells that can receive cytokine growth signals (IL-4 or IL-13) from infiltrating immune cells, especially CD4⁺ T_H2 cells. The receptor engagement of IL-4 and IL-13 activates JAK1-STAT6 signaling, which transcriptionally upregulates MYC (32). This MYC upregulation leads to transcriptional upregulation of key glycolytic enzymes HK-II and ENO1. A recent study also showed that KRAS4A, an alternative gene product of mutated KRAS, can interact with HK-I and allosterically alter and enhance HK-I enzymatic activity (33).

Another key aspect of KRAS-driven tumors is the induction of several metabolic scavenging mechanisms that allow the tumors to recycle intracellular and extracellular metabolites, which provides metabolic flexibility and efficiency and ensures an adequate supply of biosynthetic intermediates. The recycling of intracellular and extracellular metabolites is mediated via two key scavenger mechanisms: macropinocytosis and autophagy.

Macropinocytosis is a nutrient-scavenging process present in many tumor types including cancers of the pancreas, lung, and prostate (34). Macropinocytosis uses an evolutionarily conserved endocytic pathway that enables internalization and degradation of extracellular fluid and proteins via large endocytic vesicles known as *macropinosomes*. This mechanism supports anabolic reactions and one-carbon metabolism; for example, in pancreatic cancer, macropinocytosis provides sustained levels of glutamine, a critical amino acid required for cancer cell survival (35). Mechanistically, macropinocytosis can be activated by RTK

ligands such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) that act through RAS or RAC GTPases (36). Recent studies have provided key mechanistic insights into the regulation as well as the machinery involved in micropinocytosis and may provide possible targets to selectively and potently inhibit this pathway (37) (38).

Autophagy is a catabolic process whereby recyclable cargos are sequestered in double-membrane vesicles called *autophagosomes*, which fuse with lysosomes to form *autolysosomes* (39). The contents of the autolysosome are degraded, and products such as nucleosides, fatty acids, amino acids, and sugars are recycled back into the cytosol, where they can be used in a variety of bioenergetic and anabolic reactions (40). Autophagy can play a tumor-promoting role, and inhibition of elevated autophagy causes tumor regression in lung and pancreatic cancer models (41). In addition to genetic regulation of autophagic pathways, intratumor stresses such as hypoxia and low-pH in the TME can stimulate autophagy as a survival adaptation (42,43). Genetic or pharmacologic inhibition of autophagy leads to an increase in production of reactive oxygen species (ROS), metabolic defect and elevated DNA damage leading to decrease in mitochondrial oxidative phosphorylation (44).

Despite these preclinical insights, clinical trials testing autophagy inhibitors alone in pancreatic cancer have shown limited activity. However, two randomized clinical trials combining chemotherapy with hydroxychloroquine in pancreatic cancer patients showed significantly improved response rates (45,46). Of interest, whereas KRAS mutant tumors showed increased autophagy, inhibiting the KRAS signaling pathway increased autophagy flux, prompting trials to test dual inhibition of KRAS signaling (anti-MEK1/2) and autophagy (47,48).

In summary, these many studies highlight the prominent role of oncogenic KRAS in driving metabolic reprogramming via multiple reinforcing mechanisms. Indeed, unbiased transcriptomic studies in inducible KRAS cancer models have reinforced the view that a major function of oncogenic KRAS is to drive metabolic reprogramming for cancer cell growth, proliferation, and survival.

MYC:

Deregulation of the MYC family of oncoproteins is present in virtually all cancers and occurs via multiple mechanisms including transcriptional upregulation, gene amplification, and/or protein stabilization by posttranslational modification (49). MYC can directly upregulate bioenergetic gene expression governing glucose and glutamine metabolism (50,51). Specifically, MYC upregulates GLUT1 and many glycolytic enzymes including HK-II, PFK-M1, and ENO1 (52-54). MYC also differentially regulates genes involved in purine and pyrimidine synthesis such as phosphoribosyl pyrophosphate amidotransferase (PPAT) and phosphoribosylaminoimidazole carboxylase (PRAC), phosphoriboxylaminoimidazole succinocarboxamide synthetase (PAICS), carbamoyl-phosphate synthetase (CAD), and dihydroorotate dehydrogenase (DHODH). MYC further regulates genes involved in fatty acid and cholesterol synthesis such as ACLY, acetyl-CoA carboxylase alpha (ACACA), fatty acid synthase (FASN), and stearoyl-CoA desaturase (SCD) (50).

MYC expression can be regulated by a host of transcription factors, such as CCHC-type zinc finger nucleic acid binding protein (CNBP), folate-binding protein (FBP), transcription factor 7 (TCF) that is downstream of the Wntless and Int-1 (Wnt) pathway (18), and microRNAs (miR-34, miR-145, and let-7) (55,56). Moreover, MYC can be controlled at the level of protein stability via posttranslational modifications involving phosphorylation and ubiquitination (19,57). Notably, these MYC modifications are also regulated via paracrine signaling originating from cancer-associated fibroblast (CAF) factors, such as acidic fibroblast growth factor (FGF1) (58). Together, these findings underscore the central role of MYC as an integrator of signals arising from upstream oncogene activation or extrinsic factor signaling to promote a protumorigenic metabolic state.

p53:

The p53 tumor suppressor affects many cancer hallmarks (59). Its loss-of-function in cancer increases glycolytic flux to promote anabolic metabolism and redox homeostasis (59-61). Wild-type p53 can inhibit glycolysis at many levels. First, p53 inhibits glucose uptake via repression of GLUT1 and GLUT4 expression (62). Second, p53 inhibits glycolytic flux by repressing phosphoglycerate mutase 1 (PGM1), the enzyme that converts 3-phosphoglycerate (3PG) to 2-phosphoglycerate (2PG) (63,64). Third, p53 represses TIGAR (TP53-induced glycolysis and apoptosis regulator) to lower fructose-2,6-bisphosphate levels, resulting in inhibition of glycolysis and a decrease in intracellular ROS levels (65). Beyond glycolysis, p53 decreases lipid metabolism through its transcriptional repression of SREBP-1, a master regulator of lipid metabolism (66) (67). WT p53 also induces transcriptional programs to maintain α -ketoglutarate (α -KG) pools that are utilized for chromatin modification by increasing 5-hydroxymethylcytosine (5hmC). Deletion or mutational inactivation of p53 leads to decreased 5hmC, which is associated with a dedifferentiated malignant lesion (68).

Recent studies have identified a new function of p53 in the form of lipid peroxidation-induced cell death, known as ferroptosis (69). p53 can enhance ferroptosis by regulating solute carrier family 7 member 11 (SLC7A11, also known as xCT, is a sodium-independent cystine-glutamate antiporter), spermidine/spermine N1-acetyltransferase 1 (SAT1), and glutaminase 2 (GLS2); p53 can also suppress ferroptosis by inhibiting dipeptidyl peptidase 4 (DPP4) activity or by inducing cyclin-dependent kinase inhibitor 1 A (CDKN1A/p21) (67).

LKB1-AMPK:

LKB1, also known as serine/threonine kinase 11 (STK11), is a tumor suppressor that is inactivated in Peutz–Jeghers syndrome (PJS), pancreatic cancer, non–small cell lung cancer, and cervical cancer (70-72). Germline mutations of LKB1 occur in 80% of PJS patients, conferring an increased risk of cancer, especially gastrointestinal tumors. LKB1 is a serine-threonine kinase that phosphorylates and activates AMPK, a central metabolic sensor. LKB1 also activates AMPK family kinases—salt-inducible kinase (SIK)1 and SIK3, critical for restricting growth in lung cancer (73,74). Mechanistically, genetic deletion of SIK1 and SIK3 leads to upregulation of AP1 and IL6 signaling, commonly seen in both LKB1 and SIK1/3-deficient human lung tumors. LKB1 also regulates mTORC1 via AMPK-mediated phosphorylation and inhibition of TSC2 and Raptor, the regulatory associated protein of

mTOR (75). LKB1 is a broad regulator of cellular metabolism, impacting lipid, cholesterol, and glucose metabolism in liver, muscle, and adipose tissue. Specifically, LKB1-AMPK inhibits fatty acid and cholesterol synthesis by phosphorylating the metabolic enzymes HMG-CoA reductase (HMGCR) and acetyl-CoA carboxylase 1 (ACC1) (76). Acting through SREBP1, the LKB1-AMPK pathway inhibits lipogenesis, thereby inhibiting cell growth and tumorigenesis (77). LKB1 loss in the context of KRAS activation in pancreatic cancers leads to the induction of the serine-glycine-one carbon pathway coupled to S-adenosylmethionine (SAM) generation, upregulation of DNA methyltransferases, and elevation in DNA methylation (78). Thus, LKB1 deficiency sensitizes cells and tumors to inhibition of serine biosynthesis and DNA methylation.

LKB1, together with PTEN, suppresses anti-apoptotic factors such as STAT3, JNK, MYC, and cyclooxygenase-2 (79). In addition, the LKB1-AMPK pathway phosphorylates and stabilizes p27, enabling cell survival in the setting of growth factor withdrawal and metabolic stress (80,81); importantly, this mechanism connects nutrient concentration sensing by LKB1-AMPK to cell-cycle progression via p27. With respect to nutrient availability, LKB1-AMPK can also regulate autophagy via its phosphorylation and activation of ULK1, an autophagy-initiating kinase (82). Thus, the LKB1-AMPK pathway plays a role in many aspects of metabolism central to tumor growth, and as such represents a prime target for cancer treatment. Along these lines, clinical trials of the AMPK agonist, metformin, are under way in cancer patients (<https://clinicaltrials.gov/ct2/show/NCT03238495>).

Dysregulated metabolic enzymes and oncometabolites:

Although infrequent, metabolic enzymes can be genetically altered in specific cancers. For example, the brain environment is constrained by limited serine and glycine availability, which restricts metastatic tumor growth. To overcome this metabolic constraint, breast cancers and melanoma cells, which metastasize to the brain, amplify phosphoglycerate dehydrogenase (PHGDH). PHGDH catalyzes 3-phosphoglycerate conversion to 3-phosphohydroxypyruvate, the first step of the serine biosynthesis pathway (83,84). PHGDH-mediated serine synthesis is important for nucleotide production and cell proliferation in highly aggressive brain metastatic cells (85). As serine metabolism supplies methyl groups to the one-carbon and folate pools for nucleotide biosynthesis, the inhibition of PHGDH suppresses tumor growth.

Change-of-function mutations in isocitrate dehydrogenase (IDH) 1 or 2 leads to the production of an alternative product, D-2-hydroxyglutarate (D2HG), a reduced form of α -KG. IDH1/2 mutations are observed in gliomas and acute myelogenous leukemias (AMLs), which often lead to intratumoral concentrations of D2HG in the millimolar range (86,87). The D2HG oncometabolite interferes with the function of dioxygenases that require α -KG as a co-substrate, including dioxygenases such as prolyl hydroxylases, cytosine hydroxylases, and histone demethylases. These dioxygenases regulate gene expression and the epigenetic state maintaining normal cellular differentiation programs. Similar to D2HG, another reduced metabolite of α -KG is L-2-hydroxyglutarate (L-2-HG). L-2-HG is an L-enantiomer of 2HG, which is often elevated in renal cell carcinoma (RCC) owing to loss of

L-2-HG dehydrogenase (L2HGDH). L-2-HG inhibits lysine-specific histone demethylase 6A (KDM6A), which demethylates H3K27me3. Thus, elevated levels of L-2-HG increase the repressive H3K27me3 histone mark, resulting in increased RCC tumor growth and metastasis (88).

Along similar lines, loss-of-function mutations in fumarate hydratase (FH) or succinate dehydrogenase (SDH) complex can generate excess fumarate and succinate in various tumors. Excess fumarate and succinate production can interfere with dioxygenase activity, although the tumor-promoting functions of excess fumarate and succinate are not yet established in cancer (89). To move forward, a general rule to define any metabolite as an *oncometabolite* needs to be formalized since other metabolites, such as α -ketoglutarate and S-adenosylmethionine, which also participate in epigenetic regulation, are potential oncometabolite candidates.

EXTRINSIC DRIVERS OF METABOLIC PATHWAYS

Cells use extrinsic signaling to enable metabolic processes, and evidence suggests that changes in environmental cues alter metabolic pathways (90). Extrinsic factors regulate cellular metabolism in discrete ways driven by the availability of these factors in anatomically distinct sites and by differences in the composition of resident immune, endothelial, and fibroblast cells. These differences are reflected further in the metabolism of *in vitro* versus *in vivo* model systems. For example, glutamine serves as a major carbon donor to the TCA cycle in many *ex vivo* tissue culture systems, while *in vivo* metabolic tracing shows multiple carbon sources including lactate derived from glucose and glutamine (91-94). This section reviews the factors derived from the microenvironment that dictate the metabolic profile of the tumor (Fig. 2).

Cytokines as signals for metabolic reprogramming:

Cytokine-mediated signaling involves four components: inducers (cytokine, chemokines, interleukins), sensors (membrane-bound receptors that detect and interact with the inducers), mediators (signaling molecules that are activated upon engagement of inducers), and effectors (downstream of the mediator signaling culminating into a phenotype) (95,96). Although the engagement of specific cytokines with their cognate receptors and downstream signaling leads to diverse biological outcomes, this subsection focuses only on the metabolic functions of cytokine signaling as summarized in Table 1.

Cytokine regulation of cancer metabolism.—The roles of cytokines in metabolic regulation are well studied in the context of infectious disease, tissue homeostasis, and immunity, with their roles in tumor biology are now emerging (97). For example, in pancreatic cancer, cytokines IL-4 and IL-13 promote glucose utilization by JAK1-STAT6-MYC-mediated upregulation of glycolytic enzymes HK-II and ENO1 (32). The study showed that cytokines can act directly on cancer cells to regulate metabolism. Along similar lines, in breast cancer, IL-4/IL-4R signaling increases the expression of glucose and glutamine transporters leading to increased glucose and glutamine uptake to support cancer growth (98,99).

Similarly, cytokines IL-6, TNF α , IL-17, and IL-1 β , known to influence metabolic nodes, are often detected in patients with pancreatic, breast, and colorectal cancers (100). In the TME, the cytokine IL-6 is produced by tumor-infiltrating immune, stromal, and cancer cells and activates the JAK-STAT3 pathway in immune, epithelial, and endothelial cells (101). Activated STAT3 promotes glycolysis through transcriptional induction of HIF-1 α (102) and inhibits gluconeogenesis by suppressing expression of key gluconeogenic enzymes, glucose-6 phosphatase (G6Pase), and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α) (103,104).

Analogous to IL-6, the pro-inflammatory cytokine TNF α activates two key glycolysis enzymes, PFK1 and fructose-1,6-bisphosphatase, to promote glycolytic flux (105). Similarly, in colon cancer, TNF α collaborates with IL-17 to increase expression of the glucose transporter SLC2A1 and HK-II as well as the well-known glycolysis regulators HIF-1 α and MYC (106). Interestingly, although TNF α /IL-17 regulates MYC, several known MYC targets were not upregulated including glucose transporter SLC2A3, enolase-1, pyruvate kinase M2, lactate dehydrogenase A, or 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3 (PFKFB3), suggesting multilevel and/or context-specific regulation of these targets.

Furthermore, in neuroblastoma, TNF α cooperates with IL-1 β to upregulate arginase 2 (ARG2) expression via p38 and extracellular-regulated kinases 1/2 (ERK1/2) signaling (107). Arginine plays a critical role in regulating the immune response; its breakdown to ornithine and urea by ARG2 creates a potent immunosuppressive microenvironment that suppresses T cell immunity. Similarly, increased ARG2 activity is observed in AML, leading to the creation of an immunosuppressive environment and tumor progression (108). Accordingly, small-molecule inhibitors of arginase and inducible nitric oxide synthase alleviate T cell suppression and are under clinical development.

Cytokine-mediated metabolic crosstalk between cancer cells and host cells of the TME.—Cytokines and chemokines secreted by various cell types in the TME affect the metabolism and function of host cells of the tumor including immune and fibroblast cells. For instance, CAFs, which can represent >40% to 60% of the tumor's cellular composition in breast, prostate, and pancreatic cancer, exhibit altered metabolism that is largely driven by cancer cell-derived paracrine signaling (109). For instance, CAFs co-cultured with prostate cancer (PCa) cells increase GLUT1 expression, thereby increasing glucose uptake and glycolysis and leading to increased expression of the lactate efflux transporter, MCT4, to expel intracellular lactate and maintain pH (110). Reciprocally, PCa cells also reprogram toward aerobic metabolism with a decrease in GLUT1 expression and an increase in lactate uptake via the lactate transporter MCT1.

Although the phenomenon of altered metabolism observed both in cancer and CAFs has been attributed to cell-to-cell contact, a role for cytokines or other signaling molecules is also likely. In pancreatic and breast cancers, CAFs downregulate focal adhesion kinase (FAK), which negatively regulates CCL6, CCL11, CCL12, and pentraxin-3; these chemokines engage CCR1/CCR2 in cancer cells to activate protein kinase A, leading to enhanced glycolysis (111). Another anti-inflammatory cytokine, TGF- β , secreted by both

immune and non-immune cells, promotes catabolic metabolism in CAFs (112). Increased TGF- β activity in CAFs leads to increased lactate generation, which is released and taken up by adjacent cancer cells to fuel mitochondrial metabolism and anabolic growth (112). Whereas in HCC, TGF- β upregulates glutamine transporter, SLC7A5, and mitochondrial glutaminase (GLS1) in cancer cells, thereby increasing intracellular glutamate levels that promote TCA cycle anaplerotic reactions. Furthermore, in HCC, TGF- β can upregulate the expression of genes involved in the flux of glycolytic intermediates and fatty acid metabolism (113). In general, the metabolic function of TGF- β is geared toward the regulation of oxidative metabolism in cancer cells and CAFs.

Similarly, cytokine-mediated metabolic regulation is observed in immune cells that determine phenotypic states and ultimately function. For instance, antitumor macrophages are associated with increased glycolysis, whereas protumor macrophages prefer OXPHOS metabolism (114). The glycolytic metabolism in antitumor macrophages is promoted by lipopolysaccharide (LPS) or IFN γ , whereas OXPHOS metabolism in protumor macrophages is promoted by IL-4. Enhanced glycolysis also occurs in LPS-activated dendritic cells, natural killer (NK) cells, effector T cells, and B cells.

T cell subsets, most notably T-helper 17 (T_H17), T_H1 and T_H2 cells, all show an increase in glycolysis after activation. Similarly, effector T cells are highly glycolytic, whereas memory T cells have an oxidative metabolism (115-118). Growth factor cytokines such as IL-2 and ligation of costimulatory molecules promote the switch to glycolysis through the enhancement of nutrient transporter expression and activation of the key metabolic regulator mTOR (119,120). In addition, signaling molecules from cancer cells can change the identity of immune cells by altering their metabolism. An intriguing study in ovarian cancer found that cancer cell-secreted hyaluronic acid (HA) promotes membrane-cholesterol efflux and depletion of lipid rafts from macrophages (121). Increased cholesterol efflux promoted IL-4-mediated macrophage reprogramming to M2, which included inhibition of IFN γ -induced gene expression. Genetic deletion of ABC transporters (ABCA1 and ABCG1), which mediate cholesterol efflux, reverts the tumor-promoting functions of TAMs and reduces tumor progression. This is a classic example of cancer cell-mediated signaling molecules that manipulate the metabolism of surrounding cells for cancer progression.

In addition to the requirement of specific metabolic states to maintain cell identity and function, cytokines dictate the quality and quantity of effector molecules produced by the immune cells. For instance, NK cells produce large quantities of cytokines such as IFN γ in response to cytokine stimulation. The availability of nutrient and cytokine signaling together determines the ability of NK cells to produce IFN γ . Stimulation with cytokines, including IL-2 and IL-15, upregulates the expression of nutrient receptors, including the GLUT1 glucose transporter, amino acid transporters (SLC1A5 [also known as ASCT2], SLC7A5, and SLC3A2 [also known as CD98]), and the transferrin receptor [CD71]) in NK cells. Functionally, IL-2 and IL-15 stimulation leads to increased glycolysis and oxidative phosphorylation that is required for NK-cell proliferation and cytotoxic function (122). Together, these studies demonstrate the interplay of cytokines and metabolism in normal physiology and tumor immunity.

Effect of metabolism on cytokine function.—Changes in metabolism are associated with immune alteration, modified cytokine production, and secretion by cells. In the TME, cancer and immune cells compete for the same limited metabolic resources; that is, rapidly proliferating cancer cells can starve resident immune cells of glucose, essential for cytotoxic CD8⁺ T cells and NK cell effector function, thereby hindering anticancer immunity (123,124). Glycolysis is required to regulate IFN- γ production in T cells, and glucose restriction can blunt Ca²⁺ signaling, glycolytic capacity, and cytokine production by T cells (125). At the same time, lactate produced and secreted by cancer cells via MCT4 inhibits CD8⁺ T cell function but does not affect regulatory T cell (T_{reg}) function (126,127). Glycolysis is also required for the production of granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) by cancer cells, so any restriction in glycolysis can potentially inhibit recruitment of myeloid-derived suppressor cells (128).

Another microenvironmental component that can influence cancer cell metabolism is the extracellular matrix (ECM). In addition to the ECM's mechanical cues that support cancer cell proliferation and reduce tissue permeability, the ECM can regulate glucose and lipid metabolism (129,130).

Hormones as signals of tumor metabolism:

The oncogenic properties of hormones such as estrogen and androgen are apparent in hormone-dependent cancers such as breast cancer, ovarian cancer, PCa, and endometrial cancer. Nuclear hormone receptors, which also act as transcription factors, such as androgen receptors (ARs) and estrogen receptors (ERs), play a pivotal role in the tumorigenesis of breast cancer, PCa, and endometrial cancer. Indeed, inhibitors of both ARs and ERs or the hormones themselves are available for cancer treatment. Other than their classic role in regulating proliferation and antiapoptotic pathways, both of these receptors support metabolic reprogramming as part of their protumorigenic effects. Extensive transcriptomic, genomic, and metabolomic analysis of PCa indicates that AR contributes to the reprogramming of specific cellular metabolic pathways that promote tumor growth and disease progression, including aerobic glycolysis, mitochondrial respiration, fatty acid β -oxidation, and *de novo* lipid synthesis (131). For instance, in a study in a hormone-sensitive and castration-resistant prostate cancer (CRPC), AR transcriptionally regulated the expression of mitochondrial pyruvate carrier (MPC). MPC inhibition restricts proliferation and metabolic outputs of the TCA cycle including lipogenesis and oxidative phosphorylation in an AR-driven PCa model (132). This function of MPC observed in PCa is unique, since studies in colon and other tumor types have shown that loss of MPC is associated with poor prognosis (133). In addition, AR-V7, an AR variant commonly observed in CRPC patients, stimulates glycolysis and glutaminolysis, increases citrate utilization and reductive carboxylation to produce TCA intermediates, and increased lipogenesis (134). Another recent study found that in CRPC, AR mediates its oncogenic signaling via fatty acid synthase (FAS), as inhibition of FAS leads to reduced AR signaling and reduced CRPC growth (135).

Another target of AR is calcium/calmodulin-dependent kinase kinase 2 (CAMKK2), which is overexpressed in PCa. In PCa cells, CAMKK2-dependent activation of AMPK leads to increased activity of PFK1, a rate-limiting enzyme in glycolysis that promotes glucose consumption and lactate production (136). In addition, AR regulates α -methylacyl-CoA racemase, required for β -oxidation of fatty acids (137). AR also manages ER stress by regulating the unfolded protein response (UPR) in PCa (138). The UPR genes XBP1 and IRE1 are androgen-regulated gene. Overall, AR manifests its oncogenic function in part by regulating metabolic pathways, which provide avenues for targeting of the downstream surrogates for cancer treatment.

METABOLITE CROSS-FEEDING AND TUMORIGENESIS

Cancer and non-cancer cells must cope with the enormous challenge of limited availability of nutrients and oxygen in the TME. To overcome these challenges, cancer and host cells engage in *metabolite cross-feeding* to utilize metabolic byproducts for sustaining energy and biomass production needs.

Glucose and Lactate cross-feeding:

A great example of metabolic cross-feeding involves glucose and lactate metabolism of cells in the TME, where cancer cells in the hypoxic region of the tumor undergo aerobic glycolysis and produce lactate, and cancer cells in normoxic regions use lactate to fuel their TCA cycle (139). Lactate was once considered a waste product of glycolysis, but recent studies reveal that cancer cells heavily use lactate (140). In hypoxic regions of the tumor, cancer cells increase expression of MCT4, a transporter to export lactate into the TME; in normoxic regions, however, cancer cells increase expression of MCT1, a lactate importer, to fuel anabolic metabolism. This symbiosis has been documented in tumor models such as in pancreatic cancer, where MCT1 and MCT4 expression patterns track with regional oxygen tension (141). Also, pharmacological induction of hypoxia by angiogenesis inhibitors stimulates pancreatic neuroendocrine cancer cells to overexpress MCT4 and GLUT1, enabling increased use of glucose and increased secretion of lactate to maintain intracellular pH (142). A similar but opposite glucose-lactate arrangement has been observed in PCa, in which CAFs co-cultured with cancer cells show changes in GLUT1, MCT1, and MCT4 expression; this enables the CAFs to use glucose and produce lactate, which is taken up in turn by cancer cells to fuel their anabolic growth (110).

Amino acids:

Fibroblast cells can release various metabolites such as alanine and glutamine into the TME, which can be used by cancer cells. Pancreatic stellate cells (PSCs), using the autophagy/lysosome system, generate and secrete alanine, which fuels the TCA cycle in pancreatic cancer cells (143,144). Recent identification of SLC38A2 as the critical transporter allowing the active import of alanine, may provide a novel therapeutic target to disrupt this critical metabolic crosstalk. Indeed, genetic loss of SLC38A2 causes unrecoverable metabolic crises and markedly impairs the growth of fully formed pancreatic cancers. Similarly, in ovarian cancer, CAF-secreted glutamine can be used by cancer cells to fuel growth (145). Ovarian cancer cells can also enable growth by the breakdown of arginine to citrulline and nitric

oxide with use of inducible nitric oxide synthase (iNOS); this citrulline is taken up by stromal adipocytes and converted back into arginine, which is then shuttled back to cancer cells to feed its anabolic processes (146).

Lipids:

Fibroblasts such as PSCs secrete lipids when activated during tumorigenesis. A recent study found that PSCs secrete lysophosphatidylcholines, which are used for the synthesis of i) phosphatidylcholines, a key component of cell membranes, and ii) lysophosphatidic acid (LPA), a wound-healing mediator (147). LPA synthesis is mediated by extracellular enzyme autotaxin, which is overexpressed in pancreatic cancer. Furthermore, inhibition of the autotaxin–LPA axis by genetic and pharmacological means inhibits PDAC growth.

The above studies have revealed multiple metabolic cross-feeding in the TME. The cross-feeding of metabolites enables cancer cells to acquire the metabolites necessary for their anabolic and redox homeostasis functions. However, these metabolic cross-feedings also make the cancer cells vulnerable to inhibitors of these pathways. With additional studies in *in vivo* settings, the above findings have potential for therapeutic development.

AVENUES AND HURDLES TO TARGETING METABOLISM IN TUMORS

Metabolic vulnerabilities are a long-sought target for cancer therapeutics. In 1947, the first drug to target metabolism, aminopterin, was used to treat acute lymphoblastic leukemia (148). Aminopterin is a precursor of the currently used drug methotrexate, which is a folate analog that inhibits one-carbon transfer reactions required for *de novo* nucleotide synthesis (149). The initial success of antifolates led to a new drug series called antimetabolites, and include examples such as purine analogues 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG), which inhibits 5-phosphoribosyl-1-pyrophosphatase (PRPP) amidotransferase, and pyrimidine analogue 5-fluorouracil (5-FU), which inhibits thymidylate synthase. These antimetabolites target the DNA synthesis pathway in highly proliferating cancer cells and remain some of the most successful classes of drugs in the clinic.

Although targeting the proliferative nature of cancer cells using antimetabolite therapies has been a staple in cancer treatment for decades, leading to remission and even cure, these therapeutic approaches have limitations due to associated toxicity. At the systemic level, targeting cancer cells' 'proliferative metabolism' also impacts proliferating normal cells of the bone marrow, intestinal crypts, and hair follicles. Indeed, this liability explains the common toxicities observed in patients receiving anti-metabolite therapies. Even locally within the TME, because of the intertwined nature of immune, fibroblast, and cancer cell metabolism, targeting cancer metabolic pathways while avoiding host cell metabolism has been challenging, although the clinical effectiveness of antimetabolites suggests that a therapeutic window may be possible. Along these lines, one strategy to expand the therapeutic window of antimetabolites would be to combine these agents with drugs targeting other cancer hallmarks such as immunity.

Nucleotide metabolism is one of the many metabolic dependencies of cancer cells required for their anabolic reactions to increase biomass for replication. For instance, compared to

primarily catabolic pathways in normal non-dividing cells, cancer cells balance the divergent catabolic and anabolic requirements for sustaining cellular homeostasis while also increasing cell mass (150). This anabolic metabolism in cancer cells may present potential opportunities to target these cells therapeutically, although an appreciation for its impact on host cells is a key consideration. One case in point concerns glutamine, a nonessential amino acid, that is utilized extensively by proliferating cancer cells (151). Current strategies to target glutamine metabolism involve inhibiting glutaminase (GLS1/2), the glutamine transporter SLC1A5, and utilizing glutamine analogues. Several of these approaches are currently being evaluated in clinical trials (NCT03875313, <https://clinicaltrials.gov/ct2/show/NCT03875313>). Preclinical data have shown contrasting observations on the impact of impairing glutamine metabolism on immune cell function. A recent study demonstrated that glutamine is required for cytotoxic CD8⁺ T cell and T_H1-cell function, possibly thwarting the antitumor impact of anti-glutamine therapy (152). Another study provided evidence that glutamine inhibition upregulates oxidative metabolism in T cells and supports highly activated T cell phenotypes (153). Together, these findings underscore the necessity of understanding the overall impact of metabolic perturbations beyond just the cancer cells themselves to include host cells impacting biology in the TME.

Another therapeutic strategy to disrupt cancer metabolism would be to target metabolic enzymes that are mutated in cancer. While such mutations are not common occurrences across cancers, mutations in isocitrate dehydrogenase 1/2 (IDH1/2) are often seen in glioblastoma multiforme and AML (154) and cause the production of the oncometabolite D-2-hydroxyglutarate (D2HG). The first-in-class IDH1 inhibitor, AGI-5198, now in clinical trials, reduces intratumoral D2HG levels and induces glial cell differentiation in preclinical models (155). Similarly, the IDH2 inhibitor, AG-221, increases survival in a mouse model of AML (156). Other IDH inhibitors currently in clinical trials include AG-120 and IDH305, as well as the pan-mutant IDH inhibitor AG-881. Although preclinical models show promise, IDH inhibitors are not effective in all IDH mutant tumors (157). These differential responses may relate to the importance of a specific genetic alteration in tumor maintenance (158). Specifically, IDH mutation is an early event in tumorigenesis and the accumulation of certain oncogenic events may alleviate the tumor's dependency on the IDH mutation in advanced malignancies (159). In the case of glioma, combinatorial strategies may be needed, including taking advantage of the fact that IDH mutant tumors show sensitivity to hypomethylating agents, coenzyme NAD⁺, and electron transport chain (ETC) inhibition (157,160).

Another intriguing cancer metabolism target is tryptophan-depleting enzyme indoleamine 2,3-dioxygenase (IDO) involved in the production of kynurenine, a suppressor of T cells and dendritic cell priming (161,162). Current clinical trials have shown minimal benefit which may again relate to context or to redundant activities from the other tryptophan metabolism enzyme, tryptophan-2,3-dioxygenase.

Lastly, mitochondrial OXPHOS is upregulated in a number of cancer types including leukemia, lymphoma, colorectal cancer, pancreatic ductal adenocarcinoma and endometrial carcinoma (163). In these cancers, cell growth and survival are OXPHOS dependent, encouraging the development of OXPHOS inhibitors such as IACS-010759. In Phase I

studies, IACS-010759, which inhibits complex I of the mitochondrial electron transport chain, shows tolerability along with partial responses or stable disease in a limited number of patients with prostate and colorectal cancer (164). Additional clinical study, including patient stratification, will be needed to determine whether OXPHOS inhibitors possess a therapeutic window.

These illustrative examples describe avenues and dilemmas of therapeutic targeting of cancer metabolism. Expanding our understanding of the reliance of differential metabolic pathways required for cancer and immune cell function may provide viable avenues for targeting rate-limiting nodes in key metabolic pathways operative in cancer cells, while preserving immune cell function to promote antitumor immunity. Additional studies are required to tease out the details in order to modulate the various metabolic nodes therapeutically.

CONCLUSIONS

Metabolic pathways are driven by both cell intrinsic signaling and host cell-derived extrinsic factors. Intrinsic signaling maintains the baseline metabolic state, whereas extrinsic signals fine-tune the metabolic processes based on the availability of metabolites and requirements of the cells. However, these processes are hijacked in cancer to constitutively activate metabolic nodes to serve their purpose in promoting tumor growth and immune suppression. To date, the clinical failures of GLS and IDO have increased appreciation for the shared metabolic processes between cancer and host cells and the redundant nature of many metabolic pathways leading to metabolic adaptation and escape from therapeutic intervention. For example, while aerobic glycolysis might be an obvious therapeutic target because of its vital role in supporting cancer cell growth, the same metabolic process is essential for optimal effector function of immune cells for antitumor immunity. Thus, a concerted effort is required to delineate *in vivo* the metabolic requirements of the various cell types in the TME.

Greater emphasis should be placed on the use and selection of *in vivo* genetic model systems that faithfully recapitulate the metabolic crosstalk among the various cell types in the TME and overall systemic metabolic changes. Such model systems that account for the intertwined nature of the metabolic networks may better inform clinical trials, particularly responder populations and combination therapies. In the context of clinical trials, one consideration could be to avoid radical metabolic interventions that totally inhibit a metabolic pathway, often giving rise to metabolic bypass and resistance. That is, improved outcomes may derive from the restoration of metabolic homeostasis via metronomic dosing of drugs to curtail the excessive activity of metabolic enzymes while retaining the minimal function that enables retention of antitumor activity of immune cells.

Another strategy could entail targeting systemic metabolic changes rather than focusing only on local metabolic dysregulation. For example, high circulating branched-chain amino acids feed cancer cells in non-small cell lung cancer (165), raising the intriguing possibility that inhibiting muscle breakdown or inhibiting branched-chain amino acid uptake or metabolism by cancer cells could represent a rational therapeutic approach. Further study to identify

systemic metabolic changes during carcinogenesis might provide an opportunity for supplementation or therapeutic intervention to tip the balance of metabolism toward antitumor immune response and cancer cell inhibition. For instance, a ketogenic diet might increase the efficacy of PI3K inhibitors in PDAC patients (166). Finally, extrinsic signals, emanating from immune cells or fibroblasts such as cytokines or their receptors, could serve as therapeutic targets since many of these factors support cancer cell metabolism and suppress antitumor immunity.

In conclusion, the complex metabolic requirements shared by cancer and host cells, particularly immune cells, strongly suggest that successful targeting of cancer metabolism will require a more nuanced approach based on the cancer's genotype, tumor type, TME composition and tissue location. A one-drug-fits-all approach is unlikely to provide the intended benefit, while uninformed clinical development could jeopardize the pipeline of antimetabolite therapies. Rather, a more productive approach could consider targets and drug combinations targeting multiple cancer hallmarks beyond cancer metabolism, accurate patient stratification based on genotype and biomarker analyses to guide early proof-of-concept clinical trials, and clinical trials incorporating target engagement assays and assessment of adaptive therapeutic responses and escape mechanisms. In addition, a greater focus should be placed on strategies that preserve antitumor immune cell function while inhibiting cancer cell metabolism. The promise of cancer metabolism therapy will be realized through a full understanding of the complex heterotypic interactions in the TME and the redundant mechanisms governing metabolic co-dependencies of cancer and host cells.

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STATEMENT OF SIGNIFICANCE

Cancer cell metabolic reprogramming is a consequence of the converging signals originating from both intrinsic and extrinsic factors. Intrinsic signaling maintains the baseline metabolic state, whereas extrinsic signals fine-tune the metabolic processes based on the availability of metabolites and the requirements of the cells. Therefore, successful targeting of metabolic pathways will require a nuanced approach based on the cancer's genotype, tumor microenvironment composition and tissue location.

Figure 1. Intrinsic drivers of metabolic pathways.

This schematic summarizes specific oncogenes and tumor suppressor genes that modulate metabolic pathways for tumor progression. PI3K-AKT, mTOR and cMyc pathway are integral to the maintenance of core metabolic functions in normal and cancer cells, while aberrant activation is central to tumor progression and maintenance. GLUT, Glucose transporter; HK1/2, Hexokinase 1/2; PFKM1, phosphofructokinase-M 1; ENO1, Enolase 1; MCT1, Monocarboxylate transporter 1; ACC1, Acetyl-CoA carboxylase; ACLY, ATP Citrate Lyase; HMGCR, HMG-CoA reductase.

Figure 2. Extrinsic drivers of metabolic pathways.

This schematic summarizes the factors derived from the microenvironment that dictate the metabolic profile of the tumor. Extrinsic factors such as cytokines, hormones and metabolites regulate cellular metabolism in discrete ways driven by the availability of these factors in anatomically distinct sites and by differences in the composition of resident immune, endothelial, and fibroblast cells. MPC, Mitochondrial Pyruvate; SREBP, Sterol regulatory element-binding protein.

Table 1.

Cytokine-mediated metabolic pathways

Cytokines	Sensors and Mediators	Effects on Metabolism	References
IL-2	PI3K/AKT-mTOR	Increases glucose metabolism to promote T cell differentiation.	(167,168)
IL-4	IL4R-JAK1-STAT6 Or IL4R-JAK1-STAT3	Enhances glucose and glutamine metabolism, up-regulates the expression of glucose transporter 4 (GLUT4).	(32,98,169,170)
IL-13	IL4R-IL13R-JAK1-STAT6	Regulation of MYC-dependent glycolysis enzymes hexokinase II and enolase I.	(32)
TNF- α	TNFR family	Induces insulin resistance; increases glycolysis, adenosine triphosphate (ATP) production, and lactate export; reduces vitamin metabolism.	(171-173)
IL-10	IL10R-JAK1/TYK2 mediated STAT3 activation	Promotes oxidative phosphorylation in macrophages and inhibits glucose uptake; suppresses both glycolysis and oxidative phosphorylation via inhibition of the mTORC1/S6 kinase 1 (S6K1) pathway in TLR-stimulated B cells.	(174,175)
IL-15	IL-15R-IL-2R	Stimulates fatty acid oxidation via TRAF6, enhancing CD8 T cell memory.	(176,177)
IL-6	JAK1-STAT3	Inhibits gluconeogenic gene transcription; reduces vitamin metabolism; enhances lipolysis.	(178,179)