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Oncometabolites: The Metabolic Shadow of Oncogenes

Zahra Sheikhi[1], Mohtaram Vafakhah[2], Hamed Mirzaei[2], Mahdieh Khosravi[2], Kambiz Gilany[1,2*]

[1] *Integrative Oncology Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran*

[2] *Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran*

***Corresponding Author:** Kambiz Gilany, Integrative Oncology Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran, E-mail: k.gilany@avicenna.ac.ir*

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Oncometabolites such as L-lactate, succinate, fumarate, R-2-hydroxyglutarate, kynurenine, and itaconate are emerging as pivotal drivers of cancer progression. Beyond their metabolic roles, these molecules function as signaling mediators that remodel epigenetic landscapes, reprogram the tumor microenvironment, and promote immune evasion. This review synthesizes current insights into their biochemical origins, oncogenic mechanisms, and therapeutic potential, highlighting how targeting oncometabolite-driven pathways could facilitate the development of novel cancer therapies.

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INTRODUCTION

The Renewal of Cancer Metabolism

It has been 100 years since Warburg observed that cancer cells exhibit an altered metabolic phenotype (1). Under normal oxygen conditions, differentiated cells primarily rely on the TCA cycle and oxidative phosphorylation to efficiently generate energy and supply metabolites required for protein and lipid synthesis. However, under hypoxic conditions, this process changes, and cells increase glycolysis and lactate production to meet their energy and metabolic demands (1). Unlike normal differentiated cells, which primarily rely on mitochondrial oxidative phosphorylation for energy production, most cancer cells preferentially utilize aerobic glycolysis—a phenomenon known as the Warburg effect. This appears counterintuitive because oxidative phosphorylation generates energy far more efficiently, producing 34 ATP molecules from a single glucose molecule, whereas glycolysis produces 2 ATP molecules (2). Tumor cells, on the other hand, divide quickly and require significantly more anabolic activity compared to normally differentiated cells. Accelerated glucose metabolism enables more rapid ATP production and increased carbon allocation to nucleotide, protein, and fatty acid synthesis, thereby

enhancing cell growth (3). [^{18}F]Deoxyglucose positron emission tomography takes advantage of this characteristic of cancer by enabling the visualization of glucose uptake in patients, making it a valuable tool for cancer diagnosis and monitoring treatment response (4). It has been used to validate the relationship between glucose metabolism and cell proliferation in certain human tumors. However, not all malignancies, such as pancreatic cancer, show this relationship (5). In cancer cells, however, 'aerobic glycolysis' can become deregulated, partly due to genetic mutations that affect pathways such as phosphoinositide 3-kinase–AKT and Myc.

Furthermore, heightened activation of the specific pyruvate kinase isoform PKM2 has been observed in cancer. Due to its regulated enzymatic activity, PKM2 can redirect metabolic flux from the TCA cycle toward alternative anabolic pathways (3, 6). Loss-of-function mutations in the TCA cycle enzymes fumarate hydratase (FH) and succinate dehydrogenase (SDH) lead to the accumulation of fumarate and succinate, respectively (7). Conversely, gain-of-function mutations in isocitrate dehydrogenase (IDH) result in increased production of the oncometabolite D-2-hydroxyglutarate (D-2HG) (8, 9). These aberrant metabolites interfere with normal cellular homeostasis by competitively inhibiting α-ketoglutarate–dependent (α-KG–dependent) dioxygenases—also referred to as 2-oxoglutarate–dependent dioxygenases—and by altering post-translational protein modifications (10-14). Increasing biochemical and genetic evidence highlights the roles of fumarate, succinate, and D-2HG in cellular transformation and cancer development, underscoring their significance as TCA-cycle–derived oncometabolites. These oncometabolites seem to promote tumorigenesis through a shared mechanism: they competitively inhibit α-ketoglutarate (αKG)–dependent dioxygenases, a superfamily of enzymes crucial for oxygen sensing and epigenetic regulation. This inhibition establishes a direct connection between metabolic dysfunction and abnormal gene expression in cancer.

Oncometabolites: The Beginning of a New Way of Thinking

The accumulation of lactate, succinate, fumarate, 2-HG, and, most recently, itaconate within cells drives and sustains metabolic states that promote cancer development and growth. Because of these effects, these molecules are called oncometabolites—small molecules that, when abnormally accumulated, trigger cancer-promoting signals and create an environment that supports tumor formation. Notably, all of these oncometabolites result from mutations in enzymes of the TCA cycle, highlighting the crucial role of mitochondria as signaling centers that influence key biological functions in both healthy and cancerous cells (15). Although the accumulation of oncometabolites is linked to gene mutations, their cancer-promoting actions go beyond genetics. They can directly affect multiple biological layers, altering cell signaling pathways, regulating gene expression, and modifying protein function—acting as powerful agents that shape unique cancer characteristics (Figure 1).

The Lactate

L-lactate accumulation is a hallmark of many cancers and results from the Warburg effect, where cancer cells preferentially convert pyruvate to L-lactate even in the presence of oxygen (16). While lactate production typically occurs under hypoxic conditions—such as during intense exercise—cancer cells maintain this metabolic state under aerobic conditions; hence the term "aerobic glycolysis". This shift toward lactate production was previously thought to result from mitochondrial dysfunction in cancer cells. The reaction converting pyruvate to lactate regenerates NAD^+, thereby sustaining glycolysis and ATP production when oxidative phosphorylation (OXPHOS) is impaired. However, current evidence indicates that mitochondria in most cancers remain functional, supporting both energy production and the synthesis of anabolic intermediates (17-19). Indeed, mitochondrial respiration appears essential for tumor survival, as large-scale analyses of tumor mitochondrial DNA indicate that loss-of-function mutations in respiratory components are under strong negative (purifying) selection (20).

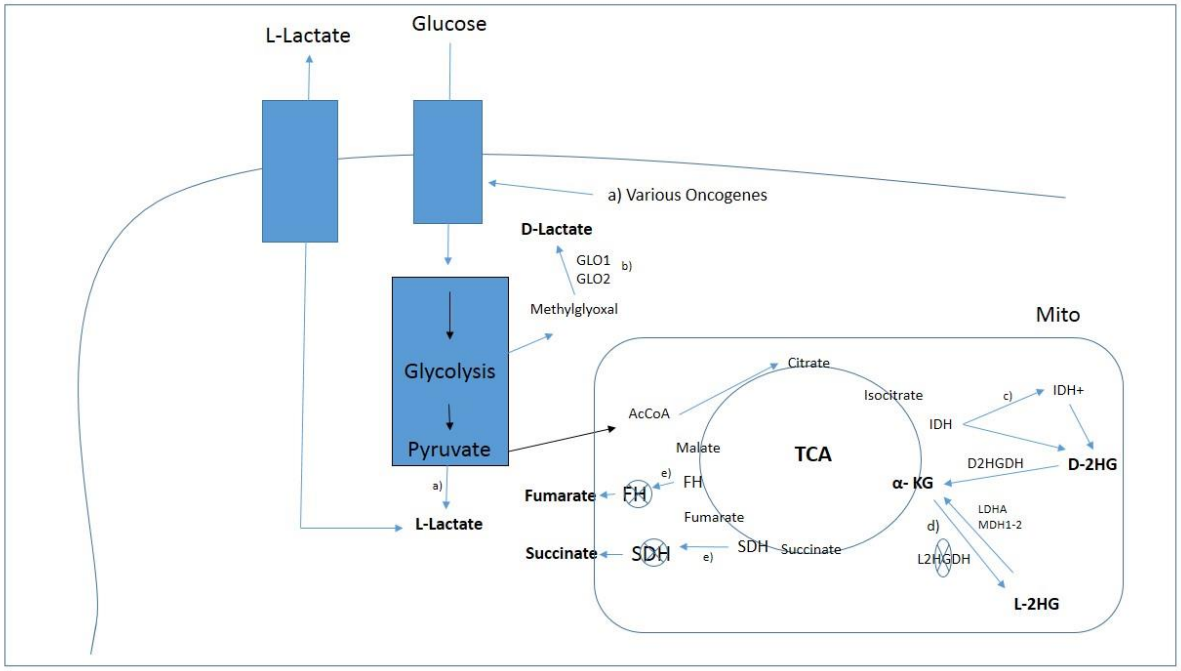


Figure 1. Origin of Oncometabolites. **a)** A range of oncogenes and tumor suppressors — including RAS, MYC, PI3K, mTOR, and p53 — can promote higher glucose uptake and enhance glycolysis through different mechanisms, ultimately resulting in increased production of L-lactate. **b)** The methylglyoxal pathway branches off from glycolysis, converting methylglyoxal into D-lactate through the sequential actions of the enzymes glyoxalase 1 (GLO1) and glyoxalase 2 (GLO2). **c)** In the TCA cycle, α-ketoglutarate (α-KG) is generated from isocitrate through the catalytic activity of isocitrate dehydrogenase 1 and 2 (IDH1/2). In addition, IDH can also produce D-2-hydroxyglutarate (D-2HG), albeit with low efficiency (as shown by the dashed line). D-2HG can also be generated under physiological conditions through the promiscuous activity of other enzymes (not shown; see main text). Mutations in IDH result in gain-of-function IDH variants (IDH*) that efficiently convert isocitrate into D-2-hydroxyglutarate (D-2HG). Under physiological conditions, the enzyme D-2-hydroxyglutarate dehydrogenase (D2HGDH) rapidly converts D-2HG back into α-ketoglutarate (α-KG). **d)** Under physiological conditions, the promiscuous activity of lactate dehydrogenase A (LDHA) or malate dehydrogenase 1/2 (MDH1/2) can convert α-ketoglutarate (α-KG) into L-2-hydroxyglutarate (L-2HG) (indicated by a dashed line). This reaction is normally balanced by the action of L-2-hydroxyglutarate dehydrogenase (L2HGDH); however, reduced L2HGDH activity in certain cancers leads to the accumulation of L-2HG. **e)** Loss-of-function mutations in components of the succinate dehydrogenase (SDH) complex or in fumarate hydratase (FH) result in the accumulation of succinate and fumarate, respectively. Abbreviations: TCA tricarboxylic acid cycle, AcCoA acetyl-coenzyme A, GLO1/GLO2 glyoxalase 1 and 2, α-KG α-ketoglutarate, IDH isocitrate dehydrogenase 1/2, IDH* mutated isocitrate dehydrogenase 1/2, D-2HG D-2-hydroxyglutarate, L-2HG L-2-hydroxyglutarate, LDHA lactate dehydrogenase A, MDH1-2 malate dehydrogenase 1/2, FH fumarate hydratase, SDH succinate dehydrogenase complex.

These findings raise important questions: What benefits do cancer cells gain from adopting aerobic glycolysis, and what initiates the Warburg effect? Examining the underlying molecular mechanisms offers some insights. One of the defining features of the Warburg effect is the upregulation of glucose and lactate transporters on the plasma membrane (17). This enables cancer cells to absorb large amounts of glucose, fueling glycolysis at an exceptionally high rate. Such elevated glycolytic activity may benefit cancer cells because its intermediates feed multiple anabolic pathways, including the pentose phosphate pathway, hexosamine biosynthesis, glycerol formation, and serine–glycine–one-carbon metabolism. A key question remains: why don't cancer cells direct pyruvate—the end product of glycolysis—into the mitochondria for conversion to acetyl-CoA and entry into the TCA cycle? One explanation is that, in tumors with very high glycolytic flux, pyruvate production exceeds the mitochondria's oxidative capacity. In this case, converting excess pyruvate into lactate not only prevents metabolic bottlenecks but also regenerates NAD^+, allowing glycolysis to continue. The lactate produced can be exported to the liver via the Cori cycle, where it is reconverted to glucose via gluconeogenesis. Alternatively, lactate can be taken up by nearby or distant cells to serve as a carbon

source or energy substrate (21, 22).

Additionally, since pyruvate could serve similar metabolic roles, another question arises: why do cancer cells preferentially secrete lactate rather than pyruvate? Is the regeneration of NAD^+ during the pyruvate-to-lactate conversion the main benefit, or does lactate itself provide a selective advantage? These possibilities are explored further in the following sections.

Unlike alterations in the TCA cycle, which are often driven by specific genetic mutations, the metabolic reprogramming underlying the Warburg effect appears to result from the combined influence of multiple oncogenic changes. Key oncogenes and tumor suppressor pathways, including p53, MYC, RAS, mTOR, and PI3K, have been shown to contribute to this shift. A comprehensive discussion of the underlying molecular mechanisms lies beyond the scope of this review; readers are therefore directed to several excellent reviews that provide detailed analyses of these processes (23, 24).

Interestingly, the D-enantiomer of lactate also accumulates due to enhanced glycolytic activity. Under normal physiological conditions, D-lactate accounts for only 1–5% of total lactate and is primarily produced either by carbohydrate-fermenting gut bacteria or via the methylglyoxal (MG) pathway, a by-product of glycolysis (Figure 1). MG is mainly generated through the non-enzymatic degradation of the glycolytic intermediate glyceraldehyde-3-phosphate. Owing to its high chemical reactivity, MG readily forms adducts with proteins, DNA, and glutathione (GSH), and its accumulation has been linked to several pathological conditions, including cancer, diabetes, and neurodegenerative diseases (25). In the context of cancer, MG contributes to tumor initiation and progression through both cell-autonomous mechanisms, directly affecting cancer cells, and non-cell-autonomous mechanisms, influencing surrounding cells and the tumor microenvironment, suggesting that it may function as an oncometabolite in its own right (25, 26). Of particular relevance here, MG is detoxified in mammalian cells via the GLO1/2 glyoxalase system, which converts it into D-lactate while regenerating GSH (Figure 1).

The Succinate

The discovery of inherited mutations in the SDHD gene in people with hereditary paragangliomas (PGLs) and pheochromocytomas (PCCs) brought renewed focus on the role of mitochondrial metabolism in cancer (27, 28). The SDH genes (SDHA, SDHB, SDHC, SDHD) encode the four subunits of the succinate dehydrogenase complex (also called mitochondrial complex II), which is important for both the TCA cycle and the electron transport chain (ETC) that helps cells generate energy (29). This complex consists of two pairs of subunits: SDHA and SDHB catalyze the conversion of succinate to fumarate, while SDHC and SDHD anchor the complex within the mitochondrial membrane (30). Mutations in these genes—found on chromosomes 1 or 11—can be of different types, like changes in single letters (missense), premature stops (nonsense), shifts in the reading frame (frameshift), or problems with how the gene is spliced, as well as insertions or deletions (31, 32). The loss of SDH function usually occurs when the second copy of the gene is lost (loss of heterozygosity), halting the conversion of succinate to fumarate (7). Studies examining small molecules within cells have found that succinate accumulates in tumors that have lost one copy of a mutated SDHx gene. This happens in several types of cancers, including kidney cancer, paragangliomas, gastrointestinal stromal tumors, pancreatic neuroendocrine tumors, and pituitary adenomas. Doctors often use immunohistochemistry (IHC) with antibodies targeting the SDHB protein to screen for SDHx mutations, because the absence of SDHB usually indicates a mutation in one of the SDHx genes. However, this test isn't perfect—sometimes the staining is uneven or faint, leading to misinterpretation. To get around this, researchers suggest measuring the actual levels of succinate or the balance between succinate and fumarate in tumors using advanced techniques like liquid chromatography-mass spectrometry. This method is more accurate for spotting SDHx mutations. Even better, it's now possible to detect the loss of these genes non-invasively using a type of MRI scan that measures succinate directly inside the body.

One common biochemical effect of succinate buildup is an increase in reactive oxygen species (ROS), likely due to SDH's role in the electron transport chain (ETC) (33, 34). Multiple studies have found that tumors with SDH mutations experience higher oxidative stress, which is linked to genomic instability and cancer development (33, 35-37). Additionally, succinate can exit the mitochondria and directly influence important enzymes in the cytoplasm and the nucleus that drive malignant transformation, as discussed in the next section (38).

The Fumarate

The FH gene encodes an important enzyme in the TCA cycle, and inherited mutations in this gene—found at chromosome 1q43—are linked to reduced enzyme activity and a buildup of fumarate inside cells (39). Among these mutations, missense and frameshift mutations are the most common and occur in conditions such as hereditary leiomyomatosis, uterine fibroids, renal cell carcinoma syndrome (HLRCC), as well as paragangliomas (PGLs) and pheochromocytomas (PCCs) (40-42). These mutations often result in a significant reduction in FH enzyme activity or premature protein truncation (43, 44). Missense mutations typically impact key regions of the enzyme, such as the active site or domains essential for stability and subunit interactions (43, 45). FH is a homotetrameric enzyme found in both mitochondria and the cytosol, where it helps convert fumarate into malate and participates in amino acid catabolism (see Figure 1) (46). Detecting FH gene defects early can be done through immunohistochemistry (IHC) tests that assess protein expression, or through metabolomics tests that detect elevated fumarate levels in cells (47, 48).

A common diagnostic approach combines FH immunostaining with IHC tests for succinated proteins (49-52). When FH is dysfunctional in mitochondria, the tests typically show no FH staining (a "negative" or "0" score) but positive staining for 2-succinocysteine, a marker of protein modification caused by fumarate buildup (50, 52, 53). The staining results are usually graded as "0" for complete loss, "1+" for weak or focal staining, and "2+" for strong, widespread staining, indicating partial loss (52).

Measuring the fumarate-to-malate ratio can also help with diagnosis, along with other metabolic changes caused by fumarate accumulation, such as the unusual activation of the enzyme argininosuccinate lyase (ASL) (54, 55).

When FH is dysfunctional, fumarate accumulates, leading to protein modifications outside the mitochondria. These changes affect protein function, alter chromatin structure, and shift gene expression, thereby promoting cancer development. The detailed biochemical mechanisms behind this are explained in later sections.

The R-2-Hydroxyglutarate

The role of the metabolite R-2HG in cancer remained largely unrecognized until 2008, when Parsons and colleagues sequenced over 20,000 genes in glioblastoma tumors and found that approximately 12% of patients harbored somatic mutations in the isocitrate dehydrogenase (IDH) gene (56). Subsequent metabolomics studies of tumor tissue, as well as blood, urine, and cerebrospinal fluid, showed that this IDH mutation leads to a substantial accumulation of R-2HG within cells (8, 57-62). Later research found the same mutation not only in grade II-III gliomas and secondary glioblastomas (63, 64), but also possibly in cancers outside the brain, such as acute myeloid leukemia (AML) (65), intrahepatic cholangiocarcinoma (66), chondrosarcomas (67), and breast cancer (68-70).

IDH is a critical TCA cycle enzyme that catalyzes the reversible oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) (see Figure 1). The three isoforms of IDH, which differ based on where they're found in the cell and the cofactors they use: IDH1 and IDH2 are homodimers that depend on NADP and are found in the cytosol and mitochondria, respectively; IDH3 is a heterotrimer that depends on NAD, acts as a regulator based on the cell's energy status, and drives the forward reaction from isocitrate to α-KG.

Most cancer-related mutations occur in IDH1 and IDH2, and these mutations don't typically overlap in the same tumor (71). The frequency of these mutations varies by cancer type—IDH1 mutations are more common in brain cancers, while in AML both IDH1 and IDH2 mutations occur at similar rates,

likely reflecting the unique metabolic needs of different tumors (71-73).

IDH mutations typically involve swapping out an arginine amino acid—specifically R132 in IDH1, and R172 or R140 in IDH2—for a histidine. This change reduces the enzyme's ability to bind its usual substrate, isocitrate, slowing the normal conversion to α-ketoglutarate (α-KG) quite a bit. In addition, the mutation increases the enzyme's affinity for NADPH, giving it a new function that allows it to convert α-ketoglutarate (α-KG) specifically into the R-2HG form (8). In glioma cells with mutated IDH1 or IDH2, the level of R-2HG can get as high as about 30 millimolar, which overwhelms the mitochondrial enzyme responsible for breaking it down (8, 74, 75), Interestingly, even tumors with the normal (wild-type) IDH enzyme produce some R-2HG, but their levels are about 100 times lower than in tumors with the mutation (76). Having just one mutated copy of the IDH gene (heterozygous mutation) appears necessary to reach these very high R-2HG levels (77). IDH mutations have proven very useful clinically because they help better classify gliomas, improving diagnosis and prognosis for patients (78-82). Many studies have examined R-2HG as a marker for IDH mutations. In acute myeloid leukemia (AML), for example, R-2HG can be measured directly in the patient's blood, where it strongly correlates with IDH mutation status (83, 84). However, while this measurement is good for diagnosis, it doesn't seem to predict overall clinical outcomes well (85, 86).

For gliomas, advances in magnetic resonance spectroscopy (MRS) now allow researchers to measure 2HG *in vivo* with good accuracy, which aligns well with IDH mutation status (87-92). While MRS measures total 2HG levels in tissue, chromatography coupled with mass spectrometry can specifically quantify the R- and S-forms in cerebrospinal fluid, blood, and urine. Yet, studies using these methods have had mixed results—some find a clear link between high 2HG levels and mutations (59-61, 93, 94), while others don't see much difference between mutated and non-mutated cases (95, 96).

These inconsistencies might come from the lack of standardized testing methods or differences in patients' disease states. For example, the blood-brain barrier may be more or less compromised in glioma patients, thereby affecting the amount of 2HG that can cross into the blood and urine (97, 98).

Besides being produced by mutated IDH enzymes, R-2HG can also come from other sources within the cell, underscoring its active role in cancer development (99) (see Figure 1). For example, in breast cancer, an oncogene called phosphoglycerate dehydrogenase (PHGDH) can cause cells to accumulate both forms of 2HG (R and S) from α-ketoglutarate (100). Another source is the overexpression of a mitochondrial enzyme, hydroxyacid-oxoacid transhydrogenase (HOT), which produces R-2HG during the conversion of 4-hydroxybutyrate to succinic semialdehyde (101, 102) (Figure 1).

Interestingly, certain immune cells—like activated T helper 17 (Th17) cells—also produce R-2HG when they shift their metabolism from oxidative phosphorylation to aerobic glycolysis in response to tumors (103). This evidence supports the idea that R-2HG's role in cancer may not depend solely on IDH mutations, opening the door to new targets for cancer treatment.

Iltaconate

Itaconate is generated from the tricarboxylic acid (TCA) cycle intermediate cis-aconitate in response to inflammatory stimuli, primarily within myeloid cells, through the activity of immune-responsive gene 1 (IRG1). Traditionally, itaconate has been recognized as an antibacterial metabolite, as its accumulation within bacteria-containing vacuoles disrupts microbial metabolism and thereby inhibits bacterial proliferation (104, 105).

More recently, IRG1 expression has been implicated in cancer progression, including in glioblastoma and ovarian carcinoma. However, the precise role of itaconate in cancer remains context-dependent and somewhat controversial. In tumors, cancer-induced IRG1 expression elevates itaconate levels, particularly in peritoneal tissue-resident macrophages, where itaconate is among the most highly induced metabolites following macrophage activation. Increased itaconate production enhances oxidative phosphorylation (OXPHOS) and reactive

oxygen species (ROS) generation, thereby activating the MAPK signaling pathway and promoting cancer cell proliferation (106).

Mechanistically, itaconate shares features with other TCA-derived oncometabolites. Owing to its structural similarity to α-ketoglutarate (α-KG), itaconate competes with α-KG for binding to TET2, thereby inhibiting its enzymatic activity and suppressing LPS-induced gene expression in macrophages (107). Furthermore, itaconate limits the polarization of tumor-associated macrophages (TAMs) toward pro-inflammatory phenotypes by downregulating chemokine genes, including Cxcl9 and Cxcl10, in a TET2-dependent manner. Consistently, blocking itaconate production has been shown to enhance anti-tumor immunity (108).

Itaconate competitively inhibits succinate dehydrogenase (SDH), likely due to its structural similarity to succinate, thereby reducing mitochondrial respiration and exerting anti-inflammatory effects during macrophage activation (109). In the tumor microenvironment (TME), $CD8^+$ T cells can take up itaconate secreted by myeloid-derived suppressor cells (MDSCs). This uptake interferes with the biosynthesis of aspartate and serine/glycine in $CD8^+$ T cells, ultimately impairing their proliferation and anti-tumor activity (110).

Due to its electrophilic α,β-unsaturated carboxylic acid moiety, itaconate can covalently modify proteins by alkylating cysteine residues, targeting key regulators such as KEAP1, transcription factor EB (TFEB), and NLRP3. Itaconate-mediated alkylation of KEAP1 activates Nrf2, thereby enhancing the expression of antioxidant and anti-inflammatory genes in macrophages (111). Similarly, itaconate alkylates TFEB, promoting its nuclear translocation and upregulating lysosomal and autophagic genes, thereby enhancing the antibacterial innate immune response (112). Moreover, itaconate modifies a specific cysteine residue (C548) on NLRP3, inhibiting NLRP3 activation and disrupting its interaction with NEK7 (113).

Notably, itaconate derivatives- including dimethyl itaconate (DI), 4-octyl itaconate (4OI), and 4-ethyl itaconate (4EI)—display distinct metabolic, electrophilic, and immunological properties compared with unmodified itaconate (114). Additionally, most findings originate from non-cancer models; these studies provide valuable insights into the potential roles of itaconate and its derivatives in tumor biology.

Kynurenine

The biosynthesis of kynurenine (KYN) is initiated by a rate-limiting step catalyzed by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), producing N-formylkynurenine, which is subsequently converted into KYN. TDO is primarily expressed in the liver, where its expression is inducible by tryptophan and various hormonal signals, whereas IDO1 is more broadly expressed and can be activated by inflammatory stimuli (115).

KYN acts as a ligand for the aryl hydrocarbon receptor (AHR). Upon binding, AHR translocates to the nucleus and regulates the expression of genes involved in stress response, cell fate determination, and tumor progression (116). For instance, AHR activation upregulates aquaporin-4 (AQP4) to enhance glioma cell motility and invasion [78], stimulates the MAPK pathway to promote gastric cancer metastasis [79], and activates PI3K–Akt signaling, leading to β-catenin nuclear translocation and colorectal cancer progression (117-119). Interestingly, AHR can also induce the expression of the tumor metastasis suppressor gene KISS1, inhibiting neuroblastoma metastasis, highlighting the context-dependent roles of KYN–AHR signaling (120). Dysregulation of this pathway has been linked to oncogenic mechanisms such as MYC-driven upregulation of tryptophan transporters and arylformamidase in colon cancer (121), as well as APC loss-mediated TDO2 induction via TCF4/β-catenin signaling (122).

Beyond its intracellular signaling functions, KYN can be exported from cancer cells or IDO1-expressing non-cancer cells via SLC7A11, contributing to ROS scavenging and NRF2 pathway activation, which protects cancer cells from ferroptosis. KYN also competes with cysteine for transport through SLC7A11, inducing pseudostarvation and activating the GCN2–ATF4 pathway, which upregulates SLC7A11 and establishes a positive feedback loop

(123). In the tumor microenvironment (TME), the identity of KYN transporters appears to be cell-type specific. For example, in cancer-repopulating cells, KYN released upon IFN-γ stimulation is transported into neighboring $CD8^+$ T cells via SLC7A8 and PAT4, where it activates AHR and enhances PDCD1 expression, contributing to T cell suppression (124).

Extracellular kynurenine (KYN) can influence a broad spectrum of cell types. In acute myeloid leukemia (AML), KYN binds to serotonin receptor 1B on osteoblasts, reshaping the bone marrow niche toward a pro-inflammatory phenotype. This leads to the secretion of the acute-phase protein serum amyloid A1 from osteoblasts into AML cells, where it activates AHR and enhances IDO1 expression, thereby further promoting KYN production in a feed-forward loop (125). Beyond hematopoietic tissues, KYN has been shown to stimulate cardiomyocyte proliferation and cardiac angiogenesis in the neonatal heart, suggesting that it may similarly enhance angiogenesis within the tumor microenvironment by acting on vascular endothelial cells (126).

This KYN-mediated activation in TAMs contributes to macrophage recruitment and $CD8^+$ T cell dysfunction (127). However, the immunosuppressive effects of KYN in vivo appear relatively modest, likely because KYN concentrations are limited in certain human cancers. Moreover, it has been suggested that T cell suppression attributed to KYN can be phenocopied by fatty acid depletion, indicating that studies conducted in lipid-deficient culture media may overestimate the immunomodulatory role of KYN (128).

The Impact of ROS

Oncometabolites such as 2-HG, succinate, and fumarate increase reactive oxygen species (ROS) production in cancer cells. When succinate builds up due to mutations, it increases mitochondrial ROS (129, 130). This extra ROS helps keep HIF-1α active, promoting tumor growth (131). But ROS can be tricky. At low levels, it can help cancer grow, but too much ROS can damage cells, cause them to die, or make treatments like chemotherapy and radiation more effective. The effects of ROS depend on the amount present and the tumor type.

Both types of 2-HG—D-2-HG and L-2-HG—can increase stress from harmful molecules called ROS, but they do it in different ways. Mutant IDH enzymes make D-2-HG in some cancers. Making D-2-HG uses up NADPH, which helps keep the cell's antioxidants working. Without enough NADPH, cells can't protect themselves well from damage (132, 133). D-2-HG also blocks part of the cell's energy machinery, which in turn produces more ROS. It lowers glutamate, which is needed to make antioxidants, worsening things. All this leads to higher ROS that can damage DNA and help cancer grow, but sometimes it also makes cancer cells easier to kill with certain treatments (133). L-2-HG works similarly, but we know less about it. It also increases ROS and decreases antioxidants in laboratory tests (134). Both forms of 2-HG cause more oxidative stress in tumors, which can either help the cancer or make it more open to treatment, depending on the situation.

Fumarate raises ROS levels differently. It chemically modifies glutathione—a key antioxidant in cells—by attaching to cysteine, thereby forming S-(2-succinyl)cysteine (2SC). This process reduces the amount of usable glutathione, weakening the cell's ability to resist oxidative stress (135).

Additionally, when fumarate accumulates, it induces reductive stress and drives the cell to rely more on the pentose phosphate pathway (PPP) of glucose metabolism. This shift makes cells that lack functional FH enzyme especially sensitive to drugs that block the PPP (136).

Genomic Instability

Genomic instability means that DNA gets damaged and isn't repaired properly, which helps cancer grow and become more diverse. It's not just a side effect of cancer—it actually helps the cancer get worse. There are two main types: chromosomal instability (CIN), where chromosomes change shape or number, and microsatellite instability (MSI), where small repeated DNA sections aren't fixed correctly. Some inherited gene mutations cause this instability in hereditary cancers, but in most cancers, it occurs due to other factors, such as changes in metabolism or gene regulation (137, 138).

Important tumor suppressors such as ATM and p53

act as the cell's guardians, regulating how cells respond to DNA damage. They help pause the cell cycle, repair DNA, or even trigger cell aging or death to keep our genetic material safe (139). But new research shows that oncometabolites—especially 2-HG, succinate, and fumarate—can disrupt these crucial defense systems.

These metabolites interfere with homologous recombination (HR), a major mechanism by which cells repair DNA double-strand breaks. When these metabolites accumulate, they inhibit certain enzymes called α-ketoglutarate–dependent dioxygenases, including KDM4B, which normally remove specific chemical marks on histones. This causes excessive accumulation of the marker H3K9me3 at DNA break sites, preventing important proteins such as TIP60 and ATM from carrying out their roles in initiating repair (140). As a result, cells must rely on less accurate repair mechanisms, which can lead to more mutations and promote cancer progression. Interestingly, adding extra α-ketoglutarate (α-KG) to the cells can undo these problems by restoring normal histone modifications and reactivating proper DNA repair (141). Oncometabolites don't just affect tumor cells—they can also impact nearby support cells like immune cells, fibroblasts, and blood vessel cells. These neighboring cells are now known to sometimes harbor mutations within the tumor environment (142). One way this might happen is through exposure to high levels of oncometabolites, such as 2-HG, which could induce oxidative stress or alter gene regulation in these non-cancerous cells, potentially leading to their malfunction or even transformation.

Epigenetic regulation

Oncometabolites can alter chromatin structure—either directly or indirectly—thereby affecting how genes are expressed.

Fumarate, succinate, and D-2HG all affect how cells reprogram their genes by blocking a group of important enzymes called α-KG-dependent dioxygenases (α-KGDDs). These enzymes normally use α-ketoglutarate (α-KG) to remove chemical tags from DNA and proteins, thereby regulating gene activity. Because fumarate, succinate, and D-2HG look very similar to α-KG, they compete with it and block these enzymes from working properly.

The two main types of enzymes affected are TETs, which remove methyl groups from DNA, and KDMs, which do the same for histones (proteins that package DNA). When these enzymes are blocked, methylation—a chemical modification—increases, altering the regulation of genes involved in DNA repair, cell death, growth, and other important functions.

One key question is which epigenetic changes drive cancer growth rather than merely being "along for the ride" as side effects of enzyme inhibition. Recently, two important targets were identified in cancers with mutant IDH proteins. In certain brain cells called oligodendrocyte progenitors, hypermethylation disrupts an insulator region near the PDGFRA gene. This allows an enhancer to mistakenly activate PDGFRA, thereby promoting tumor growth. At the same time, hypermethylation silences the tumor suppressor gene CDKN2A. Together, activating PDGFRA and inhibiting CDKN2A help drive glioma development. In IDH-mutant cancers, this DNA hypermethylation activates a cancer-promoting gene while silencing a gene that typically protects against tumors (143).

Finally, the importance of oncometabolites blocking TET and KDM enzymes in cancer development is highlighted by the fact that these enzymes are often mutated in many cancers (review (144)).

Targeting Oncometabolism: Clinical and Preclinical Perspectives

Cancer cells rewire their metabolism to support growth, survival, and immune evasion. Oncometabolites—metabolites whose dysregulation contributes to tumor progression—represent key vulnerabilities that can be therapeutically exploited (Table 1).

α-KG sits at the crossroads of the TCA cycle and epigenetic regulation, serving as a cofactor for α-KG–dependent dioxygenases, including TET DNA demethylases and JmjC histone demethylases. Mutations in IDH, SDH, or FH lead to the accumulation of oncometabolites, such as D-2-hydroxyglutarate, succinate, and fumarate, which competitively inhibit α–KG–dependent enzymes,

thereby altering the epigenetic landscape and promoting oncogenesis.

Preclinical strategies focus on restoring α-KG function or counteracting its inhibition: exogenous α-KG supplementation can partially reverse epigenetic alterations. In contrast, small molecules targeting TET or JmjC activity may restore normal gene regulation. Clinically, mutant IDH inhibitors (e.g., ivosidenib, enasidenib) reduce D-2-hydroxyglutarate levels, restore α–KG–dependent enzyme function, induce differentiation, and improve outcomes in acute myeloid leukemia and cholangiocarcinoma. Biomarkers based on epigenetic signatures are being explored to identify patients most likely to benefit from α-KG–targeted interventions.

Itaconate, a metabolite produced primarily by activated macrophages, was first recognized for its antibacterial properties, but recent evidence highlights its role in cancer progression and immune regulation. In the tumor microenvironment, itaconate can: Inhibit succinate dehydrogenase (SDH), reducing mitochondrial respiration and promoting anti-inflammatory TAM polarization. Alkylate proteins such as KEAP1, TFEB, and NLRP3, influencing antioxidant responses, lysosomal function, and inflammasome activation. Impair $CD8^+$ T cell metabolism when secreted by myeloid-derived suppressor cells, reducing proliferation and anti-tumor activity. Although direct itaconate-targeted therapies are still in early development, strategies aimed at reprogramming TAMs, modulating metabolic crosstalk**,** and enhancing immunotherapy represent promising avenues for clinical translation (145, 146).

In summary, targeting oncometabolism—through α-KG restoration or itaconate modulation—offers a multi-faceted approach to impair tumor growth, reshape the tumor microenvironment, and improve therapeutic responses. By integrating metabolic interventions with standard therapies and immunotherapy, these strategies are poised to expand the precision oncology arsenal.

Concluding Remark

Oncometabolites such as L-lactate, succinate, fumarate, R-2-hydroxyglutarate, kynurenine, and itaconate are central regulators of cancer progression, shaping metabolism, signaling, and the tumor

Table 1. Summarizing α-KG, and itaconate pathways with therapeutic strategies.

Metabolite / Pathway	Role in Cancer	Therapeutic Strategy	Clinical / Preclinical Status
α-Ketoglutarate (α-KG)	Cofactor for α-KG–dependent dioxygenases; dysregulated by IDH, SDH, FH mutations; impacts epigenetics and tumor progression	Restore α-KG function; inhibit mutant IDH; target downstream epigenetic enzymes (TET, JmjC)	IDH inhibitors (ivosidenib, enasidenib) approved; preclinical studies on α-KG supplementation and epigenetic enzyme modulation
Itaconate	Produced by TAMs; modulates SDH, ROS, Nrf2, inflammasome; impairs $CD8^+$ T cell metabolism; promotes pro-tumor TAM polarization	Reprogram TAMs; inhibit itaconate production; combine with immunotherapy to restore anti-tumor immunity	Preclinical models show immune and metabolic modulation; clinical translation in early stages

microenvironment. Targeting these metabolites and their pathways offers a promising avenue for novel therapeutic interventions, emphasizing the potential of metabolite-driven strategies to transform cancer treatment.

CONCLUSION

Oncometabolites are metabolic byproducts that arise from altered cellular metabolism in cancer cells, often driving tumor progression and influencing the tumor microenvironment. Future research will focus on their diagnostic and prognostic potential, as well as their utility as therapeutic targets for novel anti-cancer strategies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Not applicable.

REFERENCES

1. Gilany K, Vafakhah M. Hypoxia: a review. Arch Adv Biosci. 2010;1(2). doi:10.22037/jps.v1i2.1616
2. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029–1033. doi:10.1126/science.1160809
3. Ward PS, Thompson CB. Metabolic reprogramming: a cancer hallmark even Warburg did not anticipate. Cancer Cell. 2012;21(3):297–308. doi:10.1016/j.ccr.2012.02.014
4. Ben-Haim S, Ell P. 18F-FDG PET and PET/CT in the evaluation of cancer treatment response. J Nucl Med. 2009;50(1):88–99. doi:10.2967/jnumed.108.054205
5. Buck AC, Schirrmeister HH, Guhlmann CA, Diederichs CG, Shen C, Buchmann I, et al. Ki-67 immunostaining in pancreatic cancer and chronic active pancreatitis. J Nucl Med. 2001;42(5):721–725.
6. Anastasiou D, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, et al. Inhibition of pyruvate kinase M2 by reactive oxygen species. Science. 2011;334(6060):1278–1283. doi:10.1126/science.1211485
7. Pollard PJ, Brière JJ, Alam NA, Barwell J, Barclay E, Wortham NC, et al. Accumulation of Krebs cycle intermediates in FH and SDH mutant tumors. Hum Mol Genet. 2005;14(15):2231–2239. doi:10.1093/hmg/ddi227
8. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739–744. doi:10.1038/nature08617
9. Ward PS, Patel J, Wise DR, Abdel-Wahab O, Bennett BD, Coller HA, et al. Neomorphic enzyme activity of mutant IDH1 and IDH2. Cancer Cell. 2010;17(3):225–234. doi:10.1016/j.ccr.2010.01.020
10. DeBerardinis RJ, Thompson CB. Cellular metabolism and disease. Cell. 2012;148(6):1132–1144. doi:10.1016/j.cell.2012.02.032
11. Kaelin WG Jr. Cancer and altered metabolism. Cold Spring Harb Symp Quant Biol. 2011;76:1–7. doi:10.1101/sqb.2011.76.010
12. Thompson CB. Metabolic enzymes as oncogenes or tumor suppressors. N Engl J Med. 2009;360(8):813–815. doi:10.1056/NEJMe0810213
13. Yang M, Soga T, Pollard PJ, Adam J. The emerging role of fumarate as an oncometabolite. Front Oncol. 2012;2:85. doi:10.3389/fonc.2012.00085
14. Zhang Z, Tan M, Xie Z, Dai L, Chen Y, Zhao Y. Lysine succinylation as a new post-translational modification. Nat Chem Biol. 2011;7(1):58–63. doi:10.1038/nchembio.495
15. Missiroli S, Perrone M, Genovese I, Pinton P, Giorgi C. Cancer metabolism and mitochondria. EBioMedicine. 2020;59:102943. doi:10.1016/j.ebiom.2020.102943
16. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309–314.
17. DeBerardinis RJ, Chandel NS. We need to talk about the Warburg effect. Nat Metab. 2020;2(2):127–129. doi:10.1038/s42255-020-0172-2
18. Fendt SM. 100 years of the Warburg effect. Cell. 2024;187(15):3824–3828. doi:10.1016/j.cell.2024.06.026
19. Kim J, DeBerardinis RJ. Metabolic heterogeneity in cancer. Cell Metab. 2019;30(3):434–446. doi:10.1016/j.cmet.2019.08.013
20. Ju YS, Alexandrov LB, Gerstung M, Martincorena I, Nik-Zainal S, Ramakrishna M, et al. Mitochondrial DNA mutations in cancer. eLife. 2014;3:e02935. doi:10.7554/eLife.02935
21. Chen YJ, Mahieu NG, Huang X, Singh M, Crawford PA, Johnson SL, et al. Lactate metabolism and mitochondria. Nat Chem Biol. 2016;12(11):937–943. doi:10.1038/nchembio.2172

22. Sonveaux P, Végran F, Schroeder T, Wergin MC, Verrax J, Rabbani ZN, et al. Targeting lactate-fueled respiration. J Clin Invest. 2008;118(12):3930–3942. doi:10.1172/JCI36843

23. DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. Sci Adv. 2016;2(5):e1600200. doi:10.1126/sciadv.1600200

24. Faubert B, Solmonson A, DeBerardinis RJ. Metabolic reprogramming and cancer progression. Science. 2020;368(6487):eaaw5473. doi:10.1126/science.aaw5473

25. Kold-Christensen R, Johannsen M. Methylglyoxal metabolism and aging-related disease. Trends Endocrinol Metab. 2020;31(2):81–92. doi:10.1016/j.tem.2019.10.003

26. Baumann T, Dunkel A, Schmid C, Schmitt S, Hiltensperger M, Lohr K, et al. Methylglyoxal-mediated T cell paralysis. Nat Immunol. 2020;21(5):555–566. doi:10.1038/s41590-020-0666-9

27. Astuti D, Latif F, Dallol A, Dahia PL, Douglas F, George E, et al. SDHB mutations and pheochromocytoma. Am J Hum Genet. 2001;69(1):49–54. doi:10.1086/321282

28. Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, et al. SDHD mutations in paraganglioma. Science. 2000;287(5454):848–851. doi:10.1126/science.287.5454.848

29. Lancaster CRD. Succinate:quinone oxidoreductases. Biochim Biophys Acta. 2002;1553(1–2):1–6. doi:10.1016/S0005-2728(01)00240-7

30. Van Vranken JG, Na U, Winge DR, Rutter J. Assembly of succinate dehydrogenase. Crit Rev Biochem Mol Biol. 2015;50(2):168–180. doi:10.3109/10409238.2014.990556

31. Pasini B, Stratakis CA. SDH mutations in tumorigenesis. J Intern Med. 2009;266(1):19–42. doi:10.1111/j.1365-2796.2009.02111.x

32. Dannenberg H, Speel EJ, Zhao J, Saremaslani P, van der Harst E, Roth J, et al. Chromosomal losses in pheochromocytomas. Am J Pathol. 2000;157(2):353–359. doi:10.1016/S0002-9440(10)64547-0

33. Guzy RD, Sharma B, Bell E, Chandel NS, Schumacker PT. SdhB loss triggers tumorigenesis. Mol Cell Biol. 2008;28(2):718–731. doi:10.1128/MCB.01338-07

34. Yankovskaya V, Horsefield R, Törnroth S, Luna-Chavez C, Miyoshi H, Léger C, et al. Architecture of succinate dehydrogenase. Science. 2003;299(5607):700–704. doi:10.1126/science.1079605

35. Ishii T, Yasuda K, Akatsuka A, Hino O, Hartman PS, Ishii N. SDHC mutation and tumorigenesis. Cancer Res. 2005;65(1):203–209. doi:10.1158/0008-5472.CAN-04-2513

36. Owens KM, Aykin-Burns N, Dayal D, Coleman MC, Domann FE, Spitz DR. SDHD mutation and genomic instability. Free Radic Biol Med. 2012;52(1):160–166. doi:10.1016/j.freeradbiomed.2011.10.441

37. Slane BG, Aykin-Burns N, Smith BJ, Kalen AL, Goswami PC, Domann FE, et al. SDHC mutation and oxidative stress. Cancer Res. 2006;66(15):7615–7620. doi:10.1158/0008-5472.CAN-06-0204

38. Flavahan WA, Drier Y, Johnstone SE, Hemming ML, Tarjan DR, Hegazi E, et al. Chromosomal topology in SDH-deficient GISTs. Nature. 2019;575(7781):229–233. doi:10.1038/s41586-019-1668-y

39. Wyvekens N, Valtcheva N, Mischo A, Helmchen B, Hermanns T, Choschzick M, et al. FH-deficient renal cell carcinoma. Genes Chromosomes Cancer. 2020;59(11):611–624. doi:10.1002/gcc.22879

40. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline FH mutations. Nat Genet. 2002;30(4):406–410. doi:10.1038/ng849

41. Castro-Vega LJ, Buffet A, De Cubas AA, Cascón A, Menara M, Khalifa E, et al. FH mutations and paragangliomas. Hum Mol Genet. 2014;23(9):2440–2446. doi:10.1093/hmg/ddt639

42. Clark GR, Sciacovelli M, Gaude E, Walsh DM, Kirby G, Simpson MA, et al. FH mutations and pheochromocytoma. J Clin Endocrinol Metab. 2014;99(10):E2046–E2050. doi:10.1210/jc.2014-1650

43. Alam NA, Rowan AJ, Wortham NC, Pollard PJ, Mitchell M, Tyrer J, et al. FH mutations in leiomyomatosis. Hum Mol Genet. 2003;12(11):1241–1252. doi:10.1093/hmg/ddg138

44. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, et al. FH mutations in North America. Am J Hum Genet. 2003;73(1):95–106. doi:10.1086/376435

45. Picaud S, Kavanagh KL, Yue WW, Lee WH, Muller-Knapp S, Gileadi O, et al. Structural basis of FH deficiency. J Inherit Metab Dis. 2011;34(3):671–676. doi:10.1007/s10545-011-9282-8

46. Estévez M, Skarda J, Spencer J, Banaszak L, Weaver TM. Human fumarase mutation. Protein Sci. 2002;11(6):1552–1557. doi:10.1110/ps.0200302

47. Casey RT, McLean MA, Challis BG, McVeigh TP, Warren AY, Mendil L, et al. Fumarate metabolic signature. Clin Cancer Res. 2020;26(2):391–399. doi:10.1158/1078-0432.CCR-19-0877

48. Richter S, Gieldon L, Pang Y, Peitzsch M, Huynh T, Letón R, et al. Metabolome-guided genomics. Genet Med. 2019;21(3):705–717. doi:10.1038/s41436-018-0122-1

49. Buelow B, Cohen J, Nagymanyoki Z, Frizzell N, Joseph NM, McCalmont T, et al. 2SC and FH immunohistochemistry. Am J Surg Pathol.

2016;40(7):982–988. doi:10.1097/PAS.0000000000000625

50. Chen YB, Brannon AR, Toubaji A, Dudas ME, Won HH, Al-Ahmadie HA, et al. HLRCC-associated renal cancer. Am J Surg Pathol. 2014;38(5):627–637. doi:10.1097/PAS.0000000000000168

51. Joseph NM, Solomon DA, Frizzell N, Rabban JT, Zaloudek C, Garg K. FH aberrations in uterine leiomyomas. Am J Surg Pathol. 2015;39(11):1529–1539. doi:10.1097/PAS.0000000000000504

52. Trpkov K, Hes O, Agaimy A, Bonert M, Martinek P, Magi-Galluzzi C, et al. FH-deficient renal cell carcinoma. Am J Surg Pathol. 2016;40(7):865–875. doi:10.1097/PAS.0000000000000626

53. Carter CS, Skala SL, Chinnaiyan AM, McHugh JB, Siddiqui J, Cao X, et al. FH and SDH in cutaneous leiomyomas. Am J Surg Pathol. 2017;41(6):801–809. doi:10.1097/PAS.0000000000000822

54. Heinonen HR, Mehine M, Mäkinen N, Pasanen A, Pitkänen E, Karhu A, et al. Metabolomic profiling of uterine leiomyomas. Br J Cancer. 2017;117(12):1855–1864. doi:10.1038/bjc.2017.331

55. Zheng L, MacKenzie ED, Karim SA, Hedley A, Blyth K, Kalna G, et al. ASL reversal in FH-deficient cancer. Cancer Metab. 2013;1(1):12. doi:10.1186/2049-3002-1-12

56. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. Genomic analysis of glioblastoma. Science. 2008;321(5897):1807–1812. doi:10.1126/science.1164382

57. Borger DR, Goyal L, Yau T, Poon RT, Ancukiewicz M, Deshpande V, et al. Circulating 2-hydroxyglutarate. Clin Cancer Res. 2014;20(7):1884–1890. doi:10.1158/1078-0432.CCR-13-2649

58. Delahousse J, Verlingue L, Broutin S, Legoupil C, Touat M, Doucet L, et al. D-2HG as surrogate marker. Eur J Cancer. 2018;90:83–91. doi:10.1016/j.ejca.2017.11.027

59. Lombardi G, Corona G, Bellu L, Puppa AD, Pambuku A, Fiduccia P, et al. Plasma and urinary 2HG. Oncologist. 2015;20(5):562–570. doi:10.1634/theoncologist.2014-0397

60. Natsumeda M, Igarashi H, Nomura T, Ogura R, Tsukamoto Y, Kobayashi T, et al. 2HG accumulation and survival. Acta Neuropathol Commun. 2014;2:158. doi:10.1186/s40478-014-0158-8

61. Sim HW, Nejad R, Zhang W, Nassiri F, Mason W, Aldape KD, et al. Tissue 2HG as biomarker. Clin Cancer Res. 2019;25(11):3366–3373. doi:10.1158/1078-0432.CCR-18-3317

62. Winter H, Kaisaki PJ, Harvey J, Giacopuzzi E, Ferla MP, Pentony MM, et al. Circulating biomarkers in cholangiocarcinoma. Cancers (Basel). 2019;11(12):1895. doi:10.3390/cancers11121895

63. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. IDH1 codon 132 mutation. Acta Neuropathol. 2008;116(6):597–602. doi:10.1007/s00401-008-0455-2

64. Kang MR, Kim MS, Oh JE, Kim YR, Song SY, Seo SI, et al. IDH1 mutations in cancers. Int J Cancer. 2009;125(2):353–355. doi:10.1002/ijc.24379

65. Mardis ER, Ding L, Dooling DJ, Larson DE, McLellan MD, Chen K, et al. AML genome sequencing. N Engl J Med. 2009;361(11):1058–1066. doi:10.1056/NEJMoa0903840

66. Borger DR, Tanabe KK, Fan KC, Lopez HU, Fantin VR, Straley KS, et al. IDH mutations in cholangiocarcinoma. Oncologist. 2012;17(1):72–79. doi:10.1634/theoncologist.2011-0386

67. Amary MF, Bacsi K, Maggiani F, Damato S, Halai D, Berisha F, et al. IDH mutations in chondrosarcoma. J Pathol. 2011;224(3):334–343. doi:10.1002/path.2913

68. Chiang S, Weigelt B, Wen HC, Pareja F, Raghavendra A, Martelotto LG, et al. IDH2 mutations in breast cancer. Cancer Res. 2016;76(24):7118–7129. doi:10.1158/0008-5472.CAN-16-1534

69. Fathi AT, Sadrzadeh H, Comander AH, Higgins MJ, Bardia A, Perry A, et al. IDH1 mutation in breast cancer. Oncologist. 2014;19(6):602–607. doi:10.1634/theoncologist.2014-0035

70. Minemura H, Takagi K, Sato A, Yamaguchi M, Hayashi C, Miki Y, et al. IDH isoforms in breast carcinoma. Breast Cancer. 2021;28(4):915–926. doi:10.1007/s12282-021-01224-5

71. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH mutations in gliomas. N Engl J Med. 2009;360(8):765–773. doi:10.1056/NEJMoa0808710

72. Wang HY, Tang K, Liang TY, Zhang WZ, Li JY, Wang W, et al. IDH1 vs IDH2 in gliomas. J Exp Clin Cancer Res. 2016;35:86. doi:10.1186/s13046-016-0361-4

73. Shen Y, Zhu YM, Fan X, Shi JY, Wang QR, Yan XJ, et al. AML mutation patterns. Blood. 2011;118(20):5593–5603. doi:10.1182/blood-2011-05-354845

74. Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, et al. 2HG detection by MRS. Nat Med. 2012;18(4):624–629. doi:10.1038/nm.2682

75. Gross S, Cairns RA, Minden MD, Driggers EM, Bittinger MA, Jang HG, et al. 2HG in AML. J Exp Med. 2010;207(2):339–344. doi:10.1084/jem.20092506

76. Lin AP, Abbas S, Kim SW, Ortega M, Bouamar H, Escobedo Y, et al. D2HGDH regulation. Nat Commun. 2015;6:7768. doi:10.1038/ncomms8768

77. Jin G, Reitman ZJ, Duncan CG, Spasojevic I, Gooden DM, Rasheed BA, et al. Wild-type IDH1 disruption. Cancer Res. 2013;73(2):496–501. doi:10.1158/0008-5472.CAN-12-2592

78. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. WHO CNS tumor classification. Acta Neuropathol. 2016;131(6):803–820. doi:10.1007/s00401-016-1545-1

79. Bleeker FE, Atai NA, Lamba S, Jonker A, Rijkeboer D, Bosch KS, et al. Prognostic IDH1 mutation. Acta Neuropathol. 2010;119(4):487–494. doi:10.1007/s00401-010-0641-0

80. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. Prognosis in anaplastic astrocytomas. Acta Neuropathol. 2010;120(6):707–718. doi:10.1007/s00401-010-0780-3

81. Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, et al. IDH1 mutation as prognostic biomarker. J Clin Oncol. 2009;27(25):4150–4154. doi:10.1200/JCO.2009.21.9832

82. Wang F, Zheng Z, Guan J, Qi D, Zhou S, Shen X, et al. Prognostic gene panel for glioblastoma. EBioMedicine. 2018;37:68–77. doi:10.1016/j.ebiom.2018.10.031

83. DiNardo CD, Propert KJ, Loren AW, Paietta E, Sun Z, Levine RL, et al. Serum 2HG predicts IDH mutations. Blood. 2013;121(24):4917–4924. doi:10.1182/blood-2013-03-491977

84. Miller A, Tong AW, Sweetman L, Theiss A, Murtaza M, Daoud Y, et al. AML with elevated D-2HG. Blood. 2017;130(Suppl 1).

85. Balss J, Thiede C, Bochtler T, Okun J, Saadati M, Benner A, et al. Pretreatment D-2HG levels in AML. Leukemia. 2016;30(4):782–788. doi:10.1038/leu.2015.327

86. Brunner AM, Neuberg DS, Wander SA, Sadrzadeh H, Ballen KK, Amrein PC, et al. IDH mutations and chemotherapy response. Cancer. 2019;125(4):541–549. doi:10.1002/cncr.31810

87. Andronesi OC, Kim GS, Gerstner E, Batchelor T, Tzika AA, Fantin VR, et al. 2HG detection by spectral-editing MRS. Sci Transl Med. 2012;4(116):116ra4. doi:10.1126/scitranslmed.3002693

88. Branzoli F, Di Stefano AL, Capelle L, Ottolenghi C, Valabrègue R, Deelchand DK, et al. IDH status by MRS. Neuro Oncol. 2018;20(7):907–916. doi:10.1093/neuonc/nox233

89. Choi C, Raisanen JM, Ganji SK, Zhang S, McNeil SS, An Z, et al. Longitudinal 2HG MRS. J Clin Oncol. 2016;34(33):4030–4039. doi:10.1200/JCO.2016.67.1222

90. Esmaeili M, Vettukattil R, Bathen TF. 2HG as MR biomarker. Transl Oncol. 2013;6(2):92–98. doi:10.1593/tlo.12280

91. Tietze A, Choi C, Mickey B, Maher EA, Ulhøi BP, Sangill R, et al. Noninvasive IDH assessment. J Neurosurg. 2018;128(2):391–399. doi:10.3171/2016.10.JNS161386

92. Radoul M, Hong D, Gillespie AM, Najac C, Viswanath P, Pieper RO, et al. Metabolic biomarkers of mutant IDH inhibition. Metabolites. 2021;11(2):109. doi:10.3390/metabo11020109

93. Ballester LY, Lu G, Zorofchian S, Vantaku V, Putluri V, Yan Y, et al. CSF metabolomics in CNS tumors. Acta Neuropathol Commun. 2018;6(1):85. doi:10.1186/s40478-018-0586-8

94. Kalinina J, Ahn J, Devi NS, Wang L, Li Y, Olson JJ, et al. D-2HG in CSF. Clin Cancer Res. 2016;22(24):6256–6265. doi:10.1158/1078-0432.CCR-16-0646

95. Cuccarini V, Antelmi L, Pollo B, Paterra R, Calatozzolo C, Nigri A, et al. In vivo 2HG MRS. Neurol Sci. 2020;41(2):347–355. doi:10.1007/s10072-019-04093-4

96. Fathi AT, Nahed BV, Wander SA, Iafrate AJ, Borger DR, Hu R, et al. Urinary 2HG in glioma. Oncologist. 2016;21(2):214–219. doi:10.1634/theoncologist.2015-0304

97. Belykh E, Shaffer KV, Lin C, Byvaltsev VA, Preul MC, Chen L. Blood–brain barrier and neurosurgery. Front Oncol. 2020;10:739. doi:10.3389/fonc.2020.00739

98. Nduom EK, Yang C, Merrill MJ, Zhuang Z, Lonser RR. Blood–brain barrier in tumors. J Neurosurg. 2013;119(2):427–433. doi:10.3171/2013.3.JNS122226

99. Engqvist MKM, Eßer C, Maier A, Lercher MJ, Maurino VG. Mitochondrial 2HG metabolism. Mitochondrion. 2014;19:275–281. doi:10.1016/j.mito.2014.02.003

100. Fan J, Teng X, Liu L, Mattaini KR, Looper RE, Vander Heiden MG, et al. PHGDH produces D-2HG. ACS Chem Biol. 2015;10(2):510–516. doi:10.1021/cb500683c

101. Mishra P, Tang W, Putluri V, Dorsey TH, Jin F, Wang F, et al. ADHFE1 as breast cancer oncogene. J Clin Invest. 2018;128(1):323–340. doi:10.1172/JCI96287

102. Struys EA, Verhoeven NM, Brunengraber H, Jakobs C. D-2HG formation in lymphoblasts. FEBS Lett. 2004;557(1–3):115–120. doi:10.1016/S0014-5793(03)01463-4

103. Xu T, Stewart KM, Wang X, Liu K, Xie M, Ryu JK, et al. Metabolic control of TH17/Treg balance. Nature. 2017;548(7666):228–233. doi:10.1038/nature23475

104. Michelucci A, Cordes T, Ghelfi J, Pailot A, Reiling N, Goldmann O, et al. IRG1 and itaconic acid. Proc Natl Acad Sci U S A. 2013;110(19):7820–7825. doi:10.1073/pnas.1218599110

105. Schuster EM, Epple MW, Glaser KM, Mihlan M, Lucht K, Zimmermann JA, et al. TFEB-induced itaconate synthesis. Nat Metab. 2022;4(7):856–871. doi:10.1038/s42255-022-00593-4

106. Weiss JM, Davies LC, Karwan M, Ileva L, Ozaki MK, Cheng RY, et al. Itaconic acid in tumor crosstalk. J Clin Invest. 2018;128(9):3794–3805. doi:10.1172/JCI99169

107. Chen LL, Morcelle C, Cheng ZL, Chen X, Xu Y, Gao Y, et al. Itaconate inhibits TET enzymes. Nat Cell Biol. 2022;24(3):353–363. doi:10.1038/s41556-022-00853-0

108. Chen YJ, Li GN, Li XJ, Wei LX, Fu MJ, Cheng ZL, et al. Targeting IRG1 enhances immunotherapy. Sci Adv. 2023;9(17):eadg0654. doi:10.1126/sciadv.adg0654

109. Lampropoulou V, Sergushichev A, Bambouskova M, Nair S, Vincent EE, Loginicheva E, et al. Itaconate and inflammation. Cell Metab. 2016;24(1):158–166. doi:10.1016/j.cmet.2016.06.004

110. Zhao H, Teng D, Yang L, Xu X, Chen J, Jiang T, et al. Myeloid-derived itaconate. Nat Metab. 2022;4(12):1660–1674. doi:10.1038/s42255-022-00647-7

111. Mills EL, Ryan DG, Prag HA, Dikovskaya D, Menon D, Zaslona Z, et al. Itaconate activates Nrf2. Nature. 2018;556(7699):113–117. doi:10.1038/nature25986

112. Zhang Z, Chen C, Yang F, Zeng YX, Sun P, Liu P, et al. Itaconate and antibacterial immunity. Mol Cell. 2022;82(15):2844–2857.e10. doi:10.1016/j.molcel.2022.06.025

113. Hooftman A, Angiari S, Hester S, Corcoran SE, Runtsch MC, Ling C, et al. Itaconate inhibits inflammasome. Cell Metab. 2020;32(3):468–478.e7. doi:10.1016/j.cmet.2020.07.016

114. Swain A, Bambouskova M, Kim H, Andhey PS, Duncan D, Auclair K, et al. Itaconate derivatives and interferon regulation. Nat Metab. 2020;2(7):594–602. doi:10.1038/s42255-020-0210-0

115. Dolšak A, Gobec S, Sova M. IDO and TDO as therapeutic targets. Pharmacol Ther. 2021;221:107746. doi:10.1016/j.pharmthera.2020.107746

116. Marszalek-Grabska M, Walczak K, Gawel K, Wicha-Komsta K, Wnorowska S, Wnorowski A, et al. Kynurenine metabolism. Pharmacol Ther. 2021;225:107845. doi:10.1016/j.pharmthera.2021.107845

117. Du L, Xing Z, Tao B, Li T, Yang D, Li W, et al. IDO1/TDO in glioma malignancy. Signal Transduct Target Ther. 2020;5(1):10. doi:10.1038/s41392-020-0119-2

118. Xiang Z, Li J, Song S, Wang J, Cai W, Hu W, et al. IDO1 metabolite feedback in gastric cancer. J Exp Clin Cancer Res. 2019;38(1):314. doi:10.1186/s13046-019-1307-4

119. Bishnupuri KS, Alvarado DM, Khouri AN, Shabsovich M, Chen B, Dieckgraefe BK, et al. Kynurenine activates PI3K–Akt. Cancer Res. 2019;79(6):1138–1150. doi:10.1158/0008-5472.CAN-18-2004

120. Wu PY, Yu IS, Lin YC, Chang YT, Chen CC, Lin KH, et al. AhR activation by kynurenine. Cancer Res. 2019;79(21):5550–5562. doi:10.1158/0008-5472.CAN-19-0862

121. Venkateswaran N, Lafita-Navarro MC, Hao YH, Kilgore JA, Perez-Castro L, Braverman J, et al. MYC and kynurenine pathway. Genes Dev. 2019;33(17–18):1236–1251. doi:10.1101/gad.327395.119

122. Lee R, Li J, Li J, Wu CJ, Jiang S, Hsu WH, et al. Synthetic essentiality of TDO2. Cancer Discov. 2022;12(7):1702–1717. doi:10.1158/2159-8290.CD-21-1140

123. Fiore A, Zeitler L, Russier M, Groß A, Hiller MK, Parker JL, et al. Kynurenine import via SLC7A11. Mol Cell. 2022;82(5):920–932.e7. doi:10.1016/j.molcel.2022.01.017

124. Liu Y, Liang X, Dong W, Fang Y, Lv J, Zhang T, et al. Kynurenine transfer induces PD-1. Cancer Cell. 2018;33(3):480–494.e7. doi:10.1016/j.ccell.2018.02.005

125. Galán-Díez M, Borot F, Ali AM, Zhao J, Gil-Iturbe E, Shan X, et al. Kynurenine and AML. Cancer Discov. 2022;12(4):1106–1123. doi:10.1158/2159-8290.CD-21-0835

126. Zhang D, Ning J, Ramprasath T, Yu C, Zheng X, Song P, et al. Kynurenine and heart regeneration. Nat Commun. 2022;13:6371. doi:10.1038/s41467-022-34002-7 (Retracted)

127. Takenaka MC, Gabriely G, Rothhammer V, Mascanfroni ID, Wheeler MA, Chao CC, et al. AHR/CD39 in glioblastoma. Nat Neurosci. 2019;22(5):729–740. doi:10.1038/s41593-019-0370-y

128. Siska PJ, Jiao J, Matos C, Singer K, Berger RS, Dettmer K, et al. Kynurenine and T cell metabolism. EBioMedicine. 2021;74:103742. doi:10.1016/j.ebiom.2021.103742

129. Casas-Benito A, Martínez-Herrero S, Martínez A. Succinate-directed cancer therapy. Cancers (Basel). 2023;15(10):2862. doi:10.3390/cancers15102862

130. Tretter L, Patocs A, Chinopoulos C. Succinate in tumorigenesis. Biochim Biophys Acta Bioenerg. 2016;1857(8):1086–1101. doi:10.1016/j.bbabio.2016.03.012

131. Yang JX, Chuang YC, Tseng JC, Liu YL, Lai CY, Lee AYL, et al. PDLIM2 and mitochondrial ROS. J Exp Clin Cancer Res. 2024;43:169. doi:10.1186/s13046-024-03061-1

132. Ježek J, Cooper KF, Strich R. ROS and mitochondrial dynamics. Antioxidants (Basel). 2018;7(1):13. doi:10.3390/antiox7010013

133. Hao J, Huang Z, Zhang S, Song K, Wang J, Gao C, et al. Roles of 2-hydroxyglutarate in cancer. Pharmacol Res. 2024;209:107437. doi:10.1016/j.phrs.2024.107437

134. Peng S, Chen H, Chen L, Yang G, Liu J, Cheng X, et al. Beyond IDH mutations. Chem Res Toxicol. 2022;35(2):115–124. doi:10.1021/acs.chemrestox.1c00398

135. Sullivan LB, Martinez-Garcia E, Nguyen H, Mullen AR, Dufour E, Sudarshan S, et al. Fumarate binds glutathione. Mol Cell. 2013;51(2):236–248. doi:10.1016/j.molcel.2013.05.003

136. Zheng L, Cardaci S, Jerby L, MacKenzie ED, Sciacovelli M, Johnson TI, et al. Fumarate-induced senescence. Nat Commun. 2015;6:6001. doi:10.1038/ncomms7001

137. Darzi M, Shokrollahi-Barough M, Nazeri E, Majidzadeh-AK, Esmaeili R. Gene co-expression in liposarcoma. Mol Biol Res Commun. 2025;14(3):203–214. doi:10.22099/mbrc.2025.48562.1765

138. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability hallmark. Nat Rev Mol Cell Biol. 2010;11(3):220–228. doi:10.1038/nrm2858

139. Pandey SN, Afzal M, Uikey J, Ganesan S, Mishra S, Bansal P, et al. ATM and p53 in aging and cancer. Biogerontology. 2025;26(3):102–116. doi:10.1007/s10522-024-10073-0

140. Sulkowski PL, Sundaram RK, Oeck S, Corso CD, Liu Y, Noorbakhsh S, et al. Krebs-cycle-deficient syndromes. Nat Genet. 2018;50(8):1086–1092. doi:10.1038/s41588-018-0170-4

141. Sulkowski PL, Oeck S, Dow J, Economos NG, Mirfakhraie L, Liu Y, et al. Oncometabolites suppress DNA repair. Nature. 2020;582(7813):586–591. doi:10.1038/s41586-020-2363-0

142. Drews RM, Hernando B, Tarabichi M, Haase K, Lesluyes T, Smith PS, et al. Pan-cancer chromosomal instability. Nature. 2022;606(7916):976–983. doi:10.1038/s41586-022-04786-6

143. Rahme GJ, Javed NM, Puorro KL, Xin S, Hovestadt V, Johnstone SE, et al. Epigenetic lesions in gliomas. Cell. 2023;186(17):3674–3689.e14. doi:10.1016/j.cell.2023.07.023

144. Losman JA, Koivunen P, Kaelin WG Jr. 2-oxoglutarate-dependent dioxygenases. Nat Rev Cancer. 2020;20(12):710–726. doi:10.1038/s41568-020-00300-2

145. Gueble SE, Bindra RS. Oncometabolites and DNA damage response. Semin Radiat Oncol. 2022;32(3):206–216. doi:10.1016/j.semradonc.2022.03.002

146. Sarkar S, Chang CI, Jean J, Wu MJ. TCA cycle-derived oncometabolites and immunity. J Biomed Sci. 2025;32(1):87. doi:10.1186/s12929-025-01087-55.