

Epigenetic Regulation of Cancer Metabolism: Emerging Biochemical Mechanisms and Therapeutic Opportunities

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Abstract: Cancer is increasingly understood as a disease of both genetic and epigenetic dysregulation, with metabolic reprogramming serving as a central driving force that

reshapes the epigenome. The bidirectional crosstalk between metabolic intermediates and chromatin-modifying enzymes represents a fundamental mechanism underlying tumour initiation, progression, and therapeutic resistance.

This review systematically examines the biochemical mechanisms linking cellular metabolism to epigenetic regulation in cancer, with an emphasis on clinically actionable pathways and emerging therapeutic strategies.

A comprehensive narrative review of primary literature and clinical trial data published between 2020 and 2025 was conducted. Studies focusing on DNA methylation, histone modifications, RNA epitranscriptomics, oncometabolite biology, and epigenetic drug development in the context of cancer metabolism were included.

Key metabolites including acetyl-CoA, S-adenosylmethionine (SAM), α -ketoglutarate (α -KG), succinate, fumarate, and 2-hydroxyglutarate (2-HG) are shown to directly regulate epigenetic enzyme activity, chromatin architecture, and gene expression programmes. Oncometabolites produced by mutant isocitrate dehydrogenase (IDH1/2), succinate dehydrogenase (SDH), and fumarate hydratase (FH) competitively inhibit α -KG-dependent dioxygenases, inducing hypermethylator phenotypes.

Furthermore, N6-methyladenosine (m6A) RNA modification emerges as an integrator of metabolic and epitranscriptomic signals. The therapeutic landscape includes FDA-approved agents targeting DNMTs, HDACs, EZH2, and mutant IDH, alongside a rich pipeline of ACLY, ACSS2, BET bromodomain, and METTL3 inhibitors. Rational combination strategies exploiting epigenetic-metabolic vulnerabilities represent the frontier of precision oncology.

Keywords: *epigenetics; cancer metabolism; DNA methylation; histone modification; oncometabolite; IDH mutation; m6A; HDAC inhibitor; EZH2; therapeutic targeting.*

Introduction

Cancer is a multifactorial disease characterised by the progressive accumulation of genetic alterations and epigenetic modifications that collectively undermine normal cellular homeostasis. Over the past two decades, it has become irrefutably clear that epigenetic dysregulation is not merely a downstream consequence of malignant transformation, but

rather an active and reversible driver of tumourigenesis, metastatic progression, and resistance to therapy.[1] Unlike genetic mutations, epigenetic alterations are dynamic and potentially reversible, positioning the epigenetic machinery as an exceptionally attractive therapeutic target.[2]

Simultaneously, the metabolic reprogramming of cancer cells, most classically exemplified by the Warburg effect, wherein cells preferentially utilise aerobic glycolysis despite oxygen availability, is now recognised as a defining hallmark of cancer.[3] Crucially, the products and intermediates of these altered metabolic pathways do not function in isolation; they serve as obligate substrates, cofactors, and allosteric regulators for the enzymes that catalyse virtually all known epigenetic modifications.[4] This intimate biochemical interdependence creates a bidirectional feedback loop: the metabolic state of the cell shapes its epigenome, which in turn regulates the transcription of metabolic enzymes, perpetuating tumour-promoting programmes.[5]

The discovery of oncometabolites, metabolic intermediates that accumulate due to neomorphic enzyme mutations and directly perturb epigenetic regulation, has been particularly transformative.[6] Somatic mutations in isocitrate dehydrogenase 1 and 2 (IDH1/2) genes, for instance, result in the aberrant production of D-2-hydroxyglutarate (2-HG), which competitively inhibits a broad range of α -ketoglutarate (α -KG)-dependent dioxygenases, leading to profound global DNA and histone hypermethylation.[7] Similarly, loss-of-function mutations in succinate dehydrogenase (SDH) and fumarate hydratase (FH) cause the accumulation of succinate and fumarate, respectively, producing analogous epigenetic consequences.[8]

Beyond the classical oncometabolite paradigm, the recent characterisation of epitranscriptomic modifications, particularly N6-methyladenosine (m6A) of messenger RNA, has expanded our understanding of how metabolic sensing is integrated at the level of RNA processing and translation.[9] The methyl donor for m6A modification, S-adenosylmethionine (SAM), is itself a central node of one-carbon metabolism, linking nutrient availability to the regulation of transcriptomic landscapes in cancer.[10]

This review provides a comprehensive and current synthesis of the biochemical mechanisms through which metabolic reprogramming shapes cancer epigenetics, focusing

on DNA methylation, histone modifications, oncometabolite biology, and RNA epitranscriptomics. We further evaluate the therapeutic landscape emerging from these discoveries, encompassing approved epigenetic agents and a promising pipeline of novel compounds targeting metabolic-epigenetic vulnerabilities. Three tables and three proposed figures are included to systematise and visualise the key concepts discussed. Figure 1 presents the Bidirectional crosstalk between cancer metabolism and epigenetic regulation.

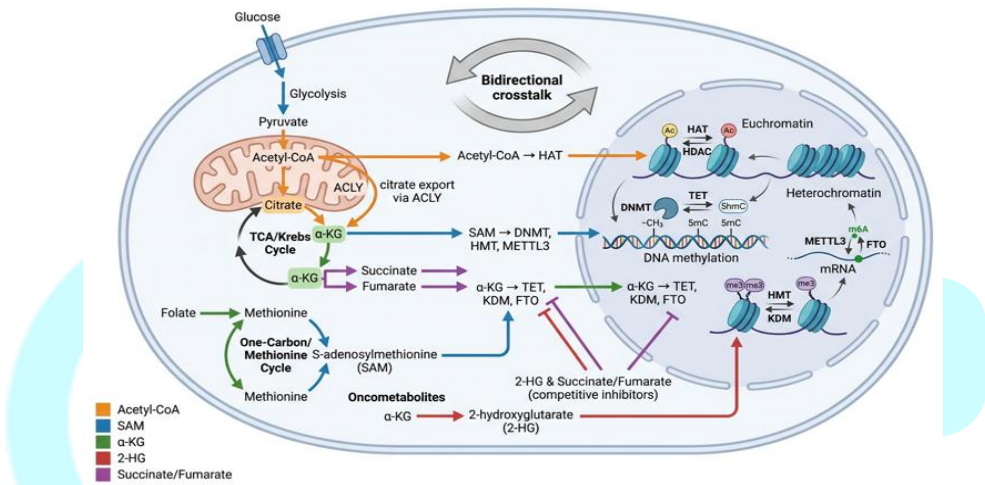


Figure 1. Bidirectional crosstalk between cancer metabolism and epigenetic regulation.

Caption: The Warburg effect and TCA cycle reprogramming generate key metabolites (acetyl-CoA, SAM, α-KG, 2-HG, succinate, fumarate) that directly modulate the activity of DNA methyltransferases (DNMTs), histone acetyltransferases/deacetylases (HATs/HDACs), histone methyltransferases/demethylases (HMTs/KDMs), and m6A RNA writers/erasers. Dashed arrows indicate feedback regulation.

Sources: Adapted from references [3, 5, 10].

DNA Methylation and Metabolic Control in Cancer

DNA methylation, the covalent addition of a methyl group to the C5 position of cytosine residues within CpG dinucleotides, is the most extensively studied epigenetic modification in cancer biology. This modification is catalysed by a family of DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) and critically depends on the availability of S-adenosylmethionine (SAM) as the universal methyl donor.[11] Cancer cells exhibit a paradoxical pattern of global DNA hypomethylation, which promotes chromosomal instability and reactivation of oncogenes, concurrent with promoter-specific

hypermethylation of tumour suppressor genes (TSGs), effectively silencing critical regulatory circuits.[1]

The SAM/S-adenosylhomocysteine (SAH) ratio, which reflects the capacity for methylation reactions, is directly governed by one-carbon metabolism (OCM). The folate and methionine cycles, which constitute OCM, are particularly sensitive to dietary methionine intake, folate availability, and the activity of key enzymes such as methionine adenosyl transferase (MAT). Bernasocchi and Mostoslavsky demonstrated that perturbations in subcellular OCM significantly alter both DNA and histone methylation landscapes in cancer, with the nuclear availability of SAM being a rate-limiting determinant of chromatin modification.[10] Disruption of this balance, as observed in rapidly proliferating cancer cells with high one-carbon metabolic flux, can selectively hypermethylate TSG promoters, contributing to tumour suppressor gene silencing.[11]

The reverse reaction, DNA demethylation, is mediated by the ten-eleven translocation (TET) family of dioxygenases, which catalyse the sequential oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC) and ultimately to unmethylated cytosine. TET enzymes are α -KG-dependent and are thus exquisitely sensitive to the cellular α -KG:2-HG ratio.⁷ In cancers harbouring IDH mutations, the accumulated oncometabolite 2-HG competitively inhibits TET activity, resulting in global 5hmC loss and a CpG island methylator phenotype (CIMP).⁷ Analogously, succinate and fumarate, which accumulate in SDH- and FH-deficient tumours respectively, inhibit TET enzymes and histone demethylases through the same competitive mechanism.[8,12] The pleiotropic epigenetic consequences of fumarate accumulation, including epithelial-to-mesenchymal transition (EMT) mediated by aberrant methylation of the miR-200 cluster promoter, have been detailed in recent mechanistic studies.[12] Table 1 summarises the principal epigenetic mechanisms linking metabolic state to chromatin regulation across major cancer types.

Table 1. Key Epigenetic Mechanisms Linking Metabolism to Cancer.

Epigenetic Mechanism	Key Metabolite/Enzyme	Cancer Types Affected	Functional Outcome
DNA Methylation	SAM/SAH ratio; DNMT1/3A/3B	Colorectal, lung, breast, AML	TSG silencing; genomic instability
Histone Acetylation	Acetyl-CoA; ACLY; ACSS2; HATs/HDACs	Glioblastoma, breast, colorectal	Oncogene activation; Warburg effect

Epigenetic Mechanism	Key Metabolite/Enzyme	Cancer Types Affected	Functional Outcome
Histone Methylation	SAM; EZH2 (H3K27me3); KMT2A	Follicular lymphoma, epithelioid sarcoma, NSCLC	TSG repression; cell differentiation block
Oncometabolite Signalling	2-HG (IDH1/2 mut.); Succinate (SDH mut.); Fumarate (FH mut.)	Glioma, AML, renal, paraganglioma	TET/KDM inhibition; hypermethylator phenotype (CIMP)
RNA m6A Modification	SAM; METTL3/METTL14 (writers); FTO/ALKBH5 (erasers)	Gastric, breast, colorectal, AML	Post-transcriptional metabolic gene regulation
Chromatin Remodelling	ATP; BRD4; SWI/SNF complex	Multiple solid tumours	Transcriptional dysregulation; drug resistance

CIMP: CpG Island Methylator Phenotype; TSG: Tumour Suppressor Gene; AML: Acute Myeloid Leukaemia; NSCLC: Non-Small Cell Lung Cancer.

Sources: Synthesised from references [1,8,10,11,12]

Histone Modifications at the Metabolic-Epigenetic Interface

Histone Acetylation and the Acetyl-CoA Nexus

Histone acetylation, catalysed by histone acetyltransferases (HATs) and reversed by histone deacetylases (HDACs), is fundamentally dependent on the cytoplasmic and nuclear concentrations of acetyl-coenzyme A (acetyl-CoA). This metabolite serves as the obligate acetyl group donor for all HAT-mediated reactions.[13] In cancer cells, the Warburg effect profoundly alters acetyl-CoA homeostasis through multiple interrelated pathways. First, the enhanced glycolytic flux in cancer cells produces pyruvate, which can be converted to acetyl-CoA via pyruvate dehydrogenase (PDH) in the mitochondria, with citrate subsequently exported to the cytoplasm. Second, ATP-citrate lyase (ACLY) cleaves cytoplasmic citrate into acetyl-CoA and oxaloacetate, directly linking TCA cycle output to histone acetylation.[14] Third, acetyl-CoA synthetase 2 (ACSS2) converts acetate, derived from histone deacetylation, lipid catabolism, or the tumour microenvironment, into acetyl-CoA, particularly under conditions of metabolic stress or nutrient deprivation.[15]

The clinical significance of this axis is underscored by evidence that ACLY overexpression correlates with poor prognosis in multiple cancer types and promotes tumour growth by sustaining histone acetylation of growth-promoting genes. Conversely, ACSS2 inhibition has demonstrated anti-tumour effects in multiple myeloma and oestrogen-deprived breast

cancer cells, in part by reducing nuclear acetyl-CoA availability and diminishing histone acetylation at oncogenic loci.[15] Importantly, the butyrate paradox in colorectal cancer elegantly illustrates the context-dependency of acetyl-CoA metabolism: in normal colonocytes, butyrate serves as an energy substrate generating acetyl-CoA; however, in Warburg-shifted cancer cells, butyrate accumulates and functions as an endogenous HDAC inhibitor, altering histone acetylation patterns to differentially regulate gene expression.[13]

Histone Methylation and the SAM-Dependent HMT/KDM Axis

Histone methylation, catalysed by histone methyltransferases (HMTs) using SAM as the methyl donor, and reversed by Jumonji C (JmjC)-domain-containing lysine demethylases (KDMs) which require α -KG as a cofactor, represents another critical node of metabolic-epigenetic integration.[16] The polycomb repressive complex 2 (PRC2), whose catalytic subunit EZH2 trimethylates histone H3 at lysine 27 (H3K27me₃), is overexpressed across a broad spectrum of malignancies and promotes TSG silencing.[17] EZH2 gain-of-function mutations are particularly prevalent in B-cell lymphomas, where they drive a hypermethylator phenotype that represses differentiation-associated gene networks.

The availability of SAM directly influences EZH2-mediated H3K27 trimethylation, creating a direct link between one-carbon metabolic flux and polycomb-mediated gene repression.[16] Conversely, oncometabolite-mediated inhibition of KDMs, which include the JMJD family of histone demethylases, results in the accumulation of repressive marks such as H3K9me₃ and H3K27me₃ in IDH-mutant tumours, further locking cells in an undifferentiated, epigenetically repressed state.⁷ The metabolic reprogramming induced by EZH2 inhibition itself is notably context-dependent, with studies showing that EZH2 suppression differentially alters glucose and glutamine metabolic networks in two-dimensional versus three-dimensional tumour cell culture models, highlighting the importance of the microenvironmental context.[17]

Oncometabolites: Biochemical Mechanisms of Epigenetic Rewiring

Oncometabolites represent perhaps the most direct and mechanistically compelling connection between altered cancer metabolism and epigenetic dysregulation. These metabolic intermediates, which accumulate due to enzyme dysfunction rather than

increased substrate flux, exert their epigenetic effects primarily through competitive inhibition of α -KG-dependent dioxygenases, a large family of enzymes that includes TET DNA demethylases, KDM histone demethylases, and prolyl hydroxylases.[6]

The IDH1/2 oncometabolite paradigm is the most extensively characterised. IDH1 (cytoplasmic) and IDH2 (mitochondrial) normally convert isocitrate to α -KG in the TCA cycle; somatic gain-of-function mutations at key arginine residues (R132 in IDH1; R140 and R172 in IDH2) confer neomorphic enzymatic activity that reduces α -KG to D-2-HG, which accumulates to millimolar concentrations, up to 100-fold above physiological levels.[18] D-2-HG competitively inhibits all α -KG-dependent dioxygenases, with particular impact on TET2, TET1, and the JmjC-domain KDMs, producing the characteristic glioma CpG island methylator phenotype (G-CIMP) observed in IDH-mutant gliomas and the broad epigenetic dysregulation seen in IDH-mutant AML.[19] Recent work by Tian et al. provided detailed mechanistic insight into the structural basis of mIDH1 inhibition and its downstream epigenetic consequences, informing the rational design of allosteric inhibitors now in clinical use.[19]

Fumarate and succinate, which accumulate in FH-deficient and SDH-deficient cancers respectively, act through the same competitive mechanism. Giallongo et al. provided a comprehensive analysis of fumarate's pleiotropic epigenetic effects, demonstrating its roles in inhibiting TET-mediated DNA demethylation, impairing histone demethylation via KDM inhibition, and inducing succination of cellular proteins including KEAP1, which activates the NRF2 antioxidant pathway, further reshaping the metabolic landscape in these tumours.[12] The resulting CIMP phenotype in SDH- and FH-mutant cancers phenocopies the epigenetic state observed in IDH-mutant tumours, despite distinct upstream genetic events.

Lactate, long regarded merely as a metabolic waste product of aerobic glycolysis, has recently been recognised as a novel epigenetic modifier through histone lactonylation. Lactyl-CoA generated from lactate can donate lactyl groups to lysine residues on histone tails, constituting a new category of histone modification that links the Warburg effect directly to chromatin regulation and gene expression in a manner distinct from acetylation.[4]. Figure 2 presents the Oncometabolite-driven epigenetic reprogramming in cancer.

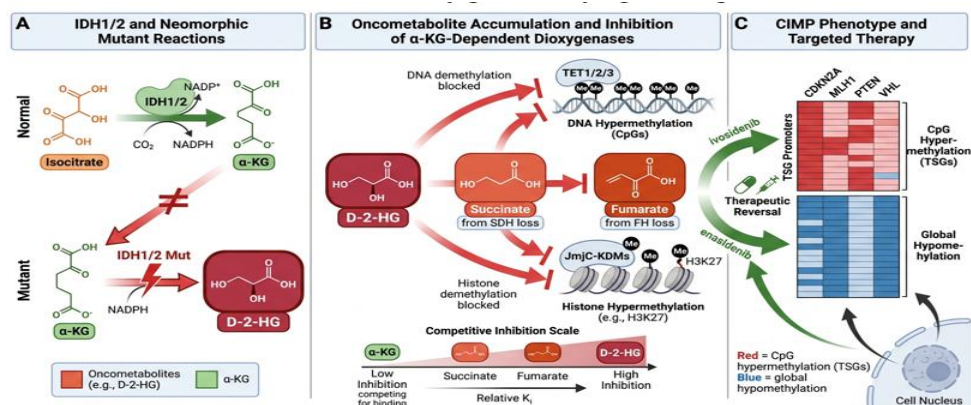


Figure 2. Oncometabolite-driven epigenetic reprogramming in cancer.

Caption: Neomorphic IDH1/2 mutations produce D-2-HG, while loss-of-function SDH and FH mutations lead to succinate and fumarate accumulation respectively. All three oncometabolites competitively inhibit α -KG-dependent dioxygenases (TET1/2/3 and JmJc-KDMs), resulting in global DNA hypermethylation, aberrant histone methylation, and the CpG Island Methylator Phenotype (CIMP). Therapeutic interventions at the IDH1 (ivosidenib) and IDH2 (enasidenib) level are illustrated.

Sources: Adapted from references [7,8,12,18,19]

RNA Epitranscriptomics: M6a Modification as a Metabolic Sensor

The field of epitranscriptomics has emerged as a critical dimension of epigenetic regulation that bridges metabolic sensing with post-transcriptional gene regulation. N6-methyladenosine (m6A), the most abundant internal modification of eukaryotic mRNA, is dynamically regulated by a set of 'writer', 'eraser', and 'reader' proteins whose activities are intimately coupled to the metabolic state of the cell.[20]

The m6A methyltransferase complex, comprising the catalytic subunit METTL3, the structural component METTL14, and the regulatory factor WTAP, deposits m6A marks on mRNA in an SAM-dependent manner.[20] Since SAM is the universal methyl donor whose availability is governed by one-carbon metabolism and methionine cycle flux, alterations in cellular methionine availability directly impinge on the m6A epitranscriptome. This makes METTL3 a molecular sensor that translates nutritional and metabolic signals into changes in mRNA stability, translation efficiency, and splicing.[21]

METTL3 is overexpressed and functionally oncogenic in multiple cancers, including AML, gastric, colorectal, and breast cancer. In AML, METTL3-mediated m6A modification promotes the translation of oncogenic mRNAs including MYC, BCL2, and PTEN by recruiting YTHDF readers and enhancing polysome loading.[21] In gastric

cancer, METTL3 coordinates m6A deposition with alterations in oxidative phosphorylation gene networks, as demonstrated by integrative proteomics and m6A microarray analyses.[22] The m6A demethylases FTO and ALKBH5 represent counterbalancing erasers whose dysregulation further shapes the cancer-specific epitranscriptome; FTO in particular has been implicated in AML differentiation arrest and metabolic reprogramming.[9]

Recent work by Mobet et al. delineated the interplay between m6A modification and major metabolic pathways in cancer, demonstrating that m6A marks on metabolic enzyme transcripts, including those encoding glycolytic enzymes, glutamine transporters, and lipid synthesis machinery, modulate the rate of translation and mRNA decay in response to nutrient cues.[9] This creates a sophisticated post-transcriptional layer of metabolic gene regulation that complements and integrates with the better-characterised chromatin-based mechanisms. The emerging class of METTL3 inhibitors (e.g., STM2457 and STC-15) represents a promising therapeutic avenue for disrupting this oncogenic epitranscriptomic programme. [9,22]

Therapeutic Landscape: Targeting Epigenetic-Metabolic Vulnerabilities

Approved Epigenetic Agents

The therapeutic exploitation of epigenetic-metabolic dependencies has yielded several FDA-approved agents that have transformed the management of specific haematological malignancies (Table 2). The DNA hypomethylating agents azacitidine and decitabine, which function as mechanism-based DNMT inhibitors causing covalent DNMT trapping and subsequent depletion, remain the cornerstone of treatment for myelodysplastic syndromes (MDS) and certain AML subtypes.[23] By globally reducing DNA methylation, these agents reactivate silenced TSGs and restore normal differentiation programmes, mechanistically reversing the epigenetic consequences of altered one-carbon metabolism.

HDAC inhibitors, including the pan-HDACi vorinostat and the class I-selective romidepsin, work by preventing histone deacetylation, thereby promoting a hyperacetylated chromatin state that reactivates growth-suppressive gene networks. These agents effectively counter the transcriptional repression mediated by tumour-associated HDACs that exploit cellular acetyl-CoA dynamics.[23] The EZH2 inhibitor tazemetostat,

the first approved histone methyltransferase inhibitor, selectively reduces H3K27me3 and has demonstrated clinical efficacy in follicular lymphoma with EZH2 activating mutations and in SMARCB1-deficient epithelioid sarcoma.[17] Tazemetostat therapy is associated with significant metabolic reprogramming of treated cells, illustrating the tight reciprocal coupling between epigenetic and metabolic states.

The mutant IDH inhibitors ivosidenib (IDH1i) and enasidenib (IDH2i) represent a landmark paradigm of targeting the metabolic-epigenetic axis: by pharmacologically suppressing 2-HG production, these agents restore α -KG-dependent dioxygenase activity, partially reverse the CIMP phenotype, and promote differentiation of leukaemia blasts.[19] The recent FDA approval of Vorasidenib, a brain-penetrant dual IDH1/2 inhibitor, for diffuse glioma with IDH mutations represents the culmination of two decades of oncometabolite research. Table 2 presents the FDA-Approved Epigenetic Drugs Targeting Cancer Metabolism.

Table 2. FDA-Approved Epigenetic Drugs Targeting Cancer Metabolism

Drug (Generic)	Class / Target	FDA-Approved Indication	Epigenetic-Metabolic Mechanism	Year of Approval
Azacitidine (Vidaza)	DNMTi	MDS, AML	Hypomethylation; TSG reactivation	2004 (MDS)
Decitabine (Dacogen)	DNMTi	MDS, AML	DNMT trapping; DNA demethylation	2006 (MDS)
Vorinostat (Zolinza)	Pan-HDACi	Cutaneous T-cell lymphoma	Histone hyperacetylation; metabolic gene re-expression	2006
Romidepsin (Istodax)	Class I HDACi	CTCL, PTCL	HDAC1/2 inhibition; apoptosis induction	2009 / 2011
Tazemetostat (Tazverik)	EZH2 inhibitor (HMTi)	Follicular lymphoma, Epithelioid sarcoma	H3K27me3 reduction; TSG derepression; metabolic reprogramming	2020
Ivosidenib (Tibsovo)	IDH1 inhibitor	AML, Cholangiocarcinoma	Reduces 2-HG; restores TET/KDM activity; demethylation	2018 / 2021
Enasidenib (Idhifa)	IDH2 inhibitor	Relapsed/Refractory AML	Reduces 2-HG production; promotes myeloid differentiation	2017

AML: Acute Myeloid Leukaemia; MDS: Myelodysplastic Syndrome; CTCL: Cutaneous T-Cell Lymphoma; PTCL: Peripheral T-Cell Lymphoma; DNMTi: DNMT Inhibitor; HDACi: HDAC Inhibitor

Sources: Compiled from references [17, 19, 23]

Emerging Pipeline and Combination Strategies

Beyond approved agents, a rich pipeline of novel compounds targets newly elucidated epigenetic-metabolic vulnerabilities (Table 3). ACLY inhibitors such as bempedoic acid (originally developed for hyperlipidaemia) and NDI-091143 are being explored as anti-cancer agents on the basis that ACLY suppression depletes nuclear acetyl-CoA, reduces oncogene-associated histone acetylation, and impairs tumour cell proliferation.[14] ACSS2 inhibitors target the tumour-microenvironment-adapted acetate utilisation pathway employed by cancer cells under nutrient deprivation, a vulnerability particularly relevant in hypoxic tumour regions.[15]

BET bromodomain inhibitors, which displace BET proteins (BRD2, BRD3, BRD4) from acetylated histones, target readers of histone acetylation rather than writers or erasers. By disrupting the BRD4-acetylated chromatin interaction that sustains MYC expression and other oncogenic transcriptional programmes, BET inhibitors (e.g., molibresib, ZEN-3694) impair the metabolic adaptations necessary for tumour growth.³ Combination strategies pairing BET inhibitors with EZH2 inhibitors show particular promise, as these two classes mechanistically counteract opposing chromatin states that cancer cells leverage for transcriptional plasticity.[17]

Targeting the one-carbon metabolic pathway to deplete SAM represents an innovative approach. Methionine restriction, MAT2A inhibitors (e.g., AG-270), and inhibitors targeting MTAP-deleted cancers exploit the synthetic lethality created by PRMT5 dependence in MTAP-null tumours, which are particularly vulnerable to impairments in SAM-dependent methylation reactions.¹⁰ METTL3 inhibitors such as STM2457 have demonstrated potent anti-leukaemic activity preclinically, and STC-15 has entered Phase I clinical trials, representing the first therapeutic targeting of the m6A epitranscriptome.[22]

A conceptually compelling direction involves combining epigenetic agents with immunotherapy. Epigenetic reprogramming by DNMTi and HDACi can enhance tumour immunogenicity by increasing the expression of neoantigens, MHC class I molecules, immune checkpoint ligands, and endogenous retroviruses, creating a more immunogenic tumour microenvironment that sensitises tumours to anti-PD-1/PD-L1 checkpoint blockade.[2] Ongoing clinical trials are investigating these combinations in diverse tumour

types, seeking to translate the mechanistic elegance of the epigenetic-metabolic-immune axis into durable clinical responses. Table 3 shows the Emerging Therapeutic Targets and Pipeline Agents in Epigenetic-Metabolic Oncology, while Figure 3 gives the Therapeutic strategies targeting the cancer epigenetic-metabolic axis.

Table 3. Emerging Therapeutic Targets and Pipeline Agents in Epigenetic-Metabolic Oncology

Target / Pathway	Agent(s) in Development	Cancer Type(s)	Development Phase	Key Reference
ACLY (Acetyl-CoA synthesis)	Bempedoic acid; NDI-091143	Breast, colorectal, NSCLC	Preclinical / Phase I	He et al. 2023 [14]
ACSS2 (Acetate metabolism)	ACSS2 inhibitors (e.g., STF-31 analogs)	Multiple myeloma, breast	Preclinical	Hao et al. 2022 [15]
BET Bromodomain (BRD4)	Molibresib (GSK525762); ZEN-3694	Castration-resistant prostate cancer; AML; TNBC	Phase I/II	Gu et al. 2024 [3]
DOT1L (H3K79 methylation)	Pinometostat (EPZ-5676)	MLL-rearranged leukemia	Phase I/II	Tao et al. 2024 [2]
METTL3 (m6A writer)	STM2457; STC-15	AML, gastric, colorectal	Preclinical / Phase I	Liu et al. 2022 [22]
IDH1/2 (Oncometabolite)	Vorasidenib (dual IDH1/2i); Olutasidenib	Glioma, AML, cholangiocarcinoma	Phase III / FDA Approved 2024	Tian et al. 2022 [19]
One-Carbon Metabolism (SAM)	Methionine restriction; MAT2A inhibitors (AG-270)	MTAP-deleted cancers, pancreatic	Phase I/II	Bernasocchi& Mostoslavsky 2024 [26]

MTAP: Methylthioadenosine Phosphorylase; **TNBC:** Triple-Negative Breast Cancer; **NSCLC:** Non-Small Cell Lung Cancer; **AML:** Acute Myeloid Leukaemia

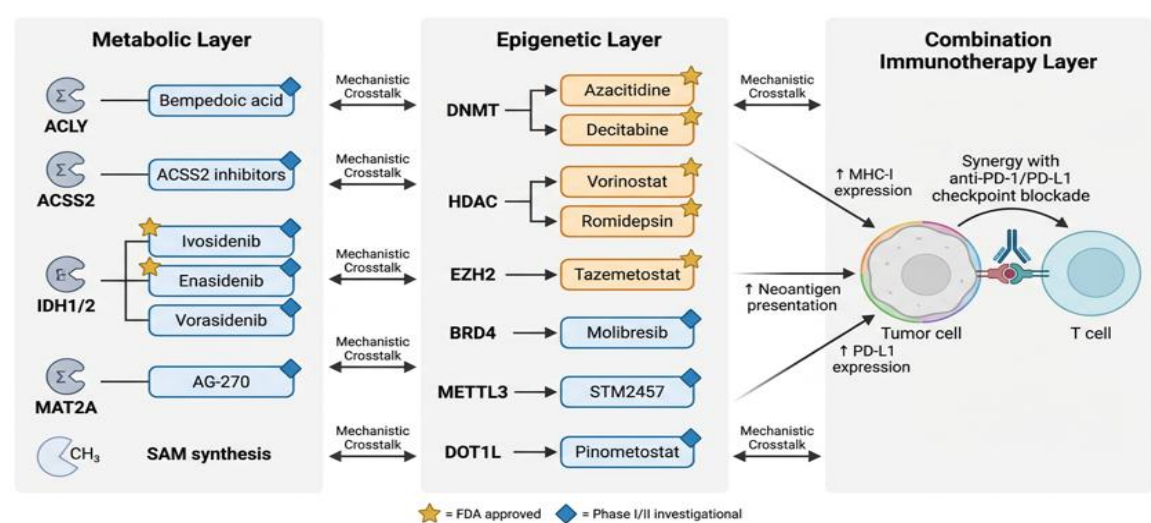


Figure 3. Therapeutic strategies targeting the cancer epigenetic-metabolic axis.

Caption: *Approved drugs (orange boxes) and pipeline agents (blue boxes) are mapped to their respective epigenetic-metabolic targets. Combination immunotherapy strategies are shown on the right panel. Arrows indicate mechanistic direction of therapeutic action.*

Sources: Adapted from references [2,14,15,17,19,22,23].

Conclusion And Future Perspectives

The epigenetic regulation of cancer metabolism represents a paradigm shift in our understanding of oncogenesis, one that dissolves the historical conceptual boundary between metabolic reprogramming and epigenetic dysregulation. The evidence reviewed herein collectively demonstrates that the cancer cell's aberrant metabolic state is not merely a means of sustaining proliferative demands but is itself a potent epigenetic driver that actively sculpts the transcriptional landscape of the tumour. Key metabolites including acetyl-CoA, SAM, α -KG, 2-HG, succinate, fumarate, and lactate function as direct molecular transducers that couple the metabolic environment to chromatin state.

The oncometabolite concept, crystallised by the discovery of IDH mutations, has been foundational, demonstrating unambiguously that a single metabolic enzyme mutation can impose a widespread and clinically meaningful epigenetic programme. The therapeutic success of mutant IDH inhibitors validates the entire conceptual framework of targeting the metabolic-epigenetic axis and provides an important template for drug development.

Looking forward, several frontiers hold exceptional promises. First, the m6A epitranscriptomic layer remains incompletely mapped in the context of specific metabolic programmes, and the development of clinical-grade METTL3 inhibitors may yield new therapeutic modalities. Second, the integration of spatial metabolomics with single-cell epigenomics promises to resolve the heterogeneity within tumours and reveal how metabolic-epigenetic states vary across microenvironmental niches. Third, the design of rational combination regimens, pairing metabolic interventions with epigenetic drugs and immune checkpoint blockade, represents the logical next step toward durable responses. Finally, the identification of novel histone modifications such as lactonylation, succinylation, and crotonylation, all of which are metabolite-derived, suggests that our current map of the cancer epigenome is still far from complete.

Collectively, these advances reinforce that the epigenetic-metabolic axis is not a peripheral feature of cancer biology but a central, druggable vulnerability that demands sustained interdisciplinary investigation and clinical translation.

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