Section: Molecular Oncology

Review Article

ONCOMETABOLITES AND METABOLIC REPROGRAMMING IN CANCER: MOLECULAR INSIGHTS AND TRANSLATIONAL PERSPECTIVES

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Received *: 09/05/2025*
Received in revised form *: 03/07/2025*
Accepted *: 22/07/2025*

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DOI: 10.70034/ijmedph.2025.3.195

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2025; 15 (3); 1057-1065

ABSTRACT

Cancer metabolism has emerged as a pivotal hallmark of malignancy, extending far beyond the classical Warburg effect to encompass diverse metabolic alterations such as glutaminolysis, lipid metabolism dysregulation, and altered amino acid and mitochondrial dynamics. Central to this rewired metabolic landscape is the aberrant accumulation of oncometabolites, small molecules such as D-2-hydroxyglutarate, succinate, fumarate, and lactate, that not only reflect metabolic derangements but actively contribute to oncogenesis. These oncometabolites exert profound intracellular effects, including epigenetic reprogramming, redox imbalance, and inhibition of differentiation, while also reshaping the tumor microenvironment (TME) through hypoxia signalling, immune modulation, and extracellular matrix remodelling.

This narrative review synthesizes current molecular insights into the origins, defining features, and mechanistic roles of key oncometabolites in cancer progression. It further explores their interactions with the TME and critically evaluates therapeutic interventions, including enzyme inhibitors, epigenetic therapies, and metabolite transport blockers. Emerging oncometabolites such as itaconate and kynurenine, microbiota-derived metabolic influences, and novel investigative tools such as spatial and single-cell metabolomics are also discussed. Additionally, the review outlines major translational barriers, including analytical challenges, lack of robust biomarkers, and intra-tumoral heterogeneity, which currently limit clinical implementation. By integrating advanced metabolomics and artificial intelligence, the manuscript emphasizes the promise of precision oncology strategies targeting metabolic vulnerabilities, positioning oncometabolites as both mechanistic drivers and actionable targets in cancer biology.

Keywords: Oncometabolites, Cancer Metabolism, Metabolic Reprogramming, Epigenetic Dysregulation, Tumor Microenvironment (TME), Precision Oncology, Therapeutic Targeting.

INTRODUCTION

Cancer is increasingly recognized not merely as a genetic disorder but as a complex disease hallmarked by profound metabolic plasticity, enabling malignant cells to adapt, proliferate, and survive under diverse and challenging microenvironmental conditions. This intrinsic metabolic flexibility, often termed metabolic reprogramming, is now acknowledged as a pivotal hallmark of malignancy. Historically, the phenomenon of cancer metabolic alteration gained early attention through the seminal works of Otto Warburg in the early 20th century, who observed that cancer cells preferentially metabolize glucose via aerobic glycolysis rather than through oxidative phosphorylation, even in oxygen-rich conditions. This seemingly paradoxical metabolic preference, known famously as the Warburg effect, initially underscored cancer metabolism research. However, contemporary investigations reveal a more intricate metabolic landscape characterized by altered glutaminolysis, dysregulated lipid metabolism, increased amino acid uptake, and aberrant mitochondrial bioenergetics, expanding the paradigm beyond Warburg's initial observations.[1,2]

A critical and increasingly recognized component within this elaborate metabolic rewiring involves small molecules termed oncometabolites. Oncometabolites are distinct metabolic intermediates that aberrantly accumulate within tumor cells due to genetic mutations or dysregulated enzyme activities. Unlike general metabolites, these molecules do not merely support the altered metabolic demands of proliferating cancer cells; instead, they play active roles in driving oncogenic processes. By exerting direct or indirect effects on cellular signaling pathways, epigenetic states, and interactions within the tumor microenvironment, oncometabolites bridge metabolic dysregulation with malignant transformation and tumor progression.[3]

The concept of oncometabolites emerged prominently with the identification of mutant isocitrate dehydrogenase enzymes (IDH1/2) in gliomas and acute myeloid leukemia, which catalyze the aberrant production and accumulation of D-2-hydroxyglutarate (D2HG). The discovery of D2HG as an oncometabolite illuminated a critical link between metabolism, genetic alterations, and cancer pathogenesis. Since then, other small molecules like succinate, fumarate, and lactate have also gained recognition for their oncogenic roles, often accumulating due to loss-of-function mutations in metabolic enzymes such as succinate dehydrogenase (SDH) and fumarate hydratase (FH) or through dysregulated metabolic flux under hypoxic conditions. Collectively, these oncometabolites are characterized by their unique capacity to modify the tumor epigenome, alter redox homeostasis, and reprogram cellular signaling networks, consequently promoting tumor initiation, progression, and resistance to therapies.[4]

Interest in cancer metabolism underwent significant rejuvenation in recent decades following technological advancements in metabolomics, genomics, and bioinformatics, which provided unprecedented resolution into the metabolic aberrations associated with malignancy. This renewed attention expanded the conceptual framework initially established by Warburg, emphasizing the dynamic interplay between genetic mutations, metabolic pathways, and environmental stresses encountered by cancer cells. Comprehensive profiling of cancer-associated metabolic alterations, facilitated by mass spectrometry-based metabolomics and sophisticated imaging modalities, further validated the critical role of metabolic adaptations in tumor biology and fostered the identification and characterization of various oncometabolites.[5]

Despite rapid advances in our understanding of cancer metabolism, a cohesive synthesis of how oncometabolites influence tumor biology remains necessary. Currently, extensive yet fragmented knowledge exists regarding the mechanistic roles of individual oncometabolites, their interactions with metabolic pathways, and their broader effects on cellular states and microenvironments. Thus, there is a need for an integrative approach that elucidates not only the molecular underpinnings of oncometabolite accumulation but also their multifaceted roles in shaping tumor epigenetics, metabolism, and interactions within the tumor microenvironment. Such integration would significantly enhance our understanding of tumorigenesis and potentially reveal vulnerabilities amenable to targeted therapeutic interventions.[3,6,7]

Consequently, this narrative review aims explicitly to synthesize and critically evaluate the current understanding of how key oncometabolites including D2HG, succinate, fumarate, and lactate influence tumor metabolism, epigenetic landscapes, and interactions with the tumor microenvironment. We will discuss molecular mechanisms through which these metabolites drive tumorigenesis, examining their impact on epigenetic regulators, redox balance, and cellular signaling cascades. Furthermore, the review will explore the intricate crosstalk between oncometabolites and immune cell populations, fibroblasts, endothelial cells, and other components within the tumor microenvironment, emphasizing how these interactions collectively support tumor progression and immune evasion. Lastly, given the translational potential of oncometabolite research, we aim to critically assess current therapeutic strategies targeting these metabolites and their associated pathways. This includes discussing the clinical efficacy of inhibitors targeting mutant metabolic enzymes such as IDH1/2, the therapeutic potential of epigenetic modulators, and emerging strategies aimed at disrupting metabolite transport or signaling pathways. The review will further highlight challenges associated with clinical translation, such as analytical constraints, biomarker development, and tumor heterogeneity, providing perspectives on overcoming these hurdles.

Search Strategy and Methodology

A literature search was conducted using comprehensive databases including PubMed, Scopus, Web of Science, and Embase. The search strategy employed was carefully designed with precise keywords and Boolean operators to effectively capture relevant literature. The utilized keywords were: ("oncometabolites" AND "metabolic reprogramming") AND ("IDH1/2" OR "succinate" OR "fumarate" OR "cancer metabolism") AND ("epigenetics" OR "therapeutic targeting"). These terms were selected based on their direct relevance to the molecular, metabolic, epigenetic, and therapeutic aspects of oncometabolites in cancer biology, thereby ensuring comprehensive coverage of pertinent literature.

Inclusion Criteria: To maintain methodological rigor and ensure the relevance of included studies, clearly defined inclusion criteria were established. Articles eligible for inclusion were: Peer-reviewed original research studies, comprehensive reviews, and clinical trials published from January 2010 to December 2025, to reflect contemporary research and recent advancements in the field. Articles explicitly

addressing the roles, mechanisms, and clinical relevance of key oncometabolites in the context of cancer, particularly focusing on IDH1/2 mutations, succinate, fumarate, and associated metabolic reprogramming. Publications specifically investigating the epigenetic modifications induced by oncometabolites and the translational implications of their therapeutic targeting. Only publications available in the English language to facilitate accurate synthesis and analysis. Exclusion Criteria: To streamline the review's relevance and enhance specificity, exclusion criteria were delineated clearly, and included: Research primarily focusing on non-cancerous metabolic conditions or disorders, ensuring that the review remains exclusively pertinent to cancer biology. Articles published as editorials, brief commentaries, letters to editors, perspectives, or preprints to maintain a high standard of peer-reviewed scientific evidence. Publications in languages other than English, avoiding linguistic inaccuracies and ensuring precise interpretation of complex scientific data.

Hallmarks of Cancer Metabolism: A Rewired Landscape

Cancer metabolism, characterized by significant plasticity, has long been recognized as a fundamental hallmark of malignancy, underscored initially by the seminal observations of Otto Warburg. The Warburg effect describes cancer cells' preferential reliance on aerobic glycolysis, glucose fermentation even in the presence of oxygen, over oxidative phosphorylation, promoting rapid ATP generation and biomass accumulation critical for accelerated tumor growth. However, contemporary understanding of cancer metabolism has extended significantly beyond this canonical pathway, identifying key roles for glutaminolysis, fatty acid oxidation, and various other altered metabolic processes. Glutaminolysis, the metabolic pathway by which glutamine is converted into intermediates fueling the TCA cycle, provides essential carbon and nitrogen sources crucial for nucleotide and amino acid biosynthesis. Similarly, cancer cells frequently exhibit modified fatty acid oxidation pathways to support survival under metabolic stress, energy production, and the maintenance of membrane integrity necessary for proliferation and metastasis.[8,9]

Integration and dysregulation of critical nutrient-sensing signaling pathways further characterize this rewired metabolic landscape. Central among these pathways are mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), hypoxia-inducible factor 1-alpha (HIF-1α), and the transcription factor MYC. mTOR functions as a primary cellular regulator, integrating signals from nutrient availability, growth factors, and energy status to promote anabolic metabolism, driving cell growth and proliferation. In contrast, AMPK serves as a metabolic sensor that activates catabolic pathways to restore energy balance under nutrient-deficient conditions, typically antagonizing mTOR signaling. Concurrently, HIF-1α stabilization in hypoxic tumor microenvironments modulates metabolic adaptation by enhancing glycolysis, reducing mitochondrial respiration, and promoting angiogenesis, crucially facilitating tumor survival and progression under stress. The oncogene MYC orchestrates comprehensive metabolic reprogramming by stimulating glycolysis, glutaminolysis, and nucleotide biosynthesis pathways, collectively fostering rapid proliferation and biomass accumulation.[10,11]

The functional consequences of cancer's metabolic rewiring are manifold, enabling tumors to sustain continuous proliferation, resist cell death under adverse conditions, maintain redox homeostasis, and support robust anabolic growth. Metabolic adaptations not only enable cancer cells to survive environmental stresses, such as nutrient scarcity, hypoxia, and oxidative stress but also facilitate the maintenance of cellular redox balance by generating reducing equivalents critical for mitigating reactive oxygen species (ROS). Additionally, the anabolic and biosynthetic pathways upregulated in cancer cells produce macromolecules essential for new cellular structures, providing a substantial advantage for tumor growth and metastasis.[12]

Within this complex and dynamically regulated metabolic network, oncometabolites emerge as critical players linking genetic mutations to altered metabolic pathways. Oncometabolites such as D2HG, succinate, fumarate, and lactate accumulate aberrantly due to specific genetic or metabolic disruptions and exert potent oncogenic effects, ranging from epigenetic modifications and redox imbalance to the induction of pseudohypoxia. For instance, D2HG, arising from mutations in IDH1/2, profoundly impacts epigenetic regulation through inhibition of α-ketoglutarate-dependent dioxygenases, leading to extensive methylation changes and impaired differentiation. Similarly, succinate and fumarate, products of mutations in SDH and FH respectively, stabilize HIF-1α through inhibition of prolyl hydroxylases, thus inducing a pseudohypoxic state that further reinforces metabolic and angiogenic pathways favorable to tumor growth. Lactate, although not directly mutation-driven, critically contributes to tumor progression by modulating immune responses, promoting angiogenesis, and altering the tumor microenvironment through acidification and signaling pathways. Thus, positioning oncometabolites within this altered metabolic framework highlights their central role in driving tumorigenesis and cancer progression, providing potential avenues for targeted therapeutic intervention.[13]

Oncometabolites: Origin, Identity, and Defining Features

Oncometabolites are a distinctive class of small molecule metabolites that aberrantly accumulate within cells due to genetic or metabolic disruptions, and exert pro-oncogenic effects through diverse biochemical mechanisms. Their pathological

accumulation, which deviates significantly from normal physiological concentrations, can induce epigenetic modifications, oxidative stress, and pseudohypoxic states, thereby driving malignant transformation and progression. These metabolites are defined not only by their elevated levels but crucially by their functional impact in promoting cancer-related phenotypes.

Oncometabolites can be classified based on the underlying molecular aberrations driving their accumulation. First, there are those arising from mutant enzyme activities, exemplified by D2HG. This metabolite specifically accumulates due to gain-of-function mutations in isocitrate dehydrogenase enzymes (IDH1/2), commonly observed in gliomas and acute myeloid leukemia (AML). Second, another subgroup arises from loss-of-function mutations affecting metabolic enzymes, such as D2HG, SDH or FH. In these cases, the metabolites succinate and fumarate accumulate respectively, as the metabolic blocks imposed by enzymatic deficiency prevent their conversion to downstream intermediates. These accumulated metabolites in turn influence oncogenesis through mechanisms like stabilization of hypoxia-inducible factors (HIF-1α), thereby promoting a pseudohypoxic environment conducive to tumor growth. Lastly, certain oncometabolites accumulate contextually, independent of direct genetic mutations in metabolic enzymes. Lactate is the archetypal example in this category, markedly accumulating under hypoxic conditions within glycolytically active tumors. Although lactate accumulation does not stem directly from genetic mutations, its substantial rise profoundly alters the tumor microenvironment, facilitating angiogenesis, immunosuppression, and acidification of the extracellular milieu.[14]

Accurate identification and quantification of oncometabolites require specialized analytical tools. Mass spectrometry (MS)-based metabolomics has emerged as the cornerstone technique for precise measurement and characterization, providing high sensitivity and specificity. Additionally, advanced imaging tracers employing techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have facilitated the non-invasive visualization and spatial mapping of these metabolites in vivo. Collectively, these methodologies are essential for unraveling the complex metabolic dysregulation inherent in cancer, ultimately guiding both diagnostic stratification and therapeutic intervention strategies.[15]

Major Oncometabolites and Their Molecular **Mechanisms**

D2HG

D2HG prominently accumulates in various cancers harbouring mutations in IDH1/2, particularly gliomas and AML. The IDH1/2 mutations alter enzyme catalytic function, driving excessive conversion of α-ketoglutarate (α-KG) to the oncometabolite D2HG. This accumulation exerts profound epigenetic consequences by competitively inhibiting α-KG-dependent dioxygenases, notably the ten-eleven translocation (TET) family of DNA hydroxylases and histone lysine demethylases (KDMs). Such inhibition disrupts normal DNA demethylation processes, fostering hypermethylation at CpG islands, termed the CpG island methylator phenotype (G-CIMP). The resultant global epigenetic reprogramming impairs cellular differentiation, facilitating tumorigenesis and maintenance of stem-like cancer cell populations.[16]

Succinate

Succinate emerges significantly in tumors characterized by SDH deficiencies, such as paragangliomas and renal cell carcinomas (RCC). Loss-of-function mutations in SDH cause accumulation of succinate, which potently inhibits prolyl hydroxylases responsible for the degradation of hypoxia-inducible factor-1α (HIF-1α). The stabilization of HIF-1α under normoxic conditions, known as pseudohypoxia, initiates transcriptional programs that enhance angiogenesis, glucose metabolism, and cell survival, mimicking cellular adaptation to hypoxia. Furthermore, succinate acts as a signalling molecule via the succinate receptor SUCNR1 (also termed GPR91), activating inflammatory pathways and reinforcing a pro-tumorigenic microenvironment conducive to tumor progression and immune evasion.[17]

Fumarate

Fumarate accumulation is a hallmark of cancers harboring mutations in the FH enzyme, including hereditary leiomyomatosis and renal cell carcinoma (HLRCC). Elevated fumarate participates in oncogenesis through a distinct mechanism termed protein succination, wherein fumarate covalently modifies cysteine residues on critical regulatory proteins. One key target is Kelch-like ECH-associated protein 1 (KEAP1), whose succination prevents effective inhibition of nuclear factor erythroid 2–related factor 2 (NRF2). This modification results in persistent NRF2 activation, enhancing cellular antioxidant defenses and creating an environment conducive to tumor survival and resistance to oxidative stress. Additionally, fumarate-driven succination has been implicated in promoting epithelial-to-mesenchymal transition (EMT) and genomic instability, further amplifying tumor aggressiveness and metastatic potential.[18]

Lactate

Lactate, while not typically associated with specific genetic mutations, accumulates substantially within glycolytically active tumors, serving pivotal functional roles. High lactate levels contribute to the acidification of the tumor microenvironment, promoting tumor cell survival and invasiveness. Lactate also facilitates angiogenesis by activating specific signaling pathways mediated through monocarboxylate transporters (MCTs) and the lactate receptor GPR81. Furthermore, lactate-driven immune evasion mechanisms significantly impair anti-tumor immune responses, including inhibition of cytotoxic T-cell function and modulation of tumor-associated macrophage polarization towards a pro-

tumorigenic phenotype. Thus, lactate effectively integrates metabolic and immune regulatory functions within the tumor microenvironment, underscoring its critical role beyond simple metabolic byproduct status.[19]

Table 1: Summary of Key Studies on Oncometabolites and Tumor Immune Modulation

Study name	Key findings
Cai M et al., (2024)[16]	D-2-HG suppresses antitumor immunity by impairing T cell function, dendritic cell maturation, NK cell cytotoxicity, and complement activation, promoting an immunosuppressive tumor microenvironment. L-2-HG enhances immune responses, especially $CD8^+$ T cell memory and cytotoxicity, demonstrating opposing immunomodulatory effects compared to D-2-HG. Targeting 2-HG through IDH inhibitors, peptide vaccines, or CAR-T cell engineering offers promising strategies to restore immune surveillance and improve cancer immunotherapy outcomes.
Baryła et al. (2022)[17]	Oncometabolites (lactate, succinate, fumarate, glutamate) actively shape the tumor microenvironment by promoting angiogenesis, immune evasion, and epithelial-to-mesenchymal transition (EMT). Lactate and succinate enhance tumor angiogenesis and suppress immunity via HIF stabilization, VEGF induction, and activation of PI3K/STAT3/ERK signaling. Fumarate and glutamate drive tumor aggressiveness by impairing DNA repair, inducing epigenetic changes, and fueling anabolic metabolism under hypoxia.
Yang et al., (2012)[18]	Fumarate accumulation due to FH mutation acts as an oncometabolite by inhibiting 2-oxoglutarate-dependent enzymes, leading to HIF stabilization and epigenetic dysregulation. Succination of cysteine residues by fumarate disrupts protein function, notably inactivating KEAP1 and activating NRF2, promoting tumor cell survival. Dual role: While oncogenic in FH-deficient cells, fumarate can be cytoprotective in other contexts like cardiac ischemia, depending on cellular compartment and concentration.
Kes et al. (2020),[19]	Lactate and succinate drive TAM polarization into a pro-angiogenic, immunosuppressive phenotype via HIF stabilization and receptor-mediated signaling (MCTs, SUCNR1). These oncometabolites activate VEGF and Arg1 expression through pathways like ERK/STAT3 and histone lactylation, promoting tumor angiogenesis. Targeting LDHA, MCTs, or SUCNR1 may prevent resistance to anti-angiogenic therapies and reprogram TAMs toward anti-tumor activity.

Legend: D-2-HG: D-2-hydroxyglutarate; L-2-HG: L-2-hydroxyglutarate; NK: Natural Killer (cells); IDH: Isocitrate Dehydrogenase; CAR-T: Chimeric Antigen Receptor T (cells); $CD8^+$: Cluster of Differentiation 8 positive; EMT: Epithelial-to-Mesenchymal Transition; HIF: Hypoxia-Inducible Factor; VEGF: Vascular Endothelial Growth Factor; PI3K: Phosphoinositide 3-Kinase; STAT3: Signal Transducer and Activator of Transcription 3; ERK: Extracellular Signal-Regulated Kinase; FH: Fumarate Hydratase; KEAP1: Kelch-like ECH-associated protein 1; NRF2: Nuclear Factor Erythroid 2–Related Factor 2; TAM: Tumor-Associated Macrophage; MCTs: Monocarboxylate Transporters; SUCNR1: Succinate Receptor 1; Arg1: Arginase 1; LDHA: Lactate Dehydrogenase A.

Epigenetic Reprogramming Induced by Oncometabolites

Oncometabolites profoundly alter the epigenetic landscape of cancer cells, primarily through inhibition of α-ketoglutarate (α-KG)-dependent dioxygenases, including ten-eleven translocation (TET) enzymes and histone lysine demethylases (KDMs). These enzymes, crucially reliant on α-KG for catalytic activity, modulate gene expression by dynamically regulating DNA and histone methylation marks. The aberrant accumulation of oncometabolites such as D2HG, succinate, and fumarate competitively inhibits these enzymes by mimicking the structure of α-KG, leading to widespread epigenetic dysregulation. One significant consequence of α-KG-dependent enzyme inhibition is genome-wide hypermethylation, notably impacting tumor suppressor genes and genes governing cellular differentiation pathways. For instance, IDH1/2-mutant tumors, prominently gliomas and AML, exhibit a distinct CpG island methylator phenotype (G-CIMP) attributed directly to elevated D2HG. This hypermethylation silences critical genes responsible for cellular differentiation and promotes a progenitor-like or stem-like cellular phenotype characterized by impaired lineage specification and enhanced self-renewal capacity. Such profound methylation shifts thus establish differentiation blocks, allowing tumor cells to retain or revert to more primitive states, which fuels tumor initiation, aggressiveness, and therapeutic resistance.[20]

Beyond DNA methylation, histone modifications mediated by histone demethylases are significantly disrupted. The inhibition of KDMs leads to aberrant histone methylation patterns, notably increases in histone H3 lysine 9 (H3K9) and lysine 27 (H3K27) methylation, which are strongly associated with transcriptional repression and heterochromatin formation. Succinate and fumarate, particularly elevated in SDH and FH-deficient cancers, similarly contribute to histone hypermethylation, establishing a chromatin environment conducive to oncogenesis. Such chromatin remodeling underscores the integrative role of metabolic and epigenetic networks in cancer biology. Critically, the epigenetic rewiring driven by these oncometabolites extends to phenotypic plasticity, conferring tumor cells with enhanced adaptability and resilience. Cells experiencing these metabolic disruptions often acquire a dedifferentiated phenotype, marked by increased expression of stem cell markers, resistance

to conventional therapies, and heightened metastatic potential. Indeed, the epigenetically mediated block in differentiation pathways connects metabolically driven mutations to clinically aggressive tumor behaviours, underscoring a direct mechanistic link between metabolic dysregulation, epigenetic alterations, and cancer progression.[21]

The epigenetic reprogramming elicited by oncometabolites such as D2HG, succinate, and fumarate represents a critical nexus point between altered tumor metabolism and malignancy. Understanding these mechanisms offers compelling translational opportunities for novel therapeutic interventions targeting the metabolic-epigenetic axis, emphasizing precision oncology approaches for tumors harboring specific metabolic vulnerabilities.

Crosstalk with the Tumor Microenvironment (TME)

Oncometabolites significantly influence tumor progression not only through intrinsic cellular mechanisms but also by modulating the TME. A pivotal mechanism through which oncometabolites mediate their impact is via hypoxia signaling pathways. Succinate and fumarate, by accumulating in tumors deficient in SDH and FH, inhibit prolyl hydroxylase enzymes, resulting in the stabilization and activation of hypoxia-inducible factor-1 alpha (HIF-1α). This phenomenon, known as pseudohypoxia, occurs even under normoxic conditions and induces transcriptional activation of genes involved in glycolysis, angiogenesis, and survival, thereby supporting tumor growth and adaptation. D2HG, accumulating in isocitrate dehydrogenase (IDH)-mutated tumors, similarly promotes pseudohypoxia by competitively inhibiting α-ketoglutarate-dependent enzymes, further amplifying oncogenic hypoxic responses. Furthermore, oncometabolites actively reshape the immune landscape within the TME, notably through their effects on tumor-associated macrophages (TAMs) and overall immune suppression. Lactate, abundantly secreted by glycolytically active tumors, markedly influences immune cell function. Elevated lactate levels promote the polarization of macrophages toward an immunosuppressive M2-like phenotype, thereby facilitating tumor evasion from immune surveillance. Additionally, lactate suppresses cytotoxic T-cell activity and reduces the functional capacity of natural killer (NK) cells, collectively resulting in a profoundly immunosuppressive milieu. Similarly, D2HG has been shown to impair T-cell function and reduce the expression of cytokines required for antitumor immunity, thereby reinforcing immune evasion mechanisms within tumors.[22,23]

The modulation of extracellular matrix (ECM) remodeling and angiogenesis constitutes another critical facet of oncometabolite-driven microenvironmental alterations. Oncometabolite-induced HIF-1α activation leads to elevated secretion of vascular endothelial growth factor (VEGF), a primary driver of tumor angiogenesis. Such increased vascularization not only ensures nutrient supply but also provides routes for metastatic dissemination. Moreover, fumarate accumulation triggers epithelial-to-mesenchymal transition (EMT) processes. It stimulates fibroblast activation, thus promoting ECM remodeling and contributing to a stiff, desmoplastic microenvironment that enhances tumor invasiveness and therapeutic resistance. Finally, emerging evidence emphasizes the role of oncometabolites as extracellular signaling molecules that exert paracrine effects within the TME. Lactate, succinate, and fumarate, once exported from tumor cells, function as signaling intermediates that communicate metabolic status to neighbouring cells. Succinate, for example, activates G-protein coupled receptor SUCNR1 (GPR91) on surrounding stromal and immune cells, leading to inflammatory signaling cascades that further promote tumor progression. Lactate, through activation of the GPR81 receptor, similarly induces pro-tumorigenic pathways such as angiogenesis, immune suppression, and metabolic cross-feeding between cancer cells and stromal components. This intercellular communication underscores the concept that oncometabolites act not merely as intracellular metabolites but as crucial extracellular messengers orchestrating dynamic, bidirectional communication within the tumor ecosystem.[24]

Understanding the intricate interplay between oncometabolites and the TME offers opportunities to intervene therapeutically. Strategies aimed at targeting oncometabolite production, release, or receptor-mediated signalling could effectively disrupt tumor-stroma communication, reshape immune responses, and enhance sensitivity to conventional treatments. Nonetheless, comprehensive characterization of these complex interactions through spatial metabolomics and advanced imaging techniques remains imperative for successfully translating such strategies into clinical practice.

Therapeutic Targeting of Oncometabolite Pathways

Therapeutic targeting of oncometabolite pathways represents a promising avenue for precision oncology, capitalizing on metabolic vulnerabilities specific to cancer cells. One prominent strategy involves enzyme inhibition, exemplified by the development and clinical approval of IDH1/2 inhibitors such as Ivosidenib and Enasidenib. These inhibitors effectively reduce the aberrant accumulation of the oncometabolite D2HG in AML harboring IDH mutations, restoring normal epigenetic states and promoting cellular differentiation. This clinical success has encouraged research efforts toward developing targeted therapies for other enzyme-driven oncometabolites, notably succinate and fumarate. Early-stage compounds targeting SDH and FH deficiencies are currently progressing through preclinical evaluation, promising potential translational implications in SDH-deficient paragangliomas, renal cell carcinoma (RCC), and FH-deficient cancers. Epigenetic

therapies also offer indirect yet impactful modulation of oncometabolite-induced alterations. DNA methyltransferase (DNMT) inhibitors like azacytidine and histone deacetylase (HDAC) inhibitors have demonstrated efficacy in reversing the global epigenetic dysregulation imposed by aberrant metabolite accumulation, especially in contexts where direct enzymatic targeting remains challenging. By alleviating transcriptional silencing of tumor suppressor genes and differentiation-promoting pathways, these therapies exhibit promising synergy with enzyme inhibitors, particularly in oncometabolite-positive tumors with pronounced epigenetic reprogramming.[25]

Another emerging strategy focuses on disrupting metabolite transport and downstream signaling. Inhibitors targeting monocarboxylate transporters (MCTs), crucial for lactate efflux and extracellular acidification, are currently being investigated in glycolytic cancers characterized by elevated lactate production. Similarly, receptor blockade approaches, such as inhibitors targeting succinate receptor 1 (SUCNR1), have shown preclinical efficacy in attenuating inflammatory signaling pathways activated by succinate accumulation. These agents underscore the therapeutic potential of intercepting extracellular signaling axes utilized by oncometabolites, opening avenues for broader applications in metabolic oncology. Synthetic lethality and combination therapeutic approaches further capitalize on vulnerabilities created by oncometabolite accumulation. Tumors harboring elevated oncometabolites often display compromised DNA repair capacities and heightened oxidative stress, rendering them susceptible to agents targeting DNA repair pathways, such as PARP inhibitors. Moreover, combining immunotherapies with metabolic reprogramming agents has emerged as a compelling strategy. By modulating the tumor microenvironment's metabolic landscape, these combinations enhance immune cell infiltration and activation, potentially overcoming immune resistance mechanisms mediated by oncometabolites. Collectively, these strategies reflect a sophisticated and integrated therapeutic framework, poised to translate metabolic vulnerabilities into meaningful clinical outcomes.[25]

Challenges in Clinical Translation

Translating the insights gained from oncometabolite research into clinical practice remains a formidable challenge, primarily due to numerous analytical and biological barriers. One of the primary obstacles is analytical in nature; the inherent instability of specific metabolites can lead to artifacts during sample collection and storage, significantly affecting accuracy and reproducibility. For instance, metabolites such as fumarate and succinate require meticulous handling and rapid stabilization procedures post-sampling to prevent degradation or artifactual formation. Furthermore, the tissue-specific context adds another layer of complexity. The metabolic profiles and the consequent interpretation of oncometabolite abundance can vary substantially between tissues, necessitating standardized and rigorously validated protocols for clinical metabolomic analysis.[26]

Another critical barrier impeding clinical translation is the paucity of robust, non-invasive biomarkers for effective oncometabolite profiling. Current diagnostic approaches frequently rely on invasive biopsy techniques, which are not always feasible or repeatable in clinical settings. Non-invasive methods, such as liquid biopsies using blood, urine, or saliva, hold great promise but require considerable advancement in sensitivity and specificity to detect low-abundance metabolites like 2-hydroxyglutarate or fumarate reliably. Advances in mass spectrometry and imaging technologies have begun to address these issues; however, their clinical utility still demands extensive validation across diverse patient populations.[27]

Additionally, tumor heterogeneity significantly complicates the interpretation and generalizability of metabolic signatures. Tumors often exhibit spatial and temporal metabolic variability, driven by genetic mutations, epigenetic alterations, and microenvironmental factors. Single-cell metabolomics and spatial metabolic imaging have underscored this complexity by highlighting the profound intra-tumoral metabolic differences, even within regions of the same tumor. This heterogeneity necessitates meticulous interpretation when translating metabolic signatures into clinically actionable insights. Personalized, spatially-resolved metabolic analyses are required to capture this complexity and guide therapeutic decisions accurately. Lastly, effective clinical translation of oncometabolite research demands context-dependent stratification in clinical trials. Stratification based merely on tumor type or genetic mutation status is insufficient, given the nuanced interplay between metabolic dysregulation, genetic drivers, and microenvironmental conditions. Precision medicine paradigms must incorporate comprehensive multi-omics profiling encompassing genetic, metabolic, and microenvironmental parameters to identify patient subgroups most likely to benefit from targeted interventions. Without such tailored approaches, therapeutic strategies risk overlooking critical factors influencing patient response, ultimately hindering clinical efficacy and patient outcomes.[26,27]

Emerging Oncometabolites and Future Directions

The rapidly evolving landscape of metabolomics continues to unveil novel oncometabolite candidates through untargeted approaches, significantly broadening our understanding of cancer metabolic reprogramming. Among these newly recognized metabolites, itaconate has recently emerged as a prominent player. Traditionally known for its role in macrophage-driven inflammation, itaconate accumulation has now been observed in several cancer types. Its dual capability to modulate inflammatory pathways and cellular metabolism highlights its potential in oncogenic signaling,

warranting deeper mechanistic studies. Similarly, kynurenine, a tryptophan-derived metabolite, has attracted attention due to its immunomodulatory properties within the tumor microenvironment. Elevated kynurenine levels, commonly linked with indoleamine 2,3-dioxygenase (IDO) activity, are associated with immune suppression and tumor progression, suggesting its role as both a biomarker and a therapeutic target. Lipid mediators, particularly oxidized phospholipids and eicosanoids, have also surfaced from recent metabolomic screenings, underscoring their involvement in tumor-promoting inflammation, angiogenesis, and metastatic dissemination.[5,25]

Additionally, the intersection between microbiota-derived metabolites and cancer metabolism represents a compelling yet underexplored avenue. Gut microbiota metabolites, such as short-chain fatty acids (SCFAs), secondary bile acids, and polyamines, profoundly influence host metabolic homeostasis and inflammatory responses, thereby modulating tumor initiation and progression. Notably, SCFAs like butyrate and propionate exhibit paradoxical roles, demonstrating both tumor-suppressive and tumor-promotive activities contingent on their concentration, context, and receptor interactions. Clarifying these dynamics necessitates integrative approaches combining microbiome sequencing, metabolomics, and functional assays to delineate the complex microbiota-cancer metabolism interface accurately.[28]

The advent of single-cell and spatial metabolomics offers unprecedented opportunities to dissect metabolic heterogeneity within tumors, a critical factor underlying resistance to conventional therapies. Traditional bulk analyses obscure crucial metabolic diversity among individual tumor cells and within distinct tumor microregions. Single-cell metabolomics enables precise metabolic profiling, identifying subpopulations with unique metabolic dependencies and vulnerabilities. Complementarily, spatial metabolomics adds an essential layer of context by mapping metabolite distributions directly onto histological sections, thus revealing microenvironment-specific metabolic adaptations. These technological advances promise enhanced resolution in understanding how intra-tumoral heterogeneity contributes to disease progression and treatment resistance, ultimately facilitating the development of tailored therapeutic interventions.[29]

Moreover, the integration of artificial intelligence (AI) into metabolomic research represents a transformative direction for biomarker discovery and validation. Machine learning algorithms, intense learning models, efficiently handle complex, high-dimensional metabolomic datasets, uncovering patterns and predictive signatures that may remain elusive through conventional statistical analyses. AI-driven pipelines can rapidly identify robust metabolomic biomarkers, predicting disease states, therapeutic responses, and prognosis with high accuracy. Despite these promising advances, the clinical translation of AI-based metabolomic biomarkers requires careful validation in diverse patient cohorts, alongside efforts to ensure the interpretability and reproducibility of findings. Continued interdisciplinary collaboration will be essential to harness the full potential of AI for metabolomics-guided precision oncology.[30]

CONCLUSION

In synthesizing the complex interplay between oncometabolites and cancer biology, this review presents a comprehensive and integrative perspective on both canonical metabolites like D2HG, succinate, fumarate, and lactate, as well as emerging candidates such as kynurenine and itaconate. It navigates through their intracellular mechanisms, ranging from epigenetic remodeling to redox imbalance, and equally emphasizes their extracellular roles in shaping the tumor microenvironment through immune suppression, pseudohypoxia, and matrix remodelling. The review distinctly foregrounds the translational implications of these findings by evaluating the therapeutic progress made with enzyme inhibitors, epigenetic modulators, and metabolite transport blockers, while also identifying the contextual challenges that hinder broad clinical applicability.

Importantly, this work highlights how recent technological advancements are redefining the investigative and diagnostic landscape. From spatial and single-cell metabolomics that resolve intra-tumoral heterogeneity to the integration of artificial intelligence for biomarker discovery, the review reflects a forward-looking stance that aligns with emerging paradigms in precision oncology. These advanced methodologies not only promise to refine the detection of metabolite signatures but also facilitate context-sensitive therapeutic stratification. Ultimately, the manuscript reinforces the notion that oncometabolites are not passive by-products of dysregulated metabolism but active oncogenic agents, demanding nuanced, multimodal, and personalized approaches to fully unlock their diagnostic and therapeutic potential.

Acknowledgements

The author gratefully acknowledges the mentorship of Dr. Naama Kanekar, Assistant Professor of Pathology, Harvard Medical School, MA, USA, whose profound expertise and insightful guidance were instrumental in shaping the scientific direction and analytical depth of this review.

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