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Targeting the Epigenetic-Metabolic Axis in the Tumor Microenvironment: How Oncometabolites Reprogram the Molecular Landscape of Cancer?

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Abstract

The traditional perspective views cancer as epigenetic disease. However, this review highlights the dynamic interplay between epigenetics and metabolism, where oncometabolites reshape the molecular architecture of the tumor microenvironment (TME). We explore how mutations in tricarboxylic acid (TCA) cycle enzymes (IDH, SDH, FH) or stress-induced metabolic reprogramming lead to the accumulation of metabolites such as D-2-hydroxyglutarate (D2HG), succinate, and fumarate. These oncometabolites act as competitive inhibitors of α-ketoglutarate–dependent dioxygenases, driving DNA hypermethylation, histone modifications, pseudohypoxia, and epitranscriptomic changes such as m6A methylation. Importantly, this crosstalk extends beyond cancer cells, reshaping immune function, promoting T-cell exhaustion via histone lactylation, and influencing ferroptosis. We also discuss emerging therapeutic strategies, including mutant IDH inhibitors, nanomedicine approaches, and AI-driven multi-omics, while acknowledging challenges posed by tumor heterogeneity and metabolic plasticity. Understanding the epigenetic–metabolic axis opens promising avenues for precision and translational oncology.

Keywords: Oncometabolites, TME, Oncology, Therapies, Ferroptosis, Nanotechnology, Tumor Heterogeneity

Introduction

From a decade, the central paradigm in oncology isolated from the genetic drivers of malignancy from the cellular metabolic adaptations. Cancer was primarily view as a disease of cumulative genetic mutations between oncogenes and tumor suppressor [1]. Continuously, these metabolic shifts observe in malignant cells with notably preference to aerobic glycolysis rather than oxidative phosphorylation, dismissed as secondary to passively downstream proliferative signaling' consequences [2]. Today, a paradigm shifts continuously progressing. Malignancy increasingly recognized globally as a unified, and dynamic "genomic-metabolic-epigenetic" ecosystem [3]. These fields entirely align the epigenetic-metabolic axis: bidirectionally network where communicate the metabolic state of a cell directly governs chromatin structure with reciprocal epigenetic reprogramming rewires cellular biochemistry [4].

This axis relies on biological reality fundamentally with almost all chromatin-modifying enzymes (i.e., DNMTs, HATs, and histone demethylases) utilize these core metabolites as an obligatory substrates or cofactors [4]. In the cellular metabolome, continuously fluctuations do not reflect energetic status merely; but also serve as primitive, highly sensitive sensory system that instruct the nucleus which networks to either active or silence [5]. Understanding this interaction is crucial for human health. Conventional chemotherapies and biologic-targeted frequently fail rapid resistance because they ignore the metabolic-epigenetic plasticity of TME [6]. While shifting the therapeutic framework focus toward this axis to move precision medicine beyond targeting single static mutations, allow clinicians to disrupt the self-reinforcing biochemical loops to sustain

tumor heterogenicity to drive clinical progression with revolution [7].

The Biochemical Foundation: Metabolic Rewiring and Oncometabolites

To understand how metabolism alters the genome then we must have to examine the alterations occurring within the mitochondrion of tumor cells. Initially, Otto Warburg hypothesized that aerobic glycolysis occurred in result of irreversible mitochondrial damage, but modern biochemistry indicates that tumor mitochondria remain highly active with serving a crucial biosynthetic and signaling hubs [8]. Under the influence of metabolic drivers (i.e., MYC and KRAS), TCA heavily rewired to meet the anabolic demands of rapidly dividing cells [9, 10]. The most dramatic appearance of this rewiring is “oncometabolites” generation; endogenous metabolic intermediates to accumulate pathologically high levels, because of specific enzymatic mutations with directly promote malignancy [11].

IDH1 & IDH2 Alterations: Evidence from Tumor Contexts

In healthy cells, IDH1 (Cytoplasmic), and IDH2 (Mitochondrial) catalyze the reversible oxidative decarboxylation of α-KG to generate NADPH through this process [12]. A functional understanding of IDH1/2 mutations mostly originates from glioma and ML models, where recurrent R132 and R140/R172 substitutions were linked to epigenetic remodeling [13]. In these systems, patient-derived tumor profiling indicated D2HG elevated levels, correlating with global hypermethylation phenotypes with cellular differentiation impairment [14, 15]. However, large cohort sequencing conducted studies report that canonical IDH mutations are rare in breast cancer [16]. While metabolic profiling of aggressive breast cancer unveiled that under hypoxic with nutrient-stressed state [17], where a convergent pattern of reduced α-KG availability. e.g. triple negative breast cancer lines exposed either to mitochondrial inhibitors or to hypoxia-derived, exhibiting transcriptional marks to resemble IDH mutant glioma epigenetics linked to differentiation with immune regulation at promotors [13].

Investigation using sing breast cancer models suggested that altering mitochondrial metabolism can modify α-KG availability with influencing TET-dependent demethylation pathways [3]. These observations suggested that the IDH paradigm shift may extend mutation beyond driven cancer types. But breast cancer may acquire temporarily IDH-like metabolic environment under environmental stress, influencing epigenetic stability without the requirements of genetic alterations [18]. This broadens the importance of oncometabolites biology clinically beyond tumors harboring alterations of classical IDH mutations.

SDH and FH dysfunctions: Lessons from Hereditary and Sporadic Tumors

In addition to neomorphic mutations, loss-of-function mutations in classical TCA cycle enzymes can trigger oncometabolite accumulation. Either homozygous or compound heterozygous inactivate the SDH (complex II of ETC), or FH leads to the accumulation massively of cellular succinate and fumarate, respectively [19]. Clinical syndrome as hereditary (paraganglioma) and FH deficient (cell carcinoma) provided beacon evidence that TCA enzymes disruptions can reshape nuclear transcriptional programs [20]. Tumor from these patients shows fumarate and succinate accumulation consistently with accompanying to α-KG-dependent dioxygenases to stabilize hypoxia inducible

pathways [21]. Fumarate or succinate accumulation linked to adaptation of oxidative stress, EMT with metastatic behavior enhancement [22]. Also, studies demonstrate that mitochondrial dysfunction may cooperate with oncogenic pathways, establishing permissive environment for tumor evolution with development [23]. Breast tumor biopsies' proteomic and metabolomic analysis have indicated metabolic rewiring characterized via glycolytic flux elevation and TCA-intermediates alteration [24]. These conditions recapitulated biochemical environment observed in SDH or FH deficient tumors partially.

Further support for this overlap succeeds with experimental models. Breast cancer cells point out mitochondrial chronic stress, developing invasive phenotypes with hypoxia-associated transcriptional programs to suggest that SDH- or FH-like signaling effects may integrate as a functional consequence of metabolic pressure than direct enzyme loss [25]. Such observations support the concept that TCA metabolism alterations, influencing tumor biology even when absent the classical SDH or FH mutations.

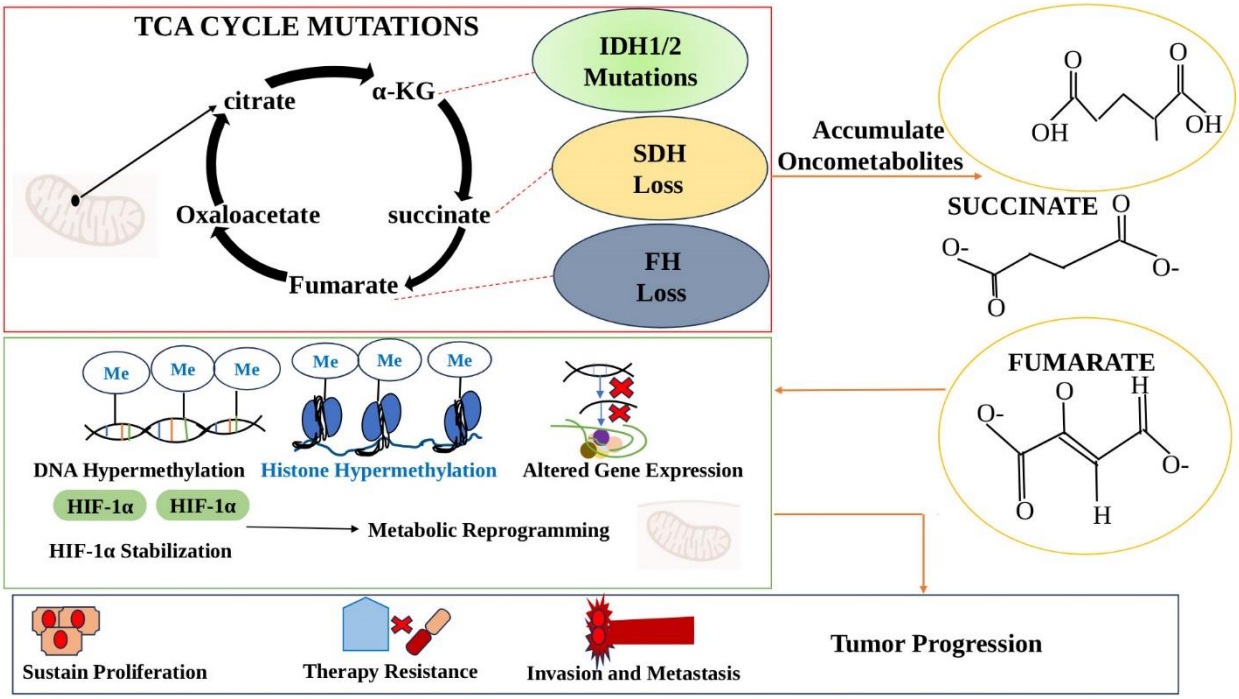

Figure 1: The schematic overview of the epigenetic-metabolic axis driven by TCA cycle dysfunctions in cancer. Mutations in IDH1/2 and SDH- or FH-loss result in the oncometabolites (D-2HG, succinate, and fumarate) accumulation; inhibiting α-KG-dependent dioxygenases and promote DNA and histone hypermethylation, HIF-1α stabilization, and aberrant gene expression. These molecular alterations induce metabolic reprogramming within TME to promote sustain proliferation, therapeutic resistance, invasion and metastasis: part of cancer progressions.

Epigenetic Reprogramming and Chromatin Remodeling

Within the nucleus, accumulation of mitochondrial oncometabolites has immediate and far-reaching consequences.

To maintain transcriptional homeostasis, so human genomes directly or indirectly rely on continuous, highly regulated enzymatic editing of DNA and histone tails [26]. Major superfamily of these editors consists of Fe^{2+}-dependent and α-KG-dependent dioxygenases. When the ratio of oncometabolites to α-KG strictly shifts in favor of former, profoundly these enzymes suffer competitive inhibition [27].

DNA Methylation Remodeling: Subtype Specific Evidence in Breast Cancer

Connection of metabolism with DNA methylation particularly became evidence from studies on IDH mutant gliomas, where D2HG accumulation was shown inducing a CIMP [28] while, studies on breast cancer unveiled a more heterogenous with subtype-dependent landscape. Analysis of genome-wide methylation of triple negative breast tumors indicates widespread promoter methylation, affecting genes that involved in epithelial differentiation and immune signaling [29]. In contrast, luminal subtypes show more stable methylation patterns, often hormone receptor regulation-associated as compare to global epigenetic instability.

Metabolomic correlations showed that methylation differences are not purely genetic. Higher glycolytic activity and reduced mitochondrial respiration with breast tumors, exhibiting stronger epigenetic drift to support the idea that metabolic stress can shape DNA methylation landscapes indirectly, even absence of canonical oncometabolites mutation [30].

Histone Modification Dynamics: Insights from Aggressive Breast Tumors

In cancer epigenetics, early mechanistic studies established that histone demethylases belonging to the JmjC domain family are sensitive to metabolic cofactors [31]. Particular-breast cancer investigations have added crucial character to this model. From high grade breast tumors clinical datasets, showing consistent EZH2 overexpression especially in metastatic and treatment-resistant diseases [32]. Using patient-derived xenografts for functional studies representing EZH2-mediated-H3K27m3 contributed to repression of differentiated-associated-genes to reinforce a stem-like transcriptional condition.

With interest, metabolic interventions that altering acetyl-CoA and α-KG modulation have shown to reverse partially these histone signatures in experimental breast cancer models [33]. While suggesting chromatin state is dynamically linked to metabolic states excepts fixed within the TME.

Pseudohypoxia via HIF-1α Stabilization

The concept of pseudohypoxia was first described in tumors with SDH or FH loss where succinate-mediated inhibition of PHDs, leading to inducible-factor-1α stabilization [34]. HIF-1α activation drives angionesis with metabolic adaptation even normoxic states in the tumors [35]. HIF-1α is an oxygen sensitive subunit. Directly behind the chromatin alterations, α-KG-dependent dioxygenases disruption triggers a condition called pseudohypoxia. In an environment where oxygen is rich, PHDs (an α-KG-dependent), and hydroxylate is the oxygen-sensitive transcription factor (HIF-1α), targeting it for ubiquitination and spontaneous proteasomal degradation. When ameliorations of either succinate or fumarate, then HIF-1α escape from degradation, because it stabilizes and translocate into the nucleus under normoxic states, to activate major transcriptional factors to drive angiogenesis to bring metabolic shifts toward glycolysis [34]. Similar, HIF-1α activation patterns are progressively observed across tumor regions within breast

cancer. Triple negative tumors unveiled HIF-1α in necrotic and hypoxic areas via histological analysis, correlating with ameliorated metastatic potential and poor prognosis [36].

Further, functional studies show that hypoxia stabilized transcriptional programs cooperating with epigenetic regulators to harmonize CSCs populations [37]. This suggests that pseudohypoxic signaling in breast cancer is not only a metabolic response but also a vast part of adaptive transcriptional network.

Oncometabolites generated by mutations in TCA enzymes to establish direct links between cellular metabolism and epigenetic dysregulation in cancer mechanistically. Accumulation of D-2-HG, resulting from gain-of-functions mutations in IDH1/2 inhibits α-KG-dependent dioxygenases (TET DNA demethylases, JmjC histone demethylases) [38]. This inhibition promotes the CIMP, H3K9 and H3K27 hypermethylation, and cellular differentiation blockade, features commonly come to observe in gliomas and AML [39].

Loss-of-function mutations in SDH and FH similarly lead to synthesize succinate and fumarate; both metabolites act as inhibitors of PHDs and TET enzymes, resultingly HIF-1α stabilization, and under normoxia [40]. In paragangliomas and pheochromocytomas, SDH loss drives HIF-1α- angiogenesis and metabolic reprogramming [41]. Meanwhile, FH deficiency in renal cell carcinoma and uterine leiomyomas-induces activate Nrf2 pathway and chromatin remodeling, to negotiate oxidative stress resistance and proliferative advantage [42].

Collectively, these findings align between metabolic-epigenetic crosstalk, where alterations in intermediary metabolism translated into stable changes in gene expression and chromatin architecture. Oncometabolite convergence on α-KG-dependent enzymes suggest to target mutant enzymes, restore α-KG availability, or blocking downstream epigenetic effectors reverse differentiation block and suppress tumor progression [43]. Understanding of these pathways is crucial to provide a rationale for developing metabolically-targeted-epigenetic-therapies in malignancies driven by metabolic mutations.

RNA Epigenetics and Epitranscriptomic Landscape in Cancer

Tumor metabolism is not only limited to DNA methylation and histone modifications, but also plays role to reshapes RNA biology with the help of epitranscriptomic regulation [44]. Progressively emerging evidence indicates that the metabolites influence RNA methylations marks, with particularly m6A, regulating RNA translation, stability, splicing, and degradation dynamically [45]. Various m6A regulators (i.e., METTL3, METTL14, FTO, ALKBH5) sensitive metabolically due the requirements of cofactors either for SAM or α-KG as cofactors [46]. Tumor cells exhibit ameliorated ALKBH5 expression via HIF-1α activation during hypoxic and nutrient-deprived state, resultantly stabilization of stemness-associated transcript as NANOG and SOX2 [47]. Similarly, fumarate and succinate accumulation cause suppression of α-KG-dependent-RNA demethylase, while leading oncogenic m6A patterns [48]. This epitranscriptomic dysregulation solely contributes to therapeutic resistance with EMT and metastatic dissemination.

Additionally, recent studies indicate that lactate accumulation influences on RNA-binding-proteins and non-coding-RNA-processing, while making connection of glycolytic metabolism with post-transcriptional regulation [49]. Collaboratively collection of the controlled epitranscriptome metabolically showing

regulatory layer extra via which tumor cells adopt to environmental stress rapidly.

Oncometabolite	Primary Mutant Enzyme Source	Enzymatic Target	Molecular Consequences	Clinical Presentation	References
D-2-HG	Mutant IDH-1/2	TET1/2, JmjC demethylases	CIMP phenotype, H3K9/27 hypermethylation, Differentiation inhibits	Gliomas, AML	[38, 39]
Succinate	SDH function-loss	TET enzymes, PHDs	HIF-1α stabilization via pseudohypoxia, tumor suppressor silencing	Paragangliomas, pheochrocytomas	[40, 41]
Fumarate	FH function-loss	TET enzymes, PHDs, Keap 1	Pseudohypoxia, Nrf2 pathway activation, chromatin remodeling	RCC, uterine leiomyomas	[43]

Table 1: **Oncometabolites, enzymatic targets, and epigenetic-phenotypic consequences in cancer*:*** It summarizes mutations in TCA cycle enzymes produce oncometabolites as D-2-HG, succinate, and fumarate to inhibit α-KG-dependent dioxygenases to lead epigenetic dysregulation, pseudohypoxia, and tumor cancer progression in cancers (i.e., glioma, AML, paraganglioma, renal cell carcinoma, and uterine leiomyomas.

m61-Dependent Cancer Stem Cells Plasticity

profoundly, cancer stem-like cells display metabolic flexibility while heavily dependent on m6A remodeling to preserve capacity of self-renewal capacity [50]. The amelioration of fatty acid oxidation and glutamine metabolism ameliorate intracellular SAM availability, while aberrant RNA methylation marks promotions. METTL3-mediated-m6A depositions the stabilizes transcript-associated-stemness signaling pathways (i.e., Wnt/β-catenin, Notch, PI3K/AKT) [51].

Crucially, m6A regulators inhibitions therapeutically has shown the ability to reduce tumor sphere formation with restoring chemotherapy sensitivity in preclinical cancer models [52]. The intersection of metabolism with RNA epigenetics suggests that we can solely apply epitrancriptomic enzymes as viable therapeutic targets in future oncology workflows.

Chromatin Accessibility and 3D Genome Reorganization

Recently advancement in Hi-C and ATAC-seq (Chromatin conformation mapping technologies) uncovered the histone marks but also high-order genome architecture [53]. Oncometabolites directly or indirectly influences via chromatin remodeling complexes modulation for TADs, enhancer-promoting loops, and chromatin accessibility [54]. Under nutrient-rich conditions, acetyl-CoA accumulation promotes histone acetylation and enhancer activation at the position of oncogenic loci (MYC, CCND1) [55]. Additionally, inhibition of chromatin remodelers

(SWI/SNF) through fumarate mediated, contributing epigenetic rigidity with lineage plasticity [55]. As increasingly recognized 3D genome reorganization as a crucial mechanism where tumor metabolism governs metastatic competence with therapy resistance [56].

Super-Enhancers and Metabolic-Dependency

To maintain oncogenic master regulators, aggressive tumors solely rely on sustained super-enhancer [57]. Generating acetyl-CoA with the help of ACLY and fatty acid metabolism fuels (H3K27) acetylation at super-enhancer regions [58]. This process deeply expands transcriptional addiction towards MYC, ESR1, HER2 signaling pathways. Targeting acetyl-CoA production by metabolic enzymes has indicated to collapse the super-enhancer activity, effectively suppressing transcriptional amplification in therapy-resistant tumors [58].

TME and Immuno-Evasion

Epigenetic-metabolic axis extend consequently far beyond the intrinsic boundaries of individual cancer cell. TME is a competitive and highly complex populated by stromal fibroblasts, infiltrating immune cells, and epithelial cells [59]. When cancer cells undergo metabolic reprogramming, actively they refine both (physical and biochemical) characteristics of this extracellular landscape to harmonize the host immune response [60].

Metabolic Competition and Nutrient Deprivation

To sustain high proliferation rates and fuels spontaneous growth, cancer cells strip the extracellular space of crucial nutrients to cause secondary epigenetic remodeling in neighboring cells [59]. Because consume vast quantity of glutamine and glucose, leaving infiltrating CTLs and NK cells fuel's starved necessity for cytokines synthesis and surveillance performance [60]. Additionally, rapidly upregulation of enzymes (i.e., IDO) degrades tryptophan-kynurenine, to deprive amino acids' immune cells necessity for survival.

Paracrine Epigenetic Rewiring of Immune Cells

Oncometabolites are not confined in the cancer cells. Malignant cells secrete high levels of 2-HG actively and lactate into the ECM via specialized monocarboxylate transporters. Take up these extracellular metabolites by infiltrating immune cells, disrupt by their own enzymatic machineries [61, 62]. i.e., when $CD8^+$ T-cells absorb extracellular 2-HG then inhibits their internal TET enzymes to lead an abnormal DNA methylation pattern, suppress key effector molecule's transcription as IFN-γ and Granzyme B [63]. Around the tumor, paracrine signaling makes protective cover, chemically translating adjacent non-functional immune cells before they can cytotoxic attack completion [61, 62]. Recent evidences demonstrate that oncometabolites are not restricted to malignancy cells with reshaping the surrounding microenvironment. Exporting oncometabolites (D2HG, lactate) by cancer cells to extracellular space, absorbing subsequently to infiltrate immune cells [61, 62]. Once reached to internalized then these metabolites initiate to interfere with epigenetic regulators (TET enzymes), resultantly DNA methylation patterns alterations with repression of transcription in key effector molecules. Subsequently, exhibition of cytotoxic T lymphocytes causes the production reduction of INF-γ and granzyme B [63].

Metabolic communications between cancer cells and immune cell populations demonstrated by recent investigation are

more complex than appreciated previously. While collectively lactate, extracellular vesicles, and metabolite-derived signaling molecules influence chromatin accessibility within macrophages and infiltrating lymphocytes. Thes alterations promote immune dysfunction, suppressing antigen presence pathways with reducing cytotoxic activity within breast cancer. This leading immunosuppressive ME favors tumor persistence with efficacy of ICIs limitations [63].

This metabolic communication progressively establishes an immunosuppressive niche, favoring persistence with progression of tumor. These interactions must have to understand for revealing novel opportunities to restore anti-tumor immunity through metabolic intervention [64].

Histone Lactylation and T-Cell Exhaustion

Highly sophisticated mechanism linking metabolism with immune invasions directly involves accumulation of final product of Warburg effect is lactate [65]. Combined study (molecular and structural biology) indicates that intracellular lactate accumulation function as a precursor of post-translational novelty modification known as histone lactylation (position: H3K18la particularly) [66]. Histone lactylation directly remodels chromatin insides TAMs and T-cells [67], driven by high levels of lactate in TME. In macrophages, histone lactylation triggers a transition away from anti-tumor (M1 phenotype) towards immunosuppressive, pro-tumor (M2 phenotype) [67]. Integration of histone acetylation recently as a novel epigenetic mechanism, creating paradigm shift with cancer metabolism alterations to dysfunction of immune [66]. Generation of the production of lactate excessively through aerobic glycolysis accumulate within TME to serve as a substrate for histone lactylation [65]. With influencing gene expression programs in both (macrophages, T lymphocytes) due to this modification cause alteration in chromatin organization [67]. Lactate concentrations elevation is recognized increasingly as a drivers of macrophage polarization with immune suppression within breast cancer [67]. Experimental studies suggested that gene expression programs of lactylation-dependent promote tissue reprogramming, chronic inflammatory response, and angiogenesis, favoring tumor growth.

In T-cells, chronic exposures to lactate-rich-environment (acidic) drives persistently histone lactylation patterns to stimulate inhibitory receptors (e.g. PD-1, CTLA-4, TIM-3) expression [67]. This locks the immune cells into terminal T-cell exhaustion condition, allows tumor to leave clearance of immune entirely. Contributions to T-cell exhaustion with favoring immune invasion via tumor collectively linked to these changes. Due to common feature of highly glycolytic tumors is accumulation of lactate, to target either lactate production or lactylation-associated pathways may provide an attractive with responsive novel therapeutic strategy to overcoming immune resistance [67].

Ferroptosis and Lipid-Peroxidation in the Metabolic-Epigenetic Axis

Emergingly highly crucial iron-dependent regulated cell death form by catastrophic lipid peroxidation called ferroptosis [68]. Oncometabolites, epigenetic remodeling, and lipid metabolism indicates increasingly ferroptotic sensitivity determination within the TME [69]. While altering ferroptotic thresholds and redox rheostat, fumarate-accumulation can induce GSH-related protein through covalent modifications [70]. Epigenetically, both histone (methylation and acetylation) regulates ferroptotic-

associated genes expression as SLC7A11, ACSL4, and GPX4 [68]. In addition, lactate-rich microenvironments suppress ferroptosis in TAMs and cytotoxic T-cells, contributing to immunosuppressive niche preservation [69].

Synergy of Ferroptosis-Immunotherapy

Recently conducted translational studies suggested that immune checkpoint blockade ameliorates ferroptosis by CD8+ T-cell-derived IF-γ, suppressing uptake of cysteine in tumor cells [68]. While spontaneously, releasing lipid-mediators have capability to remodeling immune cell recruitment through ferroptotic cancer cells. Synergically emerged strategies as ferroptosis inducers with therapies as anti-PD-1 or anti-CTLA-4 are currently explored to overcome immunotherapy resistance [68]. The metabolic-epigenetic ferroptosis regulation presents a promising with novel therapeutic frontiers in oncology (cancer biology).

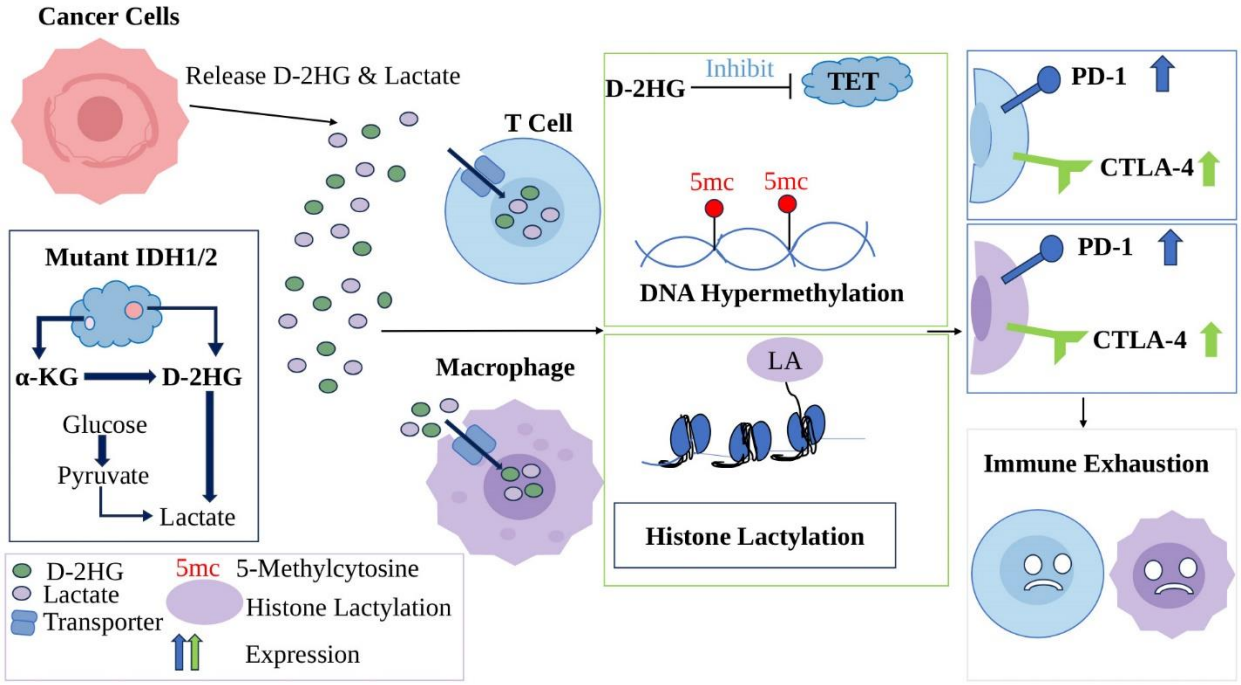

Figure 2: The mechanisms by which cancer-derived oncometabolites establishes an immunosuppressive TME. Mutant IDH1/2 and ameliorated glycolysis promote the production and extracellular release of D-HG and fumarate, taken up by infiltrating T cells and macrophages. Intracellular D-2HG inhibits TET DNA demethylases (DNA hypermethylation); while lactate promotes histone lactylation, leading to epigenetic reprogramming of immune cells. These alterations ameliorate the inhibitory immune checkpoint molecules expression (PD1 and CTLA4) to drive immune cell dysfunction and T cell exhaustion facilitate to tumor immune evasion.

Tumor Microbiome and Metabolite-Driven Epigenetic Crosstalk

Emerged intratumoral microbiome as an influential part of the TME [71]. Microbial-derived metabolites (i.e., SCFAs, tryptophan catabolites, and secondary bile acids) influence host immune responses with chromatin remodeling directly. A microbial SCFA (butyrate) act as HDACi and can harmonize apoptosis, immune activation, and differentiation [71]. Additionally,

dysbiosis-associated metabolites influence on both (estrogen metabolism and inflammatory signaling pathways) relevant with many cancers types tumorigenesis. While altering systemic availability, shaping responsiveness to chemotherapy and immune checkpoint blockade [71]. Therefore, tumor-microbiome interactions introduce as an additional regulatory framework in epigenetic-metabolic axis.

Translational Oncology (Diagnostic and Therapeutic Horizons)

Epigenetic-metabolic discovery has been extending to open new frontiers strategy in translational oncology to paradigm shift from a vulnerability to block tumors with a targeted-drugs and other therapeutic intervention made possible by efforts of scientists and researchers.

Translational Area	Application	Target	Example (Clinical Relevance)	References
Biomarkers & Liquid Biopsies	Oncometabolites used a diagnostic/prognostic marker	D2HG, succinate, fumarate secretion into blood, urine, CSF	LC-MS or MRS used to detect early relapse, therapy response, drug resistance monitoring	[72, 73]
Targeted Pharmacological Therapies	Small-molecule inhibitors of mutant enzymes	AG-120 (Ivosidenib) → IDH1 mutant; AG-221 (Enasidenib) → IDH2 mutant	Queue D2HG production, restore TET/ JmjC activity; reverse aberrant methylation; promote differentiation over cytotoxicity	[74-76]
Differentiation Therapy	Oncometabolites deprivation	Low D2HG restores TET/ JmjC demethylases activity	Chromatin uncoil, released differentiation blocks, targeted approaches with less systemic toxicity vs conventional chemotherapy	[74-76]
Multi-omics & Precision Oncology	Single-cell + spatial omics integration	ATAC-seq, metabolic mapping, and chromatin accessibility	Metabolic niches identification, hypoxic gradients, therapy-resistant subclones; personalize therapies	[77, 78]
AI-Driven Drug Discovery	Machine learning on multi-omics datasets	Metabolic vulnerabilities prediction; biomarkers identification	Accelerate transition-individualized precision cancer medicine; predict patient response to metabolic and immunotherapy	[79, 80]

			inhibitors	
CRISPR-Based Epigenome Editing	dcas9 fused to HATs / demethylases	Locus-specific chromatin remodeling at glycolysis/ lipid metabolism genes	Reverse oncometabolite-induced epigenetic abnormalities; reactive TSGs; enhance CI responsiveness	[81, 82]
Nanomedicine Delivery	pH-responsive nanomaterials/ nanoparticles	TME targeting	Reduced systemic toxicity of metabolic inhibitors; improve tumor-specific delivery	[83]

Table 2: Translational Implications of Epigenetic-Metabolic Axis in Oncology: It summarizes the current pre-clinical and clinical strategies targeting metabolic-epigenetic interfere in cancer therapy. Key areas are liquid biopsy biomarkers, mutant IDHis, differentiation therapy, multi-omics integration, AI-driven drug discovery, CRISPR-based epigenome editing, and nanomedicine delivery.

Biomarkers Discovery and Liquid Biopsies

Because oncometabolites are chemically stable with actively secreted, functions as highly particular both diagnostic and prognostic biomarkers [72] in tumor cells; as their accumulation aberrantly reflects oncogenic mutations with disease progression and therapeutic response correlatedly. Clinicians can utilize either high resolution LC-MS or MRS to detect non-invasively circulation of 2-HG levels in blood, urine, tumor tissue, or cerebrospinal fluid [72]. Longitudinal oncometabolites levels monitoring may favor early to relapse detection, therapeutic response evaluation, and emerging drug-resistance identification. While tracking these metabolic footprints make it possible for monitoring of real-time tumor burden, clonal evolution, and early therapeutic resistance before changing in the structure early on traditional appearance on CT or MRI scans. These approaches represent a promising cornerstone of precision oncology [73].

Novel Pharmacological Strategies

To target epigenetic dysregulation's metabolic origins integrated as therapeutic innovation strategy in oncology [73]. Small-molecules inhibitors have been widely used to target selectively neomorphic metabolic enzymes therapeutically with prominent considerable examples are AG-120 (Ivosidenib), AG-221 (Enasidenib), respectively targeting IDH1 and IDH2 [74, 75]. These drugs to bind directly with mutant enzymes to halt D-2-HG production. Normal intracellular harmonization restoration grants TET reactivation and JmjC demethylases, reversing berrant methylation patterns and restoring typical chromatin architecture [76]. Significantly, low-level of intracellular 2-HG restores the normal activity of TET and JmjC demethylases. Oncometabolites deprivation causes compaction of chromatin uncoils tightly to release the differentiation blocks. These agents promote crucially malignant cells differentiation rather inducing toxicity directly to offer more targeted approach with less systemic site effect [74, 75]. As conventional chemotherapy caused a cytotoxicity widespread, but these agents

enforcedly malignant blats to mature into functional with non-dividing differentiated blood cells [74, 75]. Progressively ongoing research is solely exploring metabolic inhibitors combined with cancer immunotherapy and epigenetic drugs, enhancing clinical outcomes [73].

Single-Cell-Multi-Omics and Spatial Transcriptomics

Many contemporary strategies as bulk sequencing failed to capture heterogeneity in many cancers' types TME as breast cancer. Recently, integrating single-cell-multi-omics with spatial transcriptomics and metabolomics, profiling of chromatin accessibility with spatial imaging [77, 78]. Spatial transcriptomics makes it possible to visualize hypoxic niches, metabolic gradients with immune suppression marks due to spatial transcriptomics within entire tumor architecture. Metabolic adaptations occur among cancer cells and stromal cells heterogeneously than uniformly tumor mass thoroughly uncovered by these technologies; these findings are crucially providing novel strategies to develop personalized therapies [77, 78].

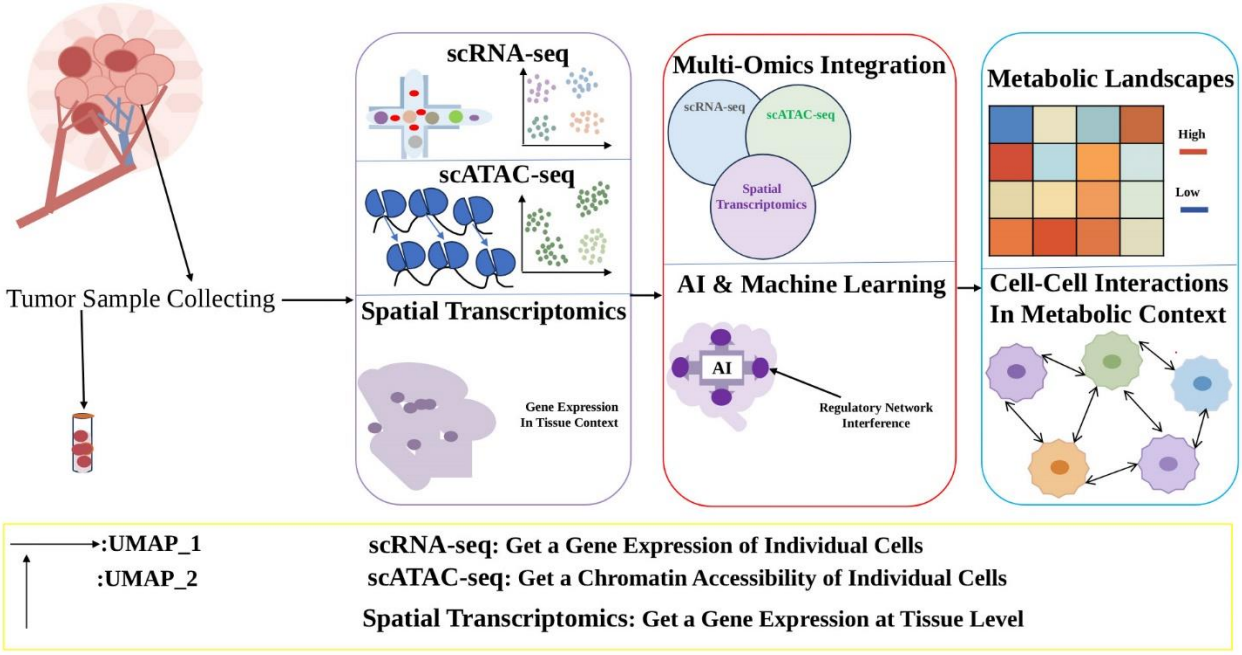

Figure 3: The workflow illustrates the integration of single cell and spatial multiomics for decoding metabolic heterogeneity within TME. Tumor samples analyze through scRNA-seq, scATAC-seq, and spatial transcriptomics to characterize cell specific expression, chromatin accessibility, and tissue specific expression and tissue spatial organization. These complementary datasets are integrated through AI and machine learning to reconstruct regulatory networks, identify metabolic landscapes, and resolve cell-cell interactions underlying tumor progression. Also, this framework advances the foundations to discover patient-specific metabolic vulnerabilities with advancing precision oncology.

AI in Multi-Omics Oncology

AI and machine learnings platforms are massively employed to evaluate the multi-omics datasets from epigenetics, imaging studies, and metabolomics [79]. Usage of predictive algorithms for novel metabolic

vulnerabilities, therapies-resistant subclones, and biomarkers marks identification with precision as compare to conventional statistical models [80]. Additionally, these approaches facilitate for the prediction of patient responsiveness to metabolic and immunotherapy inhibitors [79]. AI-driven analytics with profiling of multi-omics may enhance the paradigm shift with accelerate transition towards truly individualized precision cancer medicine [80].

CRISPR-Based Epigenome Engineering and Metabolic Editing

CRISPR technologies are not limited to genome editing only, but progressively applicable in programmable epigenetic and metabolic engineering [81, 82]. Fused inactive dCas9 with HATs, methyltransferases, and demethylases inactively, enabling locus-particular chromatin remodeling with no DNA sequence alterations. Similarly, CRISPR-based metabolic editing grant permission to target enzymes that particularly involved in glycolysis, lipid metabolism, and glutaminolysis [81, 82]. This provides opportunities to reverse oncometabolite-induced epigenetic abnormalities, minimizing the systemic (blood) toxicity. Integrated studies suggested that CRISPR-mediated silence TSGs reactivation can restore immune recognition with enhancing responsiveness to CIs [81, 82]. Ultimately, these programmable systems may possibly with enabling personalized metabolic-epigenetic dysregulation correctly.

Nanomedicine with Targeted Metabolic Delivery Systems

One of the notable issues in metabolic therapy is systemic toxicity due to metabolic pathways are crucial for normal tissues function. To improve the efficacy of tumor-specific targeting, being developed nanobiotechnology-based delivery systems [83]. Exosomes, lipid nanoparticles, biometric vesicles, and nanocarriers can deliver selectively IDHis, siRNAs, CRISPR, or epigenetic drug into tumor tissues. Particularly, pH-sensitive nanoparticles are very attractive due to acidic TMEs selectively trigger drug release [83]. Such theranostic (therapy + diagnostic) may improve substantially precision oncology applications [83].

Circadian Metabolism and Chrono-Oncology

Profoundly disruptions in circadian rhythm alters cancer metabolism, chromatin organization, and immune surveillance [84, 85]. Sole circadian regulators are CLOCK, PER, BMAL1, and CRY proteins closely interact with metabolic enzymes and modifiers of histones. Dynamically, oscillations in NAD+, acetyl-CoA, and ROS shape chromatin accessibility throught the day [84, 85]. Frequently tumor cells exploit circadian dysregulation, optimizing utilization of nutrient with evasion of apoptosis. Strategically, chronotherapy-based on circadian metabolic timing are now being efficacy maximization of chemotherapy, immunotherapy, metabolic inhibitors to reduce patient toxicity [84, 85]. Emerging of chrono-oncology may clinically provide extension related to epigenetic-metabolic axis.

Extracellular Vesicles and Metabolite Communication

Exosomes (extracellular vesicles) crucially serve as mediators between epigenetic and metabolic communication in tumor cells and stromal components [86]. Transporting metabolites, miRNAs, proteins, and chromatin-modifying enzymes have capability to reprogram recipient cells. To promote angiogenesis with metastasis niche formation [86]. i.e., breast cancer-derived exosomes to transfer lactate-associated

markers with immunosuppressive molecules into fibroblasts, macrophages, and ECs [86]. Additionally, exosomes miRNAs actively regulate crucial components require for distant tissues as glycolysis, mitochondrial activity, and epigenetic enzymes. Increasing progressively investigated on extracellular vesicles due to detectable in circulation with minimally invasive biomarkers and therapeutics vehicles [86].

Discussion and Future Directions

Our exploration of epigenetic-metabolic axis unveiled a far more integrated and plastic cancer biology as compared to previously appreciated. What has started with Warburg's observations to now blossom into a recognition that metabolism is not only a passive consequences of proliferation but also an active instructor of the genome [38, 55]. Discovery of oncometabolites as D2HG from mutant IDH, providing mechanistic links as D2HG resulting from gain-of-functions in IDH1/2 inhibits α-KG-dependent dioxygenases (TET DNA demethylases, JmjC histone demethylases) [38, 39]. As seen in aggressive cancers where environmental stress-like hypoxia, creating similar functionally "IDH-like" state; reducing α-KG-dependent dioxygenases. Loss-of-functions mutations in SDH, FH lead succinate and fumarate accumulation; both metabolites work as PHDs, TET enzymes inhibitors, driving histone modifications, DNA hypermethylation, and pseudohypoxia [40-42].

This crosstalk extends beyond cancer cells-reshape immune function with promote T-cell exhaustion through histone lactylation, as intracellular lactate accumulation act as precursor of histone lactylation at H3K18la. Epigenetic-metabolic reprogramming influences ferroptosis sensitivity with therapeutic resistance [49, 51, 66]. We discuss emerging therapeutics opportunities, targeting metabolic-epigenetic vulnerabilities, enlisting IDHis, and epigenome editing strategies [38, 74, 75].

Looking forward, real challenge is figuring out that how to hit the epigenetic-metabolic axis where mostly it hurts-inside the TME. Oncometabolites (D2HG, succinate, fumarate, and lactate) basically hijack cancer cell's control system, prepare future drugs accordingly to block them and let enzymes (TET/ JmjC) work normal again. We will also need to integrate single-cell and AI tools to map and monitor which tumor cells using which metabolic strategies to hide from therapies. Big hope is emerging inhibitors-immunotherapy-epigenome editing to turn "cold" tumors into ones actually that one's respond to treatment.

Conclusions

This review has explored how the epigenetic-metabolic axis is unified and targetable ecosystem. We have moved from seeing metabolites as fuel to signaling molecules that shape chromatin landscape. The raising challenge is to translate this complex bidirectional crosstalk into rational synergy therapies and dynamic biomarkers to anticipate tumor plasticity except defeated by it.

Abbreviations

α-KG: Alpha-Ketoglutarate, **TET:** Ten-Eleven Translocation, **JmjC:** JumonjiC, **TME:** Tumor Microenvironment, **DNMTs:** DNA Methyltransferases, **HATs:** Histone Acetyltransferases, **MYC:** Mylocytomatosis Oncogene, **KRAS:** Kirsten Rat Sarcoma Viral Oncogene Homologue, **TCA:** Tricarboxylic Acid, **IDH:** Isocitrate Dehydrogenase , **D-2-HG:** D-2-Hydroxyglutarate, **AML:** Acute Myeloid

Leukemia, **SDH:** Succinate Dehydrogenase, **FH:** Fumarate Hydratase, **FDH:** Fumarate Dehydrogenase, **ETC:** Electron Transport Chain, **Fe^{2+}:** Iron, **CIMP:** CpG Island Methylator Phenotype, **O_2:** Oxygen, **p16INK4A:** p16 Inhibitor of Cyclin-Dependent Kinase 4A, **BRCA1:** Breast Cancer Gene 1, **H3K9me3:** Histone H3 Lysine 9 Tri-Methylation, **H3K27me3:** Histone H3 Lysine 27 Tri-Methylation, **RCC:** Renal Cell Carcinoma **HIF:** Hypoxia-Inducible Factor, **PHDs:** Prolyl Hydroxylases, **EMT:** Epithelial-to-Mesenchymal Transition, **CTLs:** Cytokine T Lymphocytes, **NK:** Natural Killer, **IDO:** Indoleamine 2,3-Dioxygenase, **ECM:** Extracellular Matrix, **SCFAs:** Short-Chain Fatty Acids **TAMs:** Tumor-Associated Macrophages, **PD-1:** Programmed Death-1, **CTLA-4:** Cytotoxin T-Lymphocyte Associated Protein 4, **TIM-3:** T-Cell Immunoglobin and Mucin-Domain Containing Protein 3, **LC-MS:** Liquid Chromatography-Mass Spectrophotometry, **MRS:** Magnetic Resonance Spectroscopy, **CT:** Computed Tomography, **MRI:** Magnetic Resonance Imaging, **m6A:** N6-Methyladenosine, **METTL3:** Methyltransferase Like 3**,** **METTL14**: Methyltransferase Like 14, **FTO:** Fat Mass and Obesity-Associated Protein, **ALKBH5:** ALKB Homolog 5, **NANOG:** Nanog Homeobox, **SOX2:** SRY-Box Transcription Factor 2, **Wnt/β-catenin:** Wingless-Related Integration Site/ Beta Catenin, **Notch:** Neurogenic Locus Notch Homolog Protein, **PI3K/AKT:** Phosphoinositide 3-Kinase/Protein Kinase B, **TSGs:** Tumor Suppressor Genes, **CIs:** Checkpoint Inhibitors, **miRNAs:** Micro-Ribonucleotide Acid, **ECs:** Endothelial Cells, **CSCs:** Cancer Stem Cells, **ME:** Microenvironment

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