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Targeting Metabolic Heterogeneity in the Tumor Microenvironment: From Metabolic Plasticity to Therapeutic Vulnerability

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Abstract

Metabolic heterogeneity has emerged as a defining feature of cancer, yet its origins and therapeutic implications are often considered in a cancer cell-centric manner. Here, we summarize evidence that metabolic diversity is instead dynamically co-regulated by cancer cells, stromal and immune compartments, and by the abnormal vasculature within the tumor microenvironment (TME). We discuss how spatial and temporal fluctuations in oxygen and nutrient availability generate distinct metabolic niches that select for phenotypic plasticity and adaptive cell states. Across these niches, cancer cells differentially engage glycolysis, oxidative phosphorylation (OXPHOS), glutamine and lipid metabolism, and stress-response pathways, generating metabolic states associated with proliferation, survival, metastatic capacity, and therapy resistance. Particular attention is given to tumor endothelial cells (TECs), whose metabolic states influence vascular function and nutrient distribution and may thereby contribute to intratumoral metabolic heterogeneity. In parallel, oncogenic mutations, tissue context, and treatment-induced stress remodel pathway usage and foster the emergence of metabolically adaptable, stem-like, and drug-tolerant populations. Thus, cancer metabolic heterogeneity is shaped by cellular and environmental crosstalk rather than as a static consequence of genetic variation alone. This framework has important translational implications: effective metabolic therapies will require context-aware strategies that target specific niche liabilities while accounting for vascular state, immune function, and adaptive rewiring. Defining when and where these metabolic states create selective dependencies will be essential for translating metabolic heterogeneity into therapeutically actionable vulnerabilities.

Keywords: Tumor microenvironment; metabolic plasticity; cancer metabolism; therapy resistance; metabolic crosstalk.

1. Introduction

Cancer cell metabolism has been recognized as a central driver of tumor development since the original description of the Warburg effect (1) and is now understood as a key determinant of tumor complexity across molecular, cellular, and spatial scales (2). While early-stage tumors may arise from relatively homogeneous genetic lesions, oncogenic evolution rapidly generates phenotypically diverse cancer cell populations. Importantly, this diversity cannot be fully explained by genetic variation alone. Even among genetically similar cells, metabolic programs can diverge substantially, leading to heterogeneous proteomic, epigenomic, and metabolomic states that are not directly predictable from genomic alterations (3). This functional metabolic heterogeneity can support phenotypic plasticity and thereby contribute to therapeutic resistance and treatment failure (4).

Within this complexity, a broad distinction can be made between intertumoral heterogeneity, reflecting differences between tumor types or individual patients, and intratumoral heterogeneity, defined by distinct, spatially organized cellular compartments within a single tumor. Advances in multi-omics technologies, including transcriptomics and metabolomics, now permit metabolic heterogeneity to be examined at increasingly high cellular and spatial resolution (5). However, these advances have not yet translated into a fully integrated understanding of the multicellular interactions that shape the TME.

In tumors, cancer cells are embedded in a complex TME composed of the extracellular matrix (ECM), stromal cells, immune cells, and vasculature. Besides providing structural support and migration routes, the ECM also actively regulates signaling pathways, including integrin-mediated adhesion signaling, growth factor receptor signaling, and hypoxia-responsive pathways. Through these mechanisms, the ECM influences the phenotype and metabolic behavior of surrounding cells (6, 7). In parallel, neighboring stromal and tissue-resident immune cells influence tumor onset and development through paracrine signaling, metabolic competition and cooperation, direct cell-cell interactions and vesicle-mediated communication, and the establishment of hypoxic and inflammatory niches that collectively activate pro-tumorigenic signaling (8–10). Consequently, the TME is organized into spatially distinct niches characterized by differences in nutrient availability, oxygenation, ECM composition, and inflammatory cues. These microenvironmental gradients contribute to phenotypic plasticity and generate diverse functional and metabolic states across the tumor. Some of these states may create therapeutic dependencies, although distinguishing a targetable dependency from a reversible adaptive state remains an important experimental challenge.

Although cancer metabolism research has increasingly shifted from cancer cell-intrinsic metabolic pathways towards the multicellular metabolic interactions within the TME, the contribution of tumor endothelial cell (TEC) metabolism to spatial metabolic heterogeneity remains less well defined than cancer cell-intrinsic metabolic adaptation. As the cellular interface between circulating blood and tumor tissue, ECs are uniquely positioned to integrate mechanical, metabolic, and inflammatory cues while regulating vascular perfusion, barrier function, and immune cell trafficking. In tumors, ECs acquire profound metabolic and transcriptional adaptations that drive the formation of a structurally and functionally abnormal vasculature (11–13). The resulting defects in perfusion generate spatial gradients of nutrients, thereby establishing distinct metabolic niches throughout the tumor (11). TECs therefore participate in the spatial and metabolic organization of the TME rather than responding passively to tumor-derived cues. Defining how EC metabolism governs these processes may therefore uncover new therapeutic vulnerabilities with broad relevance across cancer types.

This review considers metabolic heterogeneity as an emergent property of interactions among malignant, stromal, immune, and vascular compartments rather than as a cancer cell-intrinsic phenotype alone. This review places particular emphasis on TEC metabolism and how vascular state intersects with nutrient availability, metabolic plasticity, and therapeutic response.

2. Metabolic heterogeneity in the TME

Cancer metabolism is not solely an intrinsic property of malignant cells but results from a complex, spatially organized ecosystem. Early observations of altered nutrient and gas fluxes in tumors led to the description of the Warburg effect, describing the high rates of glucose uptake and lactate production observed in many cancers despite oxygen availability (1). This metabolic phenotype, characterized by elevated glucose uptake and increased lactate production, is now recognized as a hallmark of cancer (14). Rather than reflecting complete suppression of mitochondrial function, the shift toward glycolysis in cancer cells is associated with a rewiring of central carbon metabolism, in which tricarboxylic acid (TCA) cycle activity and oxidative phosphorylation (OXPHOS) are partially redirected away from ATP production. This metabolic configuration supports diverting glycolytic and mitochondrial intermediates into anabolic pathways, sustaining the biosynthetic demands of rapidly proliferating cancer cells while profoundly affecting redox balance, biomass production, and cellular signaling (15).

Yet the Warburg effect, as originally conceived, captures only a fraction of the metabolic complexity now recognized within tumors. Cancer cells can shift metabolic pathway usage in response to oxygen availability, nutrient constraints, and the physical properties of the TME. As an example, lung cancer cells can exploit mannose when glucose availability or glycolysis is restricted, redirecting it toward glycolysis and the synthesis of glycosylation precursors, thereby partially sustaining proliferation under metabolic stress (16). Metabolic adaptation can also involve intracellular nutrient recycling: under metabolic stress, neuroendocrine prostate cancer relies on lysosomal programs to maintain lipid availability, while its inhibition creates a vulnerability to fatty acid synthase (FASN) blockade (17). At the interface with the TME, hyperglycemia and tissue mechanics engage heat shock factor 1 (HSF1)-dependent metabolic programs that remodel the cancer cell glycocalyx and alter immune cell surveillance (18).

Critically, this metabolic flexibility is not uniform across cells within the same tumor. Single-cell and spatial profiling approaches indicate substantial cell-to-cell and regional variation in metabolic pathway activity, energy state, and redox programs, generating intratumoral metabolic heterogeneity in addition to the metabolic variation observed between tumors (19–20). Using clustering approaches, Iqbal and colleagues identified three metabolic subtypes of breast cancer with progressively increasing degrees of metabolic deregulation, each characterized by distinct pathway dependencies and closely associated with tumor aggressiveness and patient outcome (21). In gastric cancer, integrated lipidomics and spatial transcriptomics provided a comprehensive spatial map of intratumoral metabolic heterogeneity and cell-cell metabolic interactions within the same tissue sample. By combining spatial information on metabolites and genes, this multi-omics framework revealed how metabolic reprogramming is coupled to transcriptional states, cellular architecture, and immunometabolic remodeling at the tumor-normal interface (22). More broadly, spatial metabolomics studies have shown that nutrient availability, perfusion differences, and local cell composition can generate metabolically distinct niches within tumors (23–25). For instance, in several solid tumors, cells located in well-perfused peripheral regions preferentially rely on oxidative metabolism and display enhanced biosynthetic activity, whereas cells in hypoxic cores undergo hypoxia-dependent metabolic reprogramming and increased glycolytic activity (26). Spatial transcriptomic analyses of glioblastoma have further revealed regional differences in the expression of hypoxia-responsive and metabolic genes according to their proximity to necrotic

areas (27). Similarly, osteosarcomas exhibit compartment-specific metabolic adaptations, where hypoxic regions activate alternative pathways, including proline metabolism, to maintain redox homeostasis under nutrient stress (28). These spatial studies support a model in which local oxygenation, nutrient supply, and cellular composition contribute to distinct metabolic states within the same tumor (27).

Cancer stem cells (CSCs) represent a metabolically adaptable cancer cell subpopulation whose contribution to metabolic heterogeneity stems from their capacity to switch between glycolytic and oxidative states in response to microenvironmental cues to sustain self-renewal, survival, and tumor-regenerating capacity (29). This flexibility is evident across malignancies, including leukemia, breast cancer, pancreatic cancer, and glioblastoma (30–33). Importantly, CSC metabolic plasticity also limits therapeutic efficacy: OXPHOS inhibition can impair CSC survival but may favor the emergence of compensatory glycolytic states, indicating that inhibiting one metabolic state can select for alternative pathway use. Whether combined or sequential targeting can suppress this adaptation without unacceptable toxicity remains context-dependent and requires further evaluation (34, 35). Beyond bioenergetics, CSC metabolism is linked to epigenetic maintenance, antioxidant defense, ferroptosis resistance, and immune evasion (36–39).

3. Lactate-driven TME remodeling

3.1 Lactate as a metabolic substrate

Among the metabolic intermediates that actively structure TME heterogeneity, lactate has emerged as a key molecule (Figure 1A). Lactate production is largely driven by lactate dehydrogenase A (LDHA), which catalyzes the conversion of pyruvate to lactate. Clinical studies have associated elevated LDHA expression with poorer survival in several malignancies, including lung adenocarcinoma, thyroid cancer, hematological cancers, and clear cell renal cell carcinoma (40–43). In contrast, genetic ablation of LDHA isoforms under hypoxic conditions markedly impairs tumor growth, underscoring the functional importance of fermentative glycolysis in cancer progression (44). Associations between lactate-related metabolic features and clinical outcome, together with functional studies of LDHA, support a role for lactate metabolism in tumor progression. However, these observations do not establish lactate as a broadly validated prognostic biomarker across cancer types, nor do they distinguish its effects from those of the accompanying acidic and glycolytic state.

Lactate is imported via monocarboxylate transporter 1 (MCT1), converted back to pyruvate by LDH, and oxidized in the TCA cycle to fuel mitochondrial ATP production and biosynthetic processes (45). Through this metabolic coupling, lactate shuttling between glycolytic and oxidative cancer cell populations, notably between cancer cells and cancer-associated fibroblasts (CAFs), promotes ECM remodeling, invasion, and angiogenesis by sustaining oxidative metabolism in recipient cells (46, 47). Recent evidence from non-tumor experimental systems further refines this paradigm by showing that mitochondria can generate lactate within the matrix (48). This mitochondrial lactate is exported to the cytosol, where it modulates reactive oxygen species (ROS) production, thereby revealing a previously unrecognized role for mitochondrial lactate metabolism in redox homeostasis.

3.2 Lactate as a signaling molecule

Beyond its role as a carbon source, lactate can influence the tumor niche through receptor-mediated signaling and through changes associated with extracellular acidification. Lactate-driven acidification of the TME facilitates invasion and metastasis through the activation of matrix-degrading proteases,

weakening of cell-matrix adhesion, induction of epithelial-to-mesenchymal transition (EMT), and the selection of aggressive, acid-tolerant cancer cell clones (49).

Lactate also acts as a potent immunomodulatory signal shaping immune cell polarization and function. Tumor-derived lactate promotes macrophage polarization toward non-inflammatory, tumor-supportive phenotypes and suppresses the proliferation and cytotoxic activity of T cells and natural killer (NK) cells, thereby conferring a competitive advantage to immunosuppressive phenotypes (50–52). These immunosuppressive effects are partly mediated by lactate-sensing receptors such as GPR81/HCAR1, expressed on immune and stromal cells, which transduce extracellular lactate signals into intracellular programs. Through this receptor-mediated mechanism, lactate functions not merely as a metabolic competitor but as an active ligand that reprograms immune cell behavior independently of pH changes (53, 54). Intratumoral dendritic cells (DCs) require MCT4-mediated lactate efflux to maintain intracellular pH and cGAS-STING signaling, thereby preserving their anti-tumor activity (55). In NSCLC cells, lactate has also been reported to increase CD38 expression through OXPHOS–Hippo-TAZ signaling, promoting adenosine receptor signaling, Snail induction, and EMT (56).

3.3 Lactate as an epigenetic regulator

Lactate also influences TME heterogeneity at the epigenetic level. Lactate-driven protein and histone lactylation, the covalent modification of lysine residues by lactyl groups, represents a post-translational modification that links metabolic state to transcriptional reprogramming (57). Histone lactylation marks, including H3K18la, accumulate under conditions of high glycolytic flux and have been shown to activate gene expression programs associated with tumor progression, stemness, and immune evasion. In bladder cancer-associated macrophages, lactate-induced histone lactylation promotes the expression of homeostatic and anti-inflammatory genes, contributing to the establishment of immunosuppressive tumor-associated macrophage (TAM) phenotypes in a manner distinct from classical cytokine-driven polarization (58). Lactate-associated lactylation therefore provides one mechanism by which metabolic state can influence transcriptional programs in cancer and immune cells. However, the persistence, reversibility, and relative contribution of these modifications to intratumoral heterogeneity remain incompletely defined.

4. Glutamine metabolism and immunometabolic competition

4.1 Glutamine addiction and metabolic competition

Glutamine is one of the most abundant and versatile amino acids in the human body and plays a central role in maintaining cellular and systemic metabolic homeostasis (Figure 1B). In tumors, glutamine serves as a critical carbon and nitrogen source, supporting biosynthetic processes, redox balance, and energy production through its contribution to the TCA cycle via conversion to α-ketoglutarate (αKG). This reliance on glutamine-derived carbon has led to the concept of “glutamine addiction”, whereby cancer cells become highly dependent on glutamine metabolism to sustain proliferation, survival, and metastatic spread (59–61).

Importantly, glutamine addiction is not merely a consequence of nutrient availability but reflects a profound metabolic rewiring. When extracellular glutamine becomes limiting, cancer cells can exploit alternative metabolic pathways to preserve glutamate and αKG pools. For example, N-acetyl-aspartyl-glutamate can be converted into glutamate through enzymatic pathways involving glutamate carboxylase and glutamine transaminase K (GTK) (62). Consistent with the functional importance of this pathway, genetic ablation of GTK significantly impairs tumor growth in pancreatic cancer models (63), highlighting glutamine-dependent anaplerosis as a critical metabolic vulnerability.

At the tissue level, the high glutamine demand of cancer cells profoundly reshapes nutrient availability. Using *in vivo* metabolic tracing, Reinfeld and colleagues demonstrated that cancer cells preferentially import glutamine, whereas immune cells preferentially import glucose, a nutrient-partitioning program driven by intrinsic mTORC1-dependent metabolic circuits rather than nutrient scarcity itself (64). Nevertheless, immune cells remain highly dependent on glutamine to sustain activation, proliferation, and effector differentiation (65). Competition for glutamine can therefore influence immune-cell function in nutrient-limited tumors, although the direction and magnitude of this competition depend on cell type, tumor context, and the availability of alternative substrates.

4.2 Glutamine metabolism in anti-tumor immunity: a double-edged sword

As mentioned, the metabolic competition for glutamine within the TME has important consequences for anti-tumor immunity. A compelling example is provided by type-1 conventional DCs (cDC1s), which are essential for priming cytotoxic $CD8^+$ T cell responses. Guo and colleagues showed that glutamine acts as an intercellular metabolic checkpoint regulating cancer cell-cDC1 crosstalk. Competition for glutamine uptake through SLC38A2 limits cDC1 activation and $CD8^+$ T cell priming, whereas restoring intratumoral glutamine availability enhances anti-tumor immunity and sensitizes tumors to immune checkpoint blockade and T cell-based immunotherapies (66). Additional evidence indicates that glutamine deprivation disrupts immunosuppressive TAM polarization (67).

Beyond nutrient availability, glutamine-derived glutamate can also regulate immune responses through glutamatergic signaling. In particular, loss of mGluR4 activity in DCs enhances their migration, maturation, and antigen-presenting capacity, thereby strengthening $CD8^+$ T cell and NK cell responses and suppressing tumor growth and metastasis by limiting adenyl cyclase/PKA signaling (68).

Effector T cells, NK cells and DCs rely on glutamine not only as a bioenergetic substrate but also for nucleotide synthesis, protein production and maintenance of mTORC1-dependent activation programs. Consequently, indiscriminate glutamine depletion can impair lymphocyte proliferation and cytokine production (69). In vitro, restriction of glutamine-dependent nucleotide synthesis during human T cell activation enriches FOXP3-high CD4+ populations with regulatory properties (70), raising the possibility that indiscriminate glutamine deprivation could have context-dependent immunosuppressive consequences.

Adding further complexity, glutamine metabolism can intrinsically threaten T cell survival. Zhang and colleagues recently showed that glutaminolysis in activated $CD8^+$ T cells generates ammonia that accumulates within lysosomes. Excessive ammonia accumulation disrupts lysosomal homeostasis, promotes mitochondrial dysfunction, and impairs autophagic flux, ultimately triggering a distinct form of T cell death characterized by lysosomal alkalinization and mitochondrial swelling (71). Thus, glutamine catabolism represents not only a metabolic resource for activated T cells but also a potential source of endogenous metabolic toxicity.

5. Lipid metabolic adaptation, ferroptosis and immune dysfunction

Lipid metabolism plays a central role in cellular homeostasis by providing structural components for membranes, signaling molecules, and bioenergetic substrates, and is strongly shaped by the spatial heterogeneity of the TME. Hypoxic niches promote lipid uptake and neutral lipid storage in lipid droplets, buffering lipotoxic stress while preserving substrates for membrane remodeling and oxidative metabolism upon reoxygenation (72). In this way, metabolic adaptation fosters compartmentalization of lipid resources, thereby shaping lipid availability and exchange between cancer cells, the circulation, and surrounding adipose tissue (73).

Beyond passive storage, cancer cells undergo profound metabolic adaptations that allow them to secure lipids through *de novo* synthesis, extracellular uptake, and lipid exchange with neighboring stromal and immune cells. These processes support cancer cell fitness and help maintain a metabolically resilient, tumor-supportive microenvironment (74). Among the lipid exchanges, one of the best-characterized lipid symbioses occurs between cancer cells and adipocytes. Tumor-derived signals induce adipocyte lipolysis and exosome secretion, resulting in the transfer of free fatty acids (FFA), cholesterol, and lipid-associated proteins to cancer cells (Figure 1C). These lipids are imported predominantly through CD36- and FABP-dependent pathways, fueling fatty acid oxidation (FAO), sustaining mitochondrial metabolism, and promoting invasive and metastatic phenotypes (75).

Paradoxically, the dependence on lipid remodeling can either protect against or create vulnerability to ferroptosis, a form of regulated cell death driven by iron-dependent peroxidation of polyunsaturated fatty acid (PUFA)-containing phospholipids (76, 77). *De novo* lipogenesis promotes membrane saturation and protects cancer cells from oxidative stress, whereas increased incorporation of PUFAs into membrane phospholipids enhances susceptibility to lipid peroxidation and ferroptosis. Thus, the effect of lipid remodeling depends on whether it favors oxidation-resistant saturated and monounsaturated lipids or oxidation-prone PUFA-containing phospholipids. Accordingly, increased lipid availability cannot be interpreted uniformly as pro- or anti-ferroptotic; its effect depends on lipid species, membrane incorporation, antioxidant capacity, and the metabolic state of the recipient cell.

This balance may vary across metabolically distinct TME niches, generating spatial heterogeneity in ferroptosis sensitivity (78). Ferroptosis is controlled by the balance between pro-peroxidative lipid remodeling and antioxidant defense systems. On the pro-ferroptotic side, Acyl-CoA synthetase long-chain family member 4 (ACSL4) promotes the activation of PUFAs, including arachidonic acid and adrenic acid, into acyl-CoA derivatives, whereas lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates these PUFA-containing species into membrane phospholipids (79, 80). Together, ACSL4 and LPCAT3 increase the abundance of oxidation-prone PUFA-phospholipids, thereby sensitizing cancer cells to ferroptosis. Conversely, reduced ACSL4 or LPCAT3 activity limits the availability of peroxidizable membrane substrates and can confer resistance to ferroptotic death (81).

Cancer cells counteract this vulnerability through several anti-ferroptotic defense mechanisms. The solute carrier family 7 member 11 (SLC7A11)-glutathione- glutathione peroxidase 4 (GPX4) axis represents a central protective pathway: SLC7A11 imports cystine to sustain glutathione synthesis, and GPX4 uses glutathione to detoxify phospholipid hydroperoxides before they propagate lipid peroxidation cascades (82). In parallel, GPX4-independent systems provide additional protection. Ferroptosis suppressor protein 1 (FSP1) suppresses ferroptosis by reducing coenzyme Q10 (CoQ10) to ubiquinol at the plasma membrane, generating a lipophilic antioxidant shield that neutralizes lipid peroxyl radicals independently of glutathione (81, 83). This protective pathway is also regulated by the metabolic TME. Microenvironmental prostaglandin F2α (PGF2α) directly binds FSP1 and inhibits its enzymatic activity, promoting lipid peroxidation and sensitizing cancer cells to ferroptosis. In preclinical models, PGF2α supplementation also enhances $CD8^+$ T cell-mediated immunity and responses to immunotherapy (84). Ferroptosis sensitivity therefore reflects the interaction between membrane lipid composition, cell-intrinsic antioxidant defenses, and metabolic inputs from the surrounding microenvironment.

The lipid-centered symbiosis also profoundly reshapes anti-tumor immunity. In tumor-associated macrophages, lipid-droplet-dependent long-chain fatty acid metabolism supports an immunosuppressive phenotype (85). In Tregs, tumor-driven lipid metabolic adaptation, including fatty

acid synthesis and FAO, supports expansion, survival, and suppressive function under nutrient-limited conditions (86, 87). Lipid availability can also directly shape neutrophil function in a tissue-specific manner. In liver metastases, breast and colorectal cancer (CRC) cells exploit the local abundance of palmitate to promote palmitoyltransferase 17-dependent stabilization and secretion of laminin-511, which suppresses neutrophil cancer cell-killing capacity and thereby facilitates metastatic growth (88). In cytotoxic T cells, excessive lipid uptake can become detrimental. CD8+ T cells take up oxidized phospholipids and oxidized low-density lipoproteins (LDL) through CD36-dependent mechanisms (89, 90). Accumulation of these oxidized lipids promotes membrane lipid peroxidation, impairs $CD8^+$ T cell metabolic fitness, and can ultimately drive ferroptotic cell death (90, 91). When lipid peroxide detoxification is insufficient, $CD8^+$ T cells become particularly vulnerable to ferroptotic damage; accordingly, preservation of GPX4-dependent lipid peroxide detoxification is critical for their survival, expansion, and persistence (92, 93). Thus, lipid metabolic remodeling represents a central determinant of both ferroptotic control and immune cell escape in the TME.

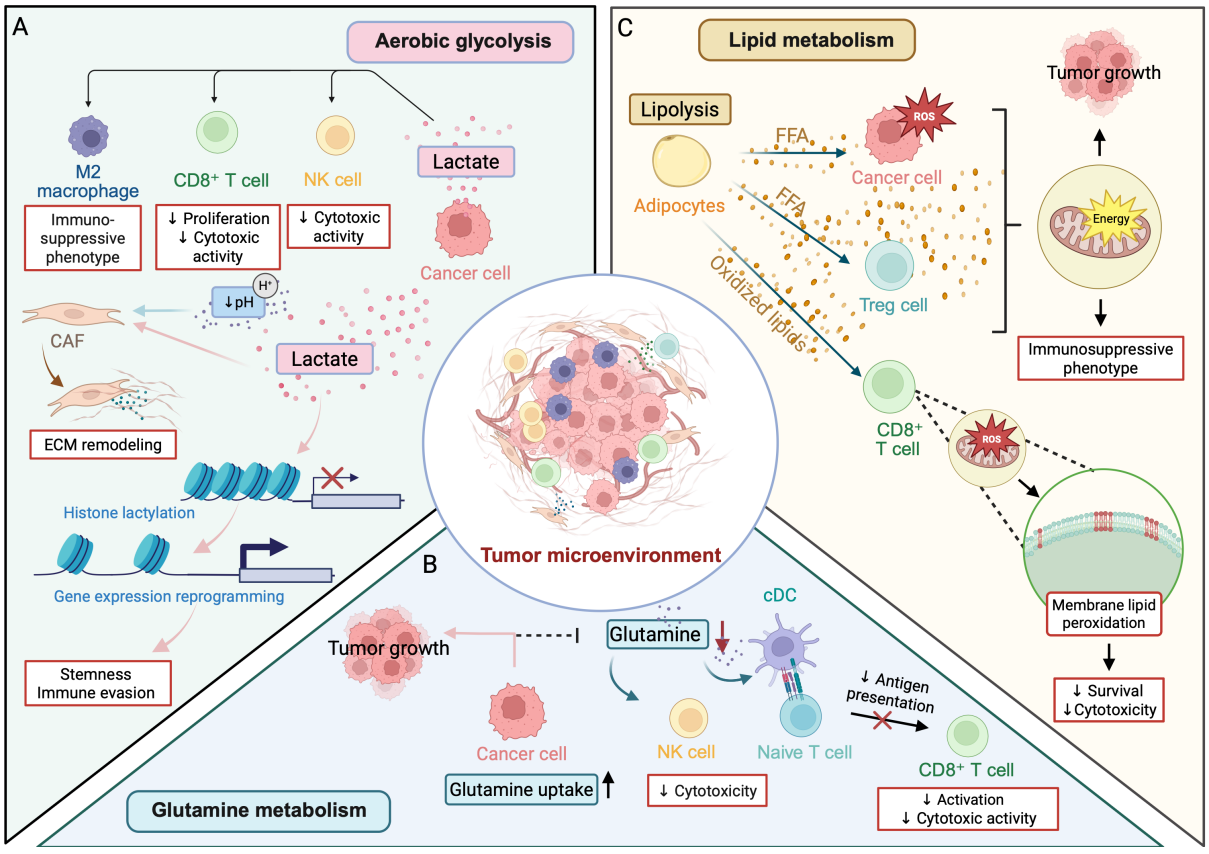


Figure 1: Metabolite-mediated regulation of cellular functions in the TME. *A: Aerobic glycolysis. Cancer cells exhibit enhanced aerobic glycolysis, increasing lactate production and extracellular acidification. Lactate accumulation promotes an immunosuppressive environment by stimulating macrophage states associated with immunosuppressive and tissue-remodeling functions, reducing $CD8^+$ T cell proliferation and cytotoxicity, and impairing NK cell function. Lactate also modulates CAF phenotype and induces histone lactylation-dependent transcriptional reprogramming, thereby contributing to cancer cell stemness and immune evasion. B: Glutamine metabolism. Increased glutamine uptake by cancer cells restricts glutamine availability to immune cells, compromising NK cell function and cDC1-mediated antigen presentation and consequently reducing $CD8^+$ T cell activation and cytotoxic activity. C: Lipid metabolism. Adipocytes release FFA through lipolysis, which are taken up by cancer and immune cells. In cancer cells, lipid metabolism supports energy production and promotes tumor growth, partly through ROS. In immune cells, lipid accumulation and ROS promote mitochondrial dysfunction and membrane lipid peroxidation, leading to $CD8^+$ T cell exhaustion and an immunosuppressive phenotype, including Treg expansion. NK, natural killer cells; CAF, cancer-associated fibroblasts; ECM, extracellular matrix; cDC, conventional dendritic cells; FFA, free fatty acids; ROS, reactive oxygen species. Treg, regulatory T cells. Created in BioRender. Cantelmo, A. R. (2026) https://BioRender.com/i9rushe.*

6. Energy charge and redox regulation as integrators of metabolic heterogeneity

Beyond nutrient availability and metabolic pathway engagement, cellular energy charge and redox balance represent fundamental layers of metabolic heterogeneity within the TME. Energy supply within cells is primarily mediated by adenine and guanine nucleotides, whose relative abundance reflects metabolic state and dictates cellular behavior (94). In rapidly growing tumors, spatial differences in nutrient and oxygen availability generate regional disparities in ATP levels, resulting in heterogeneous energetic states across tumor regions (95). Hypoxic conditions further exacerbate this heterogeneity by promoting a shift toward glycolytic ATP production, which yields less ATP *per* glucose molecule than OXPHOS and alters the ATP/ADP balance. This changes cellular energy kinetics and contributes to metabolic stress (96).

Alternative nuclear and cytosolic pathways, including poly(ADP-ribose) (PAR) metabolism, have been proposed to contribute to local ATP pools under specific conditions, further diversifying energetic states within tumors. In the nucleus, activation of PARP1 and PARP2 during DNA damage responses consumes large amounts of NAD^+ to synthesize PAR, rapidly depleting nuclear and cellular NAD^+ and indirectly suppressing ATP production by limiting NAD^+-dependent glycolysis and TCA cycle flux (97, 98). Excessive PAR accumulation, such as that triggered by calcium-induced mitochondrial ROS, can lead to severe energy depletion and PARP1-dependent cell death in pancreatic cancer cells, illustrating how dysregulated PAR turnover can collapse ATP levels in stressed tumor regions (99). Conversely, coordinated activity of PAR glycohydrolase (PARG) and ADP-ribose-processing enzymes has been proposed to contribute to local ATP generation in the nucleus, potentially supporting DNA repair and replication independently of bulk cytosolic ATP availability (100, 101). The energetic consequences of PAR metabolism are further modulated by genetic context: in isocitrate dehydrogenase (IDH)-mutant tumors, inhibition of PARG during alkylating chemotherapy sequesters NAD^+ in PAR polymers, leading to global NAD^+ depletion, impaired ATP production, and metabolic collapse, revealing a genotype-specific vulnerability rooted in nucleotide and redox imbalance (102).

Beyond the nucleus, cytosolic and extracellular purine-handling pathways also shape local energy landscapes within the TME. Cancer and stromal cells express ecto-adenylate kinase and nucleoside diphosphate kinases capable of regenerating ATP from AMP or ADP in the pericellular space (103). Together, these nuclear, cytosolic, and extracellular nucleotide cycles add a fine-grained layer of energetic heterogeneity on top of classical glycolysis *vs.* OXPHOS differences, linking DNA damage responses, redox balance, and microenvironmental signaling to spatial control of ATP availability (104). Guanine nucleotides contribute to metabolic heterogeneity by linking energy status to transcriptional and translational control. GTP availability regulates protein synthesis and growth signaling, and perturbations in GTP biosynthesis have been shown to impair RNA polymerase I activity (94). In MYC-driven small cell lung cancer (SCLC), disruption of GTP synthesis alters transcriptional output and contributes to chemoresistance (105).

In parallel, redox cofactors such as NADH, NADPH, and flavin adenine dinucleotide ($FAD/FADH_2$) play central roles in determining cellular fate. These cofactors integrate metabolic inputs from glycolysis, glutaminolysis, FAO, and mitochondrial respiration, enabling cancer cells to balance ATP production with biosynthesis and oxidative stress management (106, 107). NADPH is particularly critical for anabolic reactions and antioxidant defense, as it fuels glutathione and thioredoxin recycling. Under nutrient- or glucose-limited conditions, cancer cells exploit alternative substrates, including lactate and glutamine, to sustain NADPH production via IDH1- and malic enzyme 1 (ME1)-dependent pathways, thereby preserving redox homeostasis despite metabolic stress (108). Consistently, glucose-

6-phosphate dehydrogenase (G6PD)-dependent NADPH generation and $NADP^+$ pool expansion support metastatic potential and therapy resistance (109). ROS buffering through the glutathione system further reinforce this heterogeneity (110). Maintenance of reduced glutathione (GSH) pools through NADPH-dependent recycling is essential for buffering oxidative stress, regulating redox-sensitive signaling, and preventing ROS-induced cell death, thereby contributing to divergent metabolic and survival phenotypes within the same tumor (111).

7. Systemic, genetic, and tissue-context determinants of metabolic heterogeneity

7.1 Systemic metabolic inputs

Beyond cell-intrinsic metabolic programs and local nutrient competition within the TME, systemic nutrient availability adds another, often underappreciated, layer of metabolic heterogeneity by shaping spatially heterogeneous metabolite availability within the tumor interstitium. Systemic nutrient availability, shaped in part by diet and host metabolic state, can influence substrate availability and metabolic pathway usage within tumors in a context-dependent manner. Circulating nutrients such as glucose, fatty acids, and amino acids are heterogeneously distributed across tumors and dynamically sensed by cancer cells, leading to spatially distinct metabolic programs (112). Metabolic reprogramming in cancer also involves activation of the mTORC1-SREBP axis, which promotes *de novo* lipid synthesis and supports cancer cell growth and proliferation (113). As a result, metabolic heterogeneity is shaped not only by cancer progression stage and microenvironmental constraints, but also by inter-individual differences in systemic dietary inputs and host metabolic status (114, 115). Epidemiological studies associate dietary patterns, obesity, and metabolic disorders with the incidence and, in some settings, progression of particular cancers (116), although such associations do not establish a direct tumor-metabolic mechanism. For example, obesity has been associated with an increased incidence of several malignancies, although its impact on overall survival appears to depend on complex interactions between diet composition, nutrient excess, and the metabolic properties of the TME rather than adiposity alone (117).

Experimental studies using dietary interventions in cancer models have provided mechanistic insight into how nutrient availability modulates cancer metabolism. High-fat, Western, ketogenic, or nutrient-restricted diets have been shown to differentially reprogram metabolic pathways, either promoting or restraining tumor growth depending on tumor type and genetic context (118). For instance, high-fat diets exacerbate hyperglycemia and hyperinsulinemia in CRC models, whereas ketogenic diets can create therapeutic vulnerabilities when combined with targeted inhibitors, such as PI3K pathway blockade (119). Importantly, the metabolic impact of specific nutrients also depends on tumor stage and genotype. Replacing exogenous glucose with fructose can limit tumor initiation, while paradoxically accelerating cancer progression once the tumors are established (114).

7.2 Oncogenic and tumor suppressor-driven metabolic reprogramming

MYC activation, a potent driver of carcinogenesis across multiple cancer types, promotes the transcription of glycolytic and glutaminolytic enzymes, sustaining high proliferative capacity through enhanced glucose and glutamine catabolism (120).

KRAS mutations drive metabolic reprogramming toward increased utilization of glucose- and glutamine-derived carbon to support TCA cycle activity and biosynthesis (121). Mutant KRAS promotes hypoxia-inducible factor (HIF)-1α-dependent metabolic rewiring, increasing glucose uptake through GLUT1 and lactate production (122, 123). KRAS simultaneously reprograms glutamine

metabolism by favoring non-canonical transamination pathways that replenish TCA cycle intermediates and support anabolic growth (124), while also stimulating auxiliary nutrient-consuming pathways including the pentose phosphate pathway (PPP), hexosamine biosynthesis, and folate cycling (123).

PIK3CA mutations confer differential sensitivity to glutamine availability. Compared with wild-type (WT) cells, PIK3CA-mutant CRC cells convert more glutamine to αKG to replenish the TCA cycle and generate ATP, resulting in subpopulations with distinct survival thresholds under nutrient-limited conditions (125).

Loss or mutation of TP53 enforces wide-ranging metabolic dependencies. p53 deficiency enhances glucose uptake and glycolytic flux (126). Loss of p53-mediated repression can increase PHGDH expression and serine biosynthetic capacity (127). Pan-cancer analyses have associated TP53 mutational status with hypoxia-related metabolic programs and differences in immune-cell composition (128). In breast cancer brain metastasis (BCBM), p53 loss functionally increases metastatic formation and growth in part by upregulating SCD1 and *de novo* FAS, with astrocytes further amplifying the lipid-anabolic state via secreted metabolites. Notably, p53-deficient tumors display vulnerability to FASN inhibition *ex vivo* and *in vivo*, highlighting FAS and SCD1 as therapeutically targetable metabolic liabilities in BCBM (129).

APC loss, an early and frequent event in CRC, has been linked to a Warburg-like shift, with increased expression of glycolytic genes (*e.g.,* PKM2 and LDHA), elevated glucose consumption, and lactate secretion (130). APC mutations can also engage nutrient-sensing circuitry such as mTORC1, coupling oncogenic signaling to metabolite-availability cues (131).

7.3 Tissue-of-origin effects on mutation-driven metabolic phenotypes

A fundamental principle emerging from comparative metabolic analyses is that oncogenic mutations do not operate in a metabolic vacuum; instead, they redirect and amplify pre-existing tissue-specific metabolic programs, critically shaping mutation-driven metabolic phenotypes.

This principle is exemplified by MYC-driven liver tumors, in which MYC imposes a selective metabolic dependence on alanine catabolism. Montoya et al. used *in vivo* isotope tracing to show that MYC-driven liver cancers catabolize alanine in a GPT2-dependent manner, with alanine-derived carbon contributing to the TCA cycle, gluconeogenesis, and biosynthesis of non-essential amino acids and nucleotides (132). This dependency was functionally relevant: genetic ablation of *Gpt2* limited MYC-driven liver tumorigenesis, whereas pharmacological inhibition with L-cycloserine reduced tumor formation and slowed the growth of established liver tumors. A complementary comparison by Yuneva et al. further illustrates that metabolic phenotypes cannot be inferred from oncogene or enzyme expression alone (133). By following labeled glucose fate in MYC- and MET-driven tumors, they found increased glucose catabolism across the tumors examined, but increased lactate production only in MYC-induced liver and lung tumors, not in MET-induced liver tumors, despite elevated LDHA expression. These comparisons demonstrate that the metabolic consequences of an oncogenic driver are not fixed but depend on the signaling and tissue context in which the alteration occurs.

The influence of tissue context on metabolic heterogeneity has been further demonstrated by quantitative metabolomic analyses. In a seminal study, Sullivan and colleagues introduced identical genetic alterations, KRAS activation combined with loss of p53, into lung and pancreatic ductal adenocarcinoma cells, and implanted them subcutaneously into the same host environment. Despite identical mutations and implantation sites, tumors displayed distinct branched-chain amino acid

metabolic profiles, highlighting the critical contribution of the tissue of origin to metabolic heterogeneity within the TME. Thus, genotype is insufficient to predict metabolic behavior, as tissue of origin and microenvironmental factors strongly influence metabolic wiring (112).

7.4 Metabolic enzyme mutations and oncometabolites

Beyond oncogenes and tumor suppressors, mutations in core metabolic enzymes profoundly reshape cancer metabolism. Loss-of-function mutations in fumarate hydratase (FH) or succinate dehydrogenase (SDH) lead to accumulation of fumarate or succinate, respectively, which act as oncometabolites that disrupt αKG-dependent dioxygenase activity, alter chromatin and epigenetic regulation, and impair DNA repair pathways. Mechanistically, fumarate and succinate can inhibit αKG-dependent dioxygenases (including prolyl hydroxylases), stabilize HIF, and promote a pseudohypoxic transcriptional program (134, 135). Broader analyses of IDH-, FH-, and SDH-mutant tumors highlighted how oncometabolite accumulation reshapes chromatin states and signaling networks, with emerging evidence that these metabolites also modulate immune cell behavior (136). In IDH1/2-mutant tumors, the neomorphic production of (R)-2-hydroxyglutarate (2-HG) provides a clear example of an oncometabolite that competitively inhibits αKG-dependent dioxygenases, impairing histone demethylation and TET-mediated DNA demethylation (137). With this mechanism, IDH-mutant acute myeloid leukemia cells display a characteristic DNA hypermethylation phenotype linked to disrupted TET function (138). Together, these observations provide direct evidence that oncometabolites can enforce durable epigenetic states and stress-response programs that may shape cancer cell phenotypes within the tumor niche.

8. Stromal metabolic crosstalk in the TME

8.1 CAF-cancer cell metabolic interactions

CAFs are among the most abundant and functionally diverse stromal populations in solid tumors and undergo profound metabolic reprogramming in response to tumor-derived signals. Single-cell and spatial transcriptomic analyses have revealed metabolically distinct CAF subpopulations, including myofibroblastic CAFs (myCAFs) with high contractile and glycolytic activity and inflammatory CAFs (iCAFs) with distinct cytokine secretion and amino acid metabolic profiles (139). This metabolic heterogeneity contributes to spatial compartmentalization within the TME, with CAFs acting as metabolic intermediaries between cancer cell populations exposed to different levels of oxygen and nutrient availability. These categories should not be viewed as fixed metabolic lineages: CAF states can overlap, vary among tumor types, and change with spatial location and treatment exposure.

A well-characterized feature of CAF metabolism is the induction of a Warburg-like glycolytic phenotype, driven in part by cancer cell-secreted factors including TGF-β, exosomal miRNAs, and ROS (140–142). This cancer cell-imposed metabolic reprogramming suppresses mitochondrial oxidative metabolism in CAFs while upregulating glycolytic flux and lactate secretion, effectively converting CAFs into metabolic supporters that fuel oxidative cancer cells through metabolic symbiosis (143, 144).

Beyond lactate, CAFs serve as major sources of glutamine within the TME. Under nutrient-limited conditions, CAFs upregulate glutamine synthetase (GS) activity, enabling *de novo* glutamine synthesis from glutamate and ammonia, and export glutamine to neighboring cancer cells. This CAF-to-cancer glutamine relay sustains cancer cell anaplerosis, supports TCA cycle activity, and buffers cancer cells against the metabolic consequences of glutamine depletion (145, 146). CAFs also play a central role in lipid metabolic crosstalk, releasing lipid mediators including lysophosphatidylcholine, prostaglandins,

and FFA that are taken up by cancer cells. In pancreatic and ovarian cancers, CAF-derived lipids promote cancer cell invasiveness and chemoresistance by sustaining mitochondrial metabolism and suppressing apoptotic signaling (147). Complementing these findings, metabolomics and fatty acid tracing experiments in CRC demonstrated that cancer cells can take up CAF-secreted lipids and lipid-like metabolites to compensate for low endogenous stearoyl-CoA desaturase activity, regulating membrane fluidity and invasive potential (148).

8.2 Adipocyte-cancer cell metabolic interactions

Adipocytes represent an important stromal population in cancers arising in or metastasizing to adipose-rich environments, including CRC, breast and ovarian cancers. Tumor-derived signals (TNF-α, IL-6, and Wnt ligands) stimulate adipocyte triglyceride (TG) hydrolysis. Among these lipolytic cues, TNF-α potently stimulates adipocyte lipolysis through an adipose triglyceride lipase (ATGL)-dominant mechanism, with hormone-sensitive lipase (HSL) also contributing to TG hydrolysis. In 3T3-L1 adipocytes, ATGL silencing almost completely abolished basal and TNF-α-induced glycerol release, whereas HSL knockdown only partially reduced lipolysis, supporting a major role for ATGL in TNF-α-driven release of FFA and glycerol (149).

In ovarian cancer peritoneal metastasis, adipocyte-derived FFA accelerate metastatic outgrowth by fueling FAO-dependent energy production, with CD36 blockade significantly impairing metastatic colonization (150). In breast cancer, peritumoral adipocytes undergo delipidation and reprogram toward a cancer-associated adipocyte (CAA) phenotype characterized by reduced lipid storage, increased lipolysis, and secretion of pro-tumorigenic adipokines, including leptin and IL-6, that further stimulate cancer cell proliferation and survival signaling (151). Adipocyte-derived acetate can additionally be incorporated into acetyl-CoA pools in cancer cells, influencing histone acetylation and transcriptional states that reinforce proliferative and stem-like phenotypes (38).

9. TECs as metabolic gatekeepers of TME heterogeneity

Because TECs lie at the interface between the circulation and tumor tissue, their metabolic state can influence vascular function, nutrient delivery, and exchange between systemic and local compartments. This metabolic plasticity enables TECs to coordinate vascular function while regulating the delivery and exchange of nutrients, oxygen, growth factors, and waste products (152–154). Through heterogeneous expression of nutrient transporters and their effects on vascular perfusion and exchange, TECs can contribute to spatial metabolic gradients within tumors (12, 13). Conversely, TEC metabolism and function are themselves shaped by metabolic and environmental cues within the TME (Figure 2). TECs therefore occupy a strategically important position in tumor metabolic organization and may provide context-specific therapeutic targets where pathological endothelial states create dependencies that can be separated from normal vascular metabolism.

9.1 State-dependent metabolic specialization in endothelial subpopulations

ECs comprise a spectrum of phenotypically distinct subpopulations. Across independent single-cell atlases, a conserved set of states has emerged, including highly migratory tip cells at the leading edge of sprouting, stalk cells that elongate nascent vessels, and quiescent ECs that maintain mature vessels (12, 155, 156). Single-cell studies associate these endothelial states with distinct metabolic gene-expression programs, although transcriptional signatures do not necessarily establish metabolic flux or dependency. Glycolytic bias, for example, appears to be an intrinsic feature of the migratory tip phenotype, providing rapid ATP generation independent of oxygen availability to meet the high local

energy demands of cell migration (13). This metabolic program fuels the dynamic remodeling of the actin cytoskeleton required to generate the filopodial protrusions that guide angiogenic sprouting (154, 157). Consistent with this concept, TECs highly express actin-binding genes, including the cytoskeletal scaffold protein PDLIM5, which promotes filopodia formation and tumor angiogenesis by regulating ACTN1/ACTN4-dependent actin bundling. Accordingly, endothelial-specific deletion of *Pdlim5* disrupts filopodia formation and suppresses sprouting angiogenesis (158).

The glycolytic phenotype of TECs is functionally relevant, although its therapeutic consequences depend strongly on the degree of pathway inhibition. Partial pharmacological inhibition of the glycolytic activator PFKFB3 by 3PO attenuates the hyperglycolytic phenotype of TECs, normalizes the disorganized tumor vasculature, reinforces endothelial barrier integrity, and reduces both intratumoral hypoxia and metastatic dissemination (13). By contrast, complete PFKFB3 inhibition at higher doses of 3PO destabilizes rather than normalizes tumor vessels, indicating that the vascular response depends on the extent of glycolytic inhibition and highlighting a defined therapeutic window (159). This dependence on the degree of glycolytic inhibition has subsequently been exploited in combination therapies. In glioblastoma, dual PFKFB3/VEGF blockade prolongs the vascular normalization window achieved only transiently with anti-VEGF therapy, thereby improving chemotherapy delivery (160), while in CRC, PFKFB3 inhibition alleviates tumor hypoxia and enhances radiotherapy response through vascular normalization (161). These studies identify endothelial glycolysis as a potentially targetable stromal dependency, but they also show that outcome depends on the degree of pathway inhibition: partial suppression can promote vascular normalization, whereas stronger inhibition may destabilize the vasculature.

In contrast to the highly glycolytic tip cell phenotype, stalk cells that trail the leading edge operate under a distinct metabolic program tailored to biomass production rather than migration (162). DLL4-Notch lateral inhibition holds these cells in a proliferative fate (163, 164), and single-cell profiling of tumor endothelium consistently shows that they downregulate the glycolytic program in favor of OXPHOS, TCA cycle activity, and one-carbon metabolism (12, 155). Consistent with this metabolic state, glioblastoma-derived TECs selectively upregulate the serine synthesis pathway. Tumor-derived signals induce ATF4-dependent expression of PHGDH, the rate-limiting enzyme of this pathway, thereby sustaining nucleotide biosynthesis and EC proliferation. Endothelial-specific deletion of PHGDH reduces pathological sprouting (165), normalizes the tumor vasculature, alleviates intratumoral hypoxia, and enhances T cell infiltration and responsiveness to CAR-T therapy (166).

Proliferating TECs also adapt their metabolism to nutrient availability within the TME. In IDH1/2-mutant gliomas, cancer cells release the oncometabolite 2-hydroxyglutarate (2-HG), which ECs preferentially import via SLC1A1 and transport to mitochondria, where it remodels mitochondrial respiration to sustain angiogenesis, revealing a vascular vulnerability not targeted by IDH1 inhibitors alone (167). Interestingly, other studies have reported distinct endothelial responses to 2-HG, including reduced endothelial proliferation, migration, and tube formation through suppression of mTOR/STAT3 signaling (168). These apparently opposing effects caution against assigning a uniform endothelial phenotype to 2-HG exposure. Differences in tumor context, 2-HG concentration, endothelial state, exposure duration, or experimental system may determine whether the net response is pro- or anti-angiogenic.

TEC metabolic adaptation to locally available nutrients extends beyond tumor-derived oncometabolites. In hepatocellular carcinoma, proliferating TECs upregulate the fructose transporter SLC2A5 and

ketohexokinase, enabling fructose to fuel mitochondrial respiration through AMPK activation and thereby promote angiogenesis and metastasis (169).

9.2 Lactate as a central metabolic signaling nexus in the tumor endothelium

Lactate, produced by glycolytic TECs and Warburg-active cancer cells, can be taken up by the tumor endothelium, where it functions as both a metabolic substrate and a signaling molecule. Mechanistically, TECs import lactate through MCT1, triggering the NF-κB/IL-8 signaling axis that drives autocrine angiogenic gene expression and endothelial migration (170). Lactate uptake through MCT1 also activates HIF-1 under normoxic conditions, while pharmacological MCT1 inhibition suppresses lactate-induced HIF-1 activation and tumor angiogenesis *in vivo* (46).

TECs are also adapted to survive in the lactic-acidic TME. Unlike normal ECs, TECs maintain proliferation at interstitial lactate concentrations that impair normal endothelial growth. This tolerance is mediated by carbonic anhydrase II (CAII), which is upregulated in TECs downstream of VEGFA/VEGFR2 signaling and maintains intracellular pH homeostasis under acidic conditions. Accordingly, CAII knockdown selectively reduces TEC survival under lactic acidosis, whereas pharmacological CA inhibition *in vivo* promotes vessel maturation and increases pericyte coverage, recapitulating features observed upon bevacizumab treatment (171).

Lactate can additionally regulate TEC function through protein lactylation. In melanoma, tumor-derived lactate increases histone lactylation at the ST2 promoter in TECs, enhancing IL-33 responsiveness and promoting angiogenesis; combined LDHA and ST2 inhibition suppresses tumor growth *in vivo* (172). Beyond TECs, lactylation-dependent mechanisms in other cellular compartments may further influence the tumor vasculature. In ovarian cancer, AARS1-driven ENO1-K71 lactylation enhances lactate production, which increases H3K9la and H3K14la lactylation at the ESM1 locus and promotes ESM1 expression in TECs. Secreted ESM1 subsequently acts on TECs to promote angiogenesis (173).

These studies support several mechanisms through which lactate can influence tumor endothelial behavior, including MCT1-dependent signaling, adaptation to acidosis, and lactylation-associated transcriptional regulation. Their relative contribution likely varies with tumor type, vascular state, and local lactate exposure.

9.3 Amino acid metabolism in TECs

Glutamine is the most abundant circulating amino acid and a major anaplerotic substrate for proliferating endothelium. ECs rely on glutamine metabolism predominantly for proliferation, consistent with the distinct metabolic requirements of stalk and tip cells during angiogenic sprouting (174, 175). Genetic or pharmacological inhibition of glutaminase 1 (GLS1), which converts glutamine to glutamate, impairs EC proliferation and angiogenic function across experimental models (175–177). This dependency extends to the tumor vasculature, where endothelial-specific GLS deletion reduces tumor growth and metastasis while increasing pericyte coverage and perfusion, alleviating hypoxia, and improving chemotherapy delivery (178).

Glutamine metabolism also supports endothelial growth through aspartate production. Endothelial aspartate activates mTORC1, sustaining translation of the pro-angiogenic receptors VEGFR2 and FGFR1 while supplying pyrimidines required for nucleotide synthesis and proliferation (179). Glutamine catabolism therefore couples anaplerotic and biosynthetic demands to the translational control of angiogenic signaling.

Importantly, however, these pathways can have different consequences in endothelial versus malignant compartments. Beyond glutamine, amino acid metabolism intersects with other metabolic pathways that shape TEC function, as illustrated by the PHGDH-dependent serine synthesis program discussed above. These pathways also contribute to metabolic adaptation in malignant cells. Increased PHGDH activity in TECs supports pathological angiogenesis (166), whereas PHGDH-dependent serine synthesis in breast cancer cells can promote tumor growth and metastatic progression, highlighting the importance of this metabolic pathway across distinct tumor compartments (180).

9.4 Lipid metabolism and endothelial homeostasis

Lipid metabolism contributes to endothelial homeostasis not only by supplying carbon for TCA cycle replenishment, aspartate production, and nucleotide synthesis (162), but also by maintaining redox homeostasis (181) and endothelial identity (182), and by generating metabolites that act as pro-angiogenic signals (183).

Single-cell profiling of breast tumor endothelium identified a lipid-processing endothelial subpopulation (LIPEC), enriched in the peritumoral vasculature and characterized by expression of PPARγ-regulated lipid-handling genes (184). A retrospective analysis of more than 4,000 patients with breast cancer associated the LIPEC signature with long-term outcome among patients receiving metformin (184). This association is hypothesis-generating; retrospective data cannot establish that the endothelial state predicts metformin benefit or that PPARγ-dependent endothelial metabolism mediates the clinical association.

This metabolic feature becomes particularly relevant in lipid-rich metastatic environments. In CRC liver metastases, TECs acquire a proliferative, FAO-active phenotype characterized by increased lipid utilization. The TEC-enriched factor F3 inhibits the autophagy-lysosome pathway through JNK-ERK-p53 signaling, preventing CPT1A degradation and enhancing lipid uptake and lipophagy. This FAO-dependent state confers resistance to anti-VEGFA therapy, whereas CPT1A inhibition restores therapeutic sensitivity in preclinical models (185). Consistent with a role for endothelial FAO in therapeutic resistance, CPT1A inhibition has been shown to restore sensitivity to anti-VEGF therapy (186), supporting endothelial FAO as a potential target for overcoming resistance to angiogenesis blockade.

Lipid-dependent resistance can also arise through metabolic crosstalk between TECs and cancer cells. In hepatocellular carcinoma, apolipoprotein A2 (APOA2) promotes endothelial-to-mesenchymal transition (EndMT) through TGF-β signaling, reducing VEGFR2 expression in TECs while simultaneously inducing FAO reprogramming in adjacent cancer cells. APOA2-enriched tumors are refractory to anti-VEGFA therapy, whereas TGF-β inhibition suppresses both EndMT and cancer cell lipid reprogramming (187). These findings support a lipid-associated intercellular circuit linking endothelial plasticity and cancer cell metabolism to resistance to anti-angiogenic therapy (AAT) in the reported hepatocellular carcinoma models.

Additional regulators of endothelial lipid handling directly influence tumor vascular function. Endothelial ANGPTL4 restrains lipoprotein lipase-dependent fatty acid uptake, and its deletion increases endothelial fatty acid uptake while reducing pathological neovascularization and vascular permeability and increasing pericyte coverage (188). FABP4, an intracellular lipid chaperone enriched in tumor endothelium, similarly supports tumor angiogenesis, whereas endothelial FABP4 depletion increases oxidative stress and suppresses tumor vascularization *in vivo* (189).

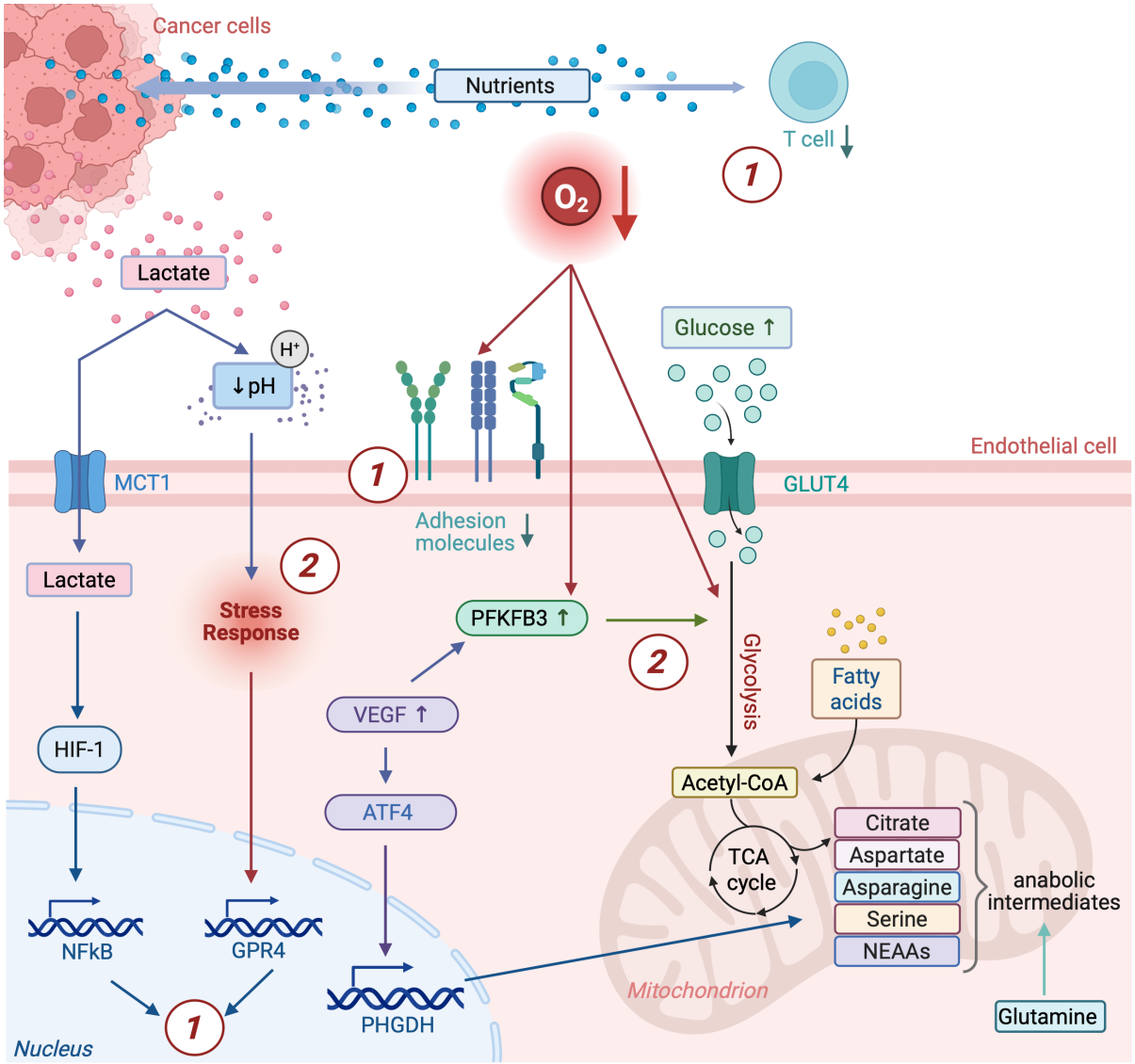


Figure 2: Metabolic and environmental regulation of EC function in the TME. *Tumor-derived metabolic cues and hypoxic stress reprogram EC metabolism and function, contributing to modulation of immune responses (1) and vascular dysfunctions (2). Lactate released by cancer cells is taken up by ECs via MCT1, promoting NF-κB/IL-8 signaling and HIF-1 activation, thereby promoting inflammatory transcriptional programs. In parallel, lactate accumulation leads to extracellular acidification, activating stress responses via GPR4 signaling. Hypoxia further amplifies endothelial dysfunction by inducing stress-response pathways associated with altered expression of adhesion molecules. Concurrently, hypoxia-driven signaling (e.g., VEGF) enhances PFKFB3 expression, promoting glycolysis and metabolic adaptation. In parallel, hypoxia and VEGF reprogram amino acid metabolism through ATF4-dependent upregulation of PHGDH, supporting de novo serine synthesis required for EC proliferation and metabolic homeostasis. Glutamine supports TCA-cycle anaplerosis and aspartate production, thereby contributing to nucleotide and protein biosynthesis. Fatty acids enter mitochondria to support biosynthesis. MCT1, monocarboxylate transporter 1; HIF-1, hypoxia inducible factor-1; NF-κB, nuclear factor kappa B; GPR4, G protein-coupled receptor 4; ICAM1, intercellular adhesion molecule 1; VCAM1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; ATF4, activating transcription factor 4; PHGDH, phosphoglycerate dehydrogenase; GLUT4, glucose transporter type 4; TCA cycle, tricarboxylic acid cycle; NEAAs, non-essential amino acids. Created in BioRender. Cantelmo, A. R. (2026) https://BioRender.com/395yxpv.*

10. Metabolic plasticity as a driver of therapeutic resistance

Therapeutic pressure can actively reshape metabolic interactions within the TME, selecting adaptive states that enable cancer cells and stromal populations to survive treatment and sustain disease

progression. This is particularly evident after AAT, which restricts vascular supply while simultaneously imposing hypoxia and nutrient limitation. Rather than simply starving the tumor, these conditions promote metabolic adaptation across multiple cellular compartments and create alternative routes of therapeutic escape. Importantly, metabolic changes detected after therapy may represent either causal resistance mechanisms or secondary adaptations in surviving cells; functional perturbation is required to distinguish the two.

One prominent adaptation to AAT is the redistribution of cancer cell metabolism according to oxygen and nutrient availability. In bevacizumab-treated glioblastoma, increased hypoxia drives a shift toward anaerobic glycolysis and lactate accumulation (190). Under these conditions, metabolic symbiosis can emerge between hypoxic MCT4^{+} glycolytic cancer cells and MCT1^{+} oxidative cells located closer to residual vessels, allowing spatially distinct cancer cell populations to exchange metabolites and sustain growth despite restricted vascular supply through the upregulation of mTOR signaling (191–193) (Figure 3). This adaptive response extends beyond glucose metabolism. In sorafenib-resistant hepatocellular carcinoma, PHGDH upregulation increases serine biosynthesis and glutathione production (194). Similarly, AAT withdrawal triggers a lipogenic rebound that promotes metastatic growth and can be suppressed by FASN or acetyl-CoA carboxylase (ACC) inhibition, revealing an acquired metabolic vulnerability after therapy (195).

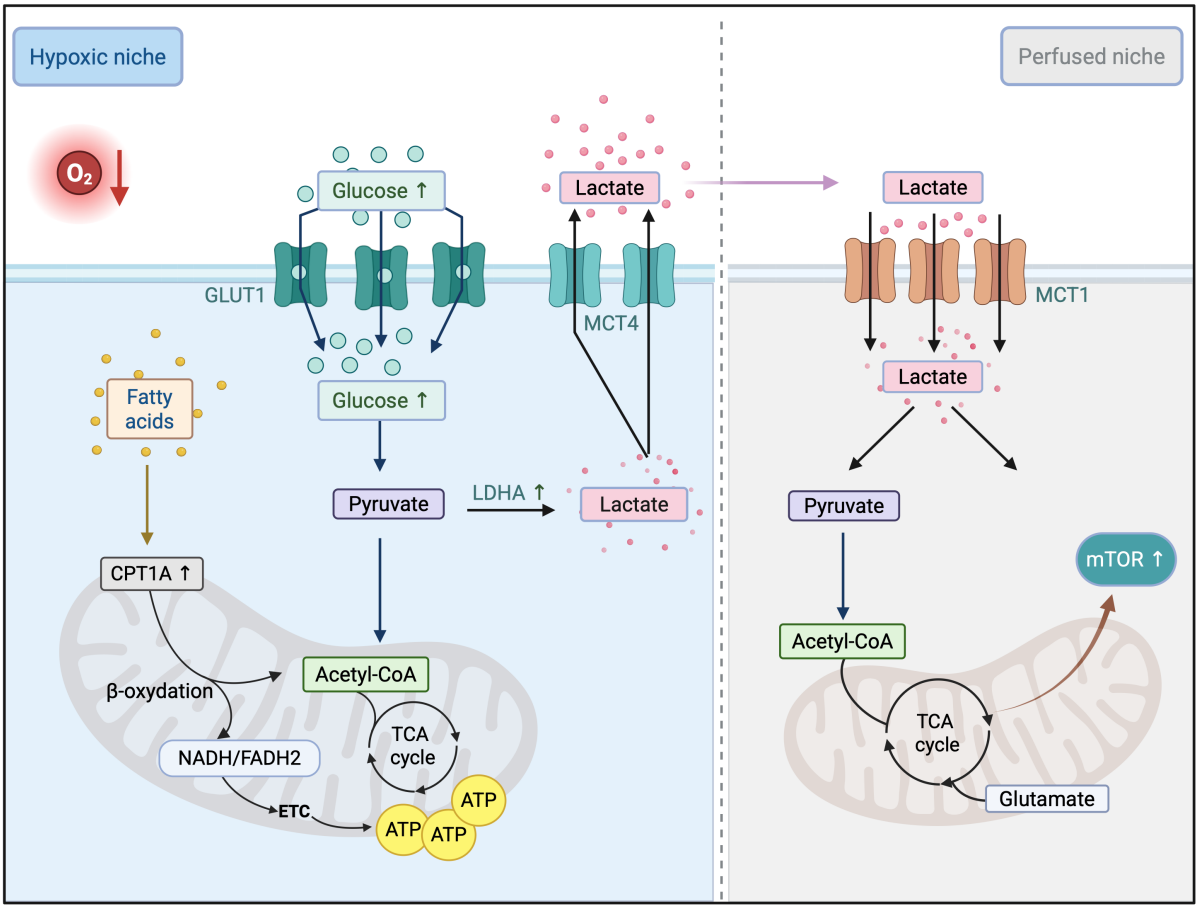


Figure 3: Metabolic adaptation of cancer cells in hypoxic *vs.* perfused niches. *Cancer cells adapt their metabolic programs according to oxygen and nutrient availability within distinct tumor niches shaped by AAT. In the hypoxic niche, reduced perfusion limits oxygen availability, promoting increased glucose uptake via GLUT1 and enhanced anaerobic glycolysis. Pyruvate is preferentially converted into lactate, which is exported through MCT4, contributing to extracellular lactate accumulation. In parallel, fatty acids enter mitochondria via CPT1A to undergo β-oxidation, contributing reducing equivalents to mitochondrial metabolism where sufficient oxygen remains available. In the perfused niche, normoxic cancer cells establish*

a metabolic symbiosis by importing lactate via MCT1 and converting it into pyruvate, which is further metabolized to acetyl-CoA to fuel the TCA cycle, supporting oxidative metabolism and biosynthesis. Lactate catabolism also enhances glutamine metabolism, promoting mTOR signaling. GLUT1, glucose transporter type 1; MCT4, monocarboxylate transporter 4; CPT1A, carnitine palmitoyltransferase 1A; NADH, nicotinamide adenine dinucleotide (reduced form); $FADH_2$, flavin adenine dinucleotide (reduced form); ETC, electron transport chain; TCA cycle, tricarboxylic acid cycle; MCT1, monocarboxylate transporter 1; mTOR, mechanistic target of rapamycin. Created in BioRender. Cantelmo, A. R. (2026) https://BioRender.com/0unp42h.

10.1 Metabolic barriers to anti-tumor immunity

Metabolic reprogramming within the TME can also limit the efficacy of anti-tumor immunity. In poorly perfused and highly glycolytic tumor regions, nutrient depletion and lactate accumulation impair effector T cell metabolism and function (196). By competing for glucose, cancer cells reduce T cell glycolytic capacity, mTOR activity, and IFN-γ production, thereby promoting T cell dysfunction and tumor progression (197). Elevated lactate levels further suppress cytotoxic T cell activity and reduce responsiveness to PD-1/PD-L1 blockade (196). Thus, enhanced cancer cell glycolysis can sustain malignant-cell metabolism while creating a metabolically restrictive environment for effector lymphocytes, contributing to resistance to immune checkpoint blockade.

Additional metabolic pathways further reinforce immune suppression. Tumor-driven tryptophan catabolism through IDO1 depletes local tryptophan and generates immunosuppressive kynurenine metabolites that promote T cell dysfunction and immune tolerance (198). Similarly, extracellular adenosine produced through CD39/CD73 activity suppresses T cell responses via A2A receptor signaling and impairs NK cell function and DC activation, thereby establishing a profoundly immunosuppressive microenvironment (199). These metabolic mechanisms therefore contribute not only to cancer cell survival but also to immune escape, limiting the efficacy of anti-tumor immune responses.

10.2 Redox and biosynthetic adaptation to cytotoxic stress

Chemotherapy and radiotherapy impose substantial oxidative stress on cancer cells. In response, resistant tumors frequently reprogram redox and biosynthetic pathways to enhance antioxidant capacity and maintain survival (200). In non-small cell lung cancer (NSCLC), cisplatin exposure induces ROS-dependent upregulation of PGC-1α, promoting mitochondrial biogenesis and OXPHOS, which supports survival and limits apoptosis (201). Chemotherapy-induced mitochondrial adaptation can also involve calcium homeostasis: in triple-negative breast cancer, the transient receptor potential melastatin 2 (TRPM2) ion channel limits mitochondrial calcium overload after chemotherapy, promoting cancer cell persistence, whereas its inhibition increases mitochondrial calcium accumulation and sensitizes cells to apoptosis (202).

Cisplatin resistance is also associated with the activation of the oxidative PPP, increasing NADPH production and glutathione-dependent ROS detoxification through enzymes such as G6PD (203, 204). Inhibition of these pathways can restore chemosensitivity, highlighting their role in acquired resistance. Similar adaptations contribute to radioresistance. By increasing antioxidant capacity through NADPH and GSH production, irradiated tumors enhance ROS detoxification and limit radiation-induced damage, with PPP activation representing a major source of antioxidant support (205, 206).

10.3 Metabolic adaptation and therapeutic resistance in cancer stem cells (CSCs)

CSCs provide a particularly clear example of metabolic plasticity under therapeutic selection. Rather than exhibiting a universal metabolic phenotype, CSCs can adopt glycolytic, oxidative, and lipid-dependent states according to tumor type, niche, and environmental pressure (207). In pancreatic ductal adenocarcinoma, the MYC/PGC-1α balance regulates switching between glycolytic and OXPHOS states, enabling CSCs to adapt their metabolic program to changing conditions (208). In AML, ROS-low leukemic stem cells depend on BCL-2-supported OXPHOS and are initially sensitive to venetoclax-based therapy (31, 209), whereas resistant populations can subsequently exploit nicotinamide and fatty acid metabolism to restore mitochondrial function (34, 35).

Tumor type and niche further shape these adaptive states. In breast cancer and glioma, CSCs maintain low intracellular ROS through elevated antioxidant capacity and NADPH production, conferring radioresistance (210). In hepatocellular and CRC, CSC states have been associated with increased lipid utilization and CD36-dependent fatty acid uptake (211), whereas in melanoma, slow-cycling CSC populations shift toward OXPHOS under targeted-therapy pressure (212).

Hypoxia adds another layer of CSC metabolic regulation, with HIF-1α-dependent programs coordinating stemness, energy metabolism, and redox homeostasis (213, 214). Spatially distinct niches, including the perivascular niche, also shape CSC metabolic plasticity by providing metabolic substrates that support persistence and therapy tolerance. Recent single-cell and organoid studies reinforce this dynamic view, indicating that therapy-resistant stem-like populations transition between metabolic states rather than relying on a single conserved metabolic program (215, 216). This plasticity may create transient windows of metabolic vulnerability, supporting sequential rather than simultaneous targeting as resistant states emerge during therapy.

10.4 Therapeutic strategies targeting TME metabolic heterogeneity: clinical translation and challenges

The metabolic heterogeneity and plasticity described above create both opportunities and major challenges for therapeutic intervention. Unlike oncogenic signaling pathways, metabolic programs are extensively shared between malignant and normal cells, vary across cellular compartments and spatial niches, and can be rapidly reconfigured under therapeutic pressure. Effective metabolic targeting therefore requires moving beyond pathway inhibition alone toward strategies that define the relevant metabolic dependency, the cellular compartment in which it operates, and the context in which it becomes therapeutically limiting. Table 1 summarizes selected metabolism-targeting agents that have reached clinical evaluation, with representative examples discussed below.

10.5 Genetically-defined and pathway-level metabolic vulnerabilities

Clinical translation has been most successful when a defined genetic alteration creates a measurable metabolic dependency and a corresponding biomarker-selected patient population. IDH1/2 mutations generate the oncometabolite 2-HG and create a discrete metabolic dependency (217). Targeting mutant IDH1 with ivosidenib produces durable responses in IDH1-mutant AML (218), while the brain-penetrant IDH1/2 inhibitor vorasidenib prolonged progression-free survival in patients with grade 2 IDH-mutant glioma (219). Notably, beyond its direct therapeutic activity, recent preclinical evidence indicates that vorasidenib pretreatment can enhance response to subsequent chemoradiation in IDH-mutant glioma (220).

Other genetic alterations similarly generate targetable metabolic dependencies. Von Hippel-Lindau (VHL) loss drives constitutive HIF-2α activity in renal cell carcinoma (RCC), enabling therapeutic

targeting with the HIF-2α antagonist belzutifan (221, 222). Likewise, loss of methylthioadenosine phosphorylase (MTAP) creates a metabolic dependency on methionine adenosyltransferase 2A (MAT2A), supporting selective MAT2A inhibition in MTAP-deleted tumors. The MAT2A inhibitor AG-270/S095033 has entered early clinical evaluation in MTAP-deleted tumors, with first-in-human studies reporting pharmacodynamic target engagement and initial evidence of antitumor activity (223).

A similar genotype-associated vulnerability has recently been identified in KRAS-driven AML, where mitochondrial NAD^+ homeostasis represents a selective metabolic dependency. Combined targeting of the mitochondrial NAD^+ transporter SLC25A51 and SDH selectively depletes mitochondrial NAD^+, inducing energetic collapse and suppressing leukemia progression (224). This vulnerability remains preclinical, however, and its therapeutic window will depend on whether mitochondrial NAD^+ depletion can be achieved selectively in malignant cells.

By contrast, pathway-level metabolic inhibitors have produced more variable clinical outcomes. The GLS inhibitor telaglenastat failed to improve progression-free survival when combined with cabozantinib in advanced RCC despite a strong preclinical rationale (225), while AZD3965 confirmed pharmacological inhibition of MCT1 but encountered dose-limiting toxicity during early clinical development (226). Similarly, the complex I inhibitor IACS-010759 showed potent preclinical activity in OXPHOS-dependent tumors (227), but phase I studies in advanced solid tumors and AML revealed lactic acidosis and peripheral neuropathy at exposures required for sustained target inhibition (228).

Therapeutic pressure can also generate new metabolic dependencies. In chemoresistant NSCLC, C/EBPβ-dependent metabolic reprogramming promotes reliance on FAO, increasing mitochondrial ATP production that sustains ATP-dependent multidrug efflux. Genetic or pharmacological inhibition of FAO restores chemosensitivity and additionally reprograms NK cell metabolism to enhance anti-tumor activity, identifying FAO as an actionable vulnerability of the chemoresistant state (229). Together, these experiences suggest that clinical tractability depends less on whether a metabolic pathway is altered in cancer than on whether inhibition exposes a sufficiently selective dependency that alternative pathways or normal tissues cannot rapidly compensate for.

Broader approaches are also being explored, including the glutamine antagonist sirpiglenastat (DRP-104), which targets multiple glutamine-dependent pathways and has shown both cancer-intrinsic and immunomodulatory activity in preclinical models (230, 231). The contrast between strong preclinical activity and variable clinical performance indicates that pathway dependence alone is insufficient for successful metabolic therapy; target engagement, normal-tissue dependence, compensatory pathway usage, and patient selection also determine the therapeutic window.

10.6 Extending metabolic targeting across the TME

The effects of metabolically targeted therapies are not necessarily confined to cancer cells. As illustrated by DRP-104, metabolic interventions can simultaneously affect malignant and non-malignant cell populations, potentially reshaping metabolic interactions across the TME. Whether such multicompartment activity improves efficacy or instead increases toxicity will depend on the selectivity of the targeted dependency. TECs provide a particularly relevant example, as targeting endothelial glycolysis, amino acid metabolism, or lipid utilization can alter vascular function and influence therapeutic response, as discussed above. Importantly, these approaches may exploit metabolic dependencies associated with pathological endothelial states without requiring complete suppression of pathways essential for normal vascular function.

Other stromal and immune populations provide complementary metabolic targets. TAMs undergo metabolic adaptation to hypoxia and tumor-derived metabolites such as lactate (50, 232), while CAFs can sustain cancer cell metabolism through nutrient exchange, including glutamine production under nutrient-limited conditions (233). Targeting these stromal metabolic programs may therefore disrupt both their intrinsic functions and the metabolic support they provide to neighboring cancer cells.

Immune-metabolic pathways have progressed further toward clinical translation. IDO1 inhibition with epacadostat failed to improve the efficacy of pembrolizumab in metastatic melanoma (234), highlighting the difficulty of translating inhibition of a single metabolic checkpoint into effective restoration of anti-tumor immunity. By contrast, CD73 blockade with oleclumab, alone or with durvalumab, has demonstrated tolerability and biomarker activity (235), and adenosine-axis combinations, including with radiotherapy and immunotherapy, remain among the most actively developed metabolic strategies (236). The NeoCOAST trial further evaluated durvalumab-based neoadjuvant combinations, including oleclumab, in resectable NSCLC (237, 238). Biomarker modulation and tolerability should not, however, be equated with clinical efficacy; whether adenosine-axis inhibition provides durable clinical benefit is likely to depend on tumor context, combination partner, and patient selection.

Adoptive cell therapies provide another setting in which TME metabolism may become therapeutically relevant. In solid tumors, CAR-T cell persistence and function are constrained by hypoxia, nutrient competition, and the accumulation of immunosuppressive metabolites. Strategies to improve the metabolic fitness of transferred T cells, including enhanced mitochondrial function and adaptation to harsh environments, may therefore complement interventions that remodel the metabolic composition of the TME (239).

The timing and sequence of interventions targeting different TME compartments may also influence therapeutic efficacy. In preclinical NSCLC, sequential anti-PD-L1 followed by anti-VEGFR2 treatment was more effective than concurrent administration (240), indicating that treatment sequence can influence efficacy in at least some preclinical settings and warrants prospective evaluation rather than assuming that concurrent administration is optimal.

10.7 Toxicity and patient selection

Toxicity remains a major constraint on the clinical development of metabolism-directed therapies because many metabolic targets are also required for normal tissue homeostasis. Biguanides carry a risk of lactic acidosis and gastrointestinal toxicity, HIF-2α antagonists can cause anemia and hypoxia-related adverse events, and inhibition of glutamine metabolism may affect highly proliferative normal tissues (228). Thus, toxicity is not simply a consequence of metabolic inhibition, but a key determinant of which metabolic vulnerabilities can be therapeutically exploited and at what level of pathway inhibition.

Patient selection is therefore critical for maximizing the therapeutic window. Beyond established genomic biomarkers, functional metabolic markers may be particularly important for TME-directed strategies, where therapeutic vulnerabilities are often defined by cellular and metabolic states rather than genetic alterations. Metabolic imaging, circulating metabolites, and single-cell profiling could complement these approaches by identifying these states and monitoring their evolution during treatment. Endothelial metabolic signatures associated with therapeutic response (241) and GLUT1 expression associated with response to neoadjuvant chemoradiotherapy in CRC (242) illustrate the potential of metabolic phenotypes for patient stratification, although prospective validation remains required. A key unresolved question is whether such functional metabolic biomarkers provide

predictive information beyond tumor genotype, histology, and established clinical biomarkers which will need to be addressed in biomarker-stratified prospective studies.

Metabolic axis	Drug	Molecular target	Clinical setting / trial phase	Treatment regimen	ClinicalTrials.gov ID
Immuno-metabolism	Oleclumab (MEDI9447)	Adenosine axis/CD73	Phase II (resectable stage III NSCLC)	Durvalumab (anti-PD-L1)	NCT03794544
			Phase III (unresectable stage III NSCLC)	Durvalumab (anti-PD-L1)	NCT05221840
Immuno-metabolism	Etrumadenant (AB928)	Adenosine-A2A/A2B	Phase Ib/II (mCRC)	Zimberelimab (anti-PD-1) + mFOLFOX6 + bevacizumab (anti-VEGF)	NCT04660812
			Phase II (advanced NSCLC)	Zimberelimab + domvanalimab	NCT04791839
			Phase II (mCRPC)	SRF617 + Zimberelimab	NCT05177770
Immuno-metabolism	Epacadostat (INCB024360)	IDO1 / Tryptophan-kynurenine axis	Phase I/II (advanced solid tumors)	Pembrolizumab (anti-PD-1)	NCT02178722
			Phase I/II (advanced solid tumors, B cell NHL, including DLBCL, and HL)	Nivolumab (anti-PD-1)	NCT02327078
			Phase I/II (advanced solid tumors)	Ipilimumab (anti-CTLA-4)	NCT01604889
			Phase I/II (advanced solid tumors)	Durvalumab (anti-PD-L1)	NCT02318277
			Phase III (unresectable or metastatic melanoma)	Pembrolizumab (anti-PD-1)	NCT02752074
Glutamine metabolism	Telaglenastat (CB-839)	GLS1	Phase II (advanced/metastatic ccRCC)	Everolimus	NCT03163667
			Phase II (advanced/metastatic ccRCC)	Cabozantinib	NCT03428217
			Phase II (ccRCC and NSCLC)	Cabozantinib, everolimus	NCT02771626
			Phase I/II (EGFR-mutated stage IV NSCLC)	Nivolumab (anti-PD-1)	NCT03831932
Arginine metabolism	Pegargiminase (ADI-PEG20)	Arginine metabolism	Phase II/III (nonepithelioid pleural mesothelioma)	Pemetrexed + cisplatin/carboplatin	NCT02709512
			Phase II (ASS1-deficient malignant pleural mesothelioma)	Monotherapy	NCT01279967
			Phase II (ASS1-deficient mesothelioma and non-squamous NSCLC)	Pemetrexed + cisplatin/carboplatin	NCT02029690

Metabolic axis	Drug	Molecular target	Clinical setting / trial phase	Treatment regimen	ClinicalTrials.gov ID
Lactate metabolism	AZD3965	MCT1	Phase I (advanced solid tumors/lymphoma, DLBCL, BL)	Monotherapy	NCT01791595
Hypoxia	Belzutifan (MK-6482)	HIF-2α	Phase II (VHL-associated ccRCC)	Monotherapy	NCT03401788
			Phase III (advanced ccRCC after PD-1/PD-L1 and VEGF-TKI)	Monotherapy	NCT04195750
			Phase II (PPGL, pNET, VHL-associated tumors, wt GIST, HIF-2α-altered solid tumors)	Monotherapy	NCT04924075
OXPHOS	Metformin hydrochloride	ETC complex I / AMPK-mTOR	Phase III (early-stage breast cancer)	Standard chemotherapy	NCT01101438
			Phase II (stage IIIa/IIIb locally advanced NSCLC)	Chemoradiotherapy	NCT02115464
			Phase II (HNSCC)	Surgery ± cisplatin/radiotherapy	NCT03048500
OXPHOS	Lixumistat (IM156)	ETC complex I	Phase I (advanced solid tumor and lymphoma)	Monotherapy	NCT03272256
			Phase Ib (advanced pancreatic cancer)	Gemcitabine + Nab-paclitaxel	NCT05497778
OXPHOS	IACS-010759	ETC complex I	Phase I (relapsed/refractory AML)	Monotherapy	NCT02882321
			Phase I (advanced solid tumors / lymphoma)	Monotherapy	NCT03291938
TCA cycle metabolism	Ivosidenib (AG-120)	Mutant IDH1 / 2-HG production	Phase I (R/R AML, untreated AML, MDS, MDS/MPN)	Monotherapy	NCT02074839
			Phase III (IDH1-mutated newly diagnosed AML)	Azacitidine	NCT03173248
			Phase III (advanced cholangiocarcinoma)	Monotherapy	NCT02989857
TCA cycle metabolism	Vorasidenib (AG-881)	Mutant IDH1/2 / 2-HG production	Phase III (grade 2 IDH-mutant glioma)	Monotherapy	NCT04164901
			Phase I (low-grade glioma)	Monotherapy	NCT03343197
			Phase I (advanced solid tumors, including glioma)	Monotherapy	NCT02481154
Lipid metabolism	Denifanstat (TVB-2640)	FASN	Phase II (HER2+ metastatic breast cancer)	Trastuzumab (anti-HER2) + paclitaxel (or endocrine therapy)	NCT03179904
			Phase II (advanced/metastatic	Monotherapy	NCT03808558

Metabolic axis	Drug	Molecular target	Clinical setting / trial phase	Treatment regimen	ClinicalTrials.gov ID
			KRAS-mutant NSCLC)		
			Phase II (first relapse of high-grade astrocytoma)	Bevacizumab (anti-VEGF)	NCT03032484
Glycolysis	PFK-158 (ACT-PFK-158)	PFKFB3	Phase I (advanced solid malignancies)	Monotherapy	NCT02044861
Glycolysis	2-Deoxy-D-glucose (2-DG)	HK	Phase I (lung, breast, pancreatic, HNC, and gastric cancers)	Monotherapy or docetaxel	NCT00096707

Table 1. Selected metabolism-targeting agents evaluated in clinical trials. *Representative clinical trials of anticancer strategies targeting metabolic pathways, showing molecular targets, clinical settings and trial phases, treatment regimens, and ClinicalTrials.gov identifiers. Cancer types and clinical terms: AML, acute myeloid leukemia; BL, Burkitt lymphoma; B cell NHL, B cell non-Hodgkin lymphoma; ccRCC, clear cell renal cell carcinoma; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin lymphoma; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; mCRPC, metastatic castration-resistant prostate cancer; mCRC, metastatic colorectal cancer; NSCLC, non-small cell lung cancer; pNET, pancreatic neuroendocrine tumor; PPGL, pheochromocytoma and paraganglioma; RCC, renal cell carcinoma; R/R, relapsed/refractory; wt GIST, wild-type gastrointestinal stromal tumor. Molecular targets, pathways and biological terms: 2-HG, 2-hydroxyglutarate; A2A/A2B, adenosine A2A/A2B receptors; AMPK, AMP-activated protein kinase; ASS1, argininosuccinate synthetase 1; CD73, cluster of differentiation 73; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; EGFR, epidermal growth factor receptor; ETC, electron transport chain; FASN, fatty acid synthase; GLS1, glutaminase 1; HER2, human epidermal growth factor receptor 2; HIF-2α, hypoxia-inducible factor 2 alpha; HK, hexokinase; IDH, isocitrate dehydrogenase; IDO1, indoleamine 2,3-dioxygenase 1; KRAS, Kirsten rat sarcoma viral oncogene homolog; MCT1, monocarboxylate transporter 1; mTOR, mechanistic target of rapamycin; OXPHOS, oxidative phosphorylation; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; TCA, tricarboxylic acid cycle; VEGF, vascular endothelial growth factor; VHL, von Hippel–Lindau. Drugs, treatment regimens and therapeutic terms: 2-DG, 2-deoxy-D-glucose; mFOLFOX6, modified folinic acid, fluorouracil, and oxaliplatin; TKI, tyrosine kinase inhibitor.*

Discussion

Evidence across experimental systems supports a view of metabolic heterogeneity as a multicellular property of the TME, arising from interactions among malignant, stromal, immune, and vascular compartments rather than from cancer cells alone. Several priorities now emerge for translating TME metabolic heterogeneity into experimentally and therapeutically actionable strategies.

First, tumor metabolism needs to be resolved at spatial and cellular resolution. Spatial metabolomics can map metabolite distributions across perivascular niches, hypoxic regions, and immune-excluded areas, whereas single-cell transcriptomics can identify the cellular populations associated with these metabolic states (241). Neither approach alone resolves metabolic flux: transcript abundance does not necessarily predict pathway activity, while spatial metabolite measurements may not identify the cells responsible for metabolite production or consumption.

Genetically encoded metabolite biosensors can complement these approaches by capturing metabolic dynamics in real time. For example, the glutamine biosensor iGlo enables monitoring of glutamine uptake, production, and consumption at cellular and subcellular resolution and can be multiplexed with lactate sensors to resolve temporal crosstalk between glucose and glutamine metabolism in individual cells (243).

A major unresolved question is whether the metabolite exchange inferred from co-localization, transcriptional programs, and ex vivo experiments occurs at quantitatively meaningful rates in vivo. Stable-isotope infusion has demonstrated the feasibility of tracing nutrient utilization directly in human tumors (244). Compartment-resolved *in vivo* tracing should now be used to determine the direction and magnitude of substrate exchange between cancer cells, TECs, immune cells, and fibroblasts, and how these fluxes change during treatment. Such measurements could distinguish genuine intercellular metabolite exchange from parallel adaptation to the same microenvironmental constraint and determine whether disrupting such metabolic interactions produces a selective therapeutic effect.

TECs represent a potentially important, but incompletely validated, compartment for metabolism-directed therapeutic development. Future studies should further establish which endothelial metabolic dependencies are conserved across tumor types and which are restricted to specific vascular states, tumor regions, or metastatic niches. TEC-selective delivery strategies and dose optimization will be important to determine whether these dependencies can be targeted while preserving normal vascular function. Direct comparison with ECs from matched normal tissues will be particularly important because many of the pathways discussed here, including glycolysis, glutaminolysis, serine synthesis, and FAO, also support physiological endothelial function. Future studies should also define which metabolic interventions enhance responses to AAT, chemotherapy, radiotherapy, or immunotherapy (245, 246).

Clinical translation will further require biomarkers that identify the relevant metabolic dependency in the appropriate cellular compartment. Spatial metabolic signatures, metabolic imaging, circulating metabolites, and cell type-specific molecular profiles should therefore be prospectively evaluated for patient stratification and pharmacodynamic monitoring. Integrating these measurements may be particularly important for targeted therapies, for which tumor genotype may be insufficient to predict response when the relevant metabolic dependency is strongly influenced by cellular state or microenvironmental context.

Treatment scheduling also warrants systematic investigation during metabolic therapy development. Metabolic dependencies can change during treatment, creating vulnerabilities that are absent at baseline. Where treatment induces a reproducible metabolic dependency, sequential or staggered therapy could be compared directly with concurrent treatment. Longitudinal metabolic profiling would be required to define when the dependency emerges, whether it persists, and whether its therapeutic window is sufficiently stable for clinical exploitation.

The therapeutic significance of metabolic heterogeneity therefore lies not in the existence of metabolic differences per se, but in identifying states that create selective, measurable, and sufficiently stable dependencies. Many of the mechanisms discussed in this review derive from specific tumor types, experimental models, or treatment contexts and should not be assumed to generalize across cancers. Translation will require functional validation of metabolic dependencies in the relevant cellular compartment, demonstration of a therapeutic window relative to normal tissues, and biomarkers that can identify when those dependencies are present. Framed in this way, metabolic plasticity represents both a major obstacle to pathway-directed therapy and a potential source of context-dependent vulnerabilities that may be exploited when their spatial and temporal boundaries are defined.

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