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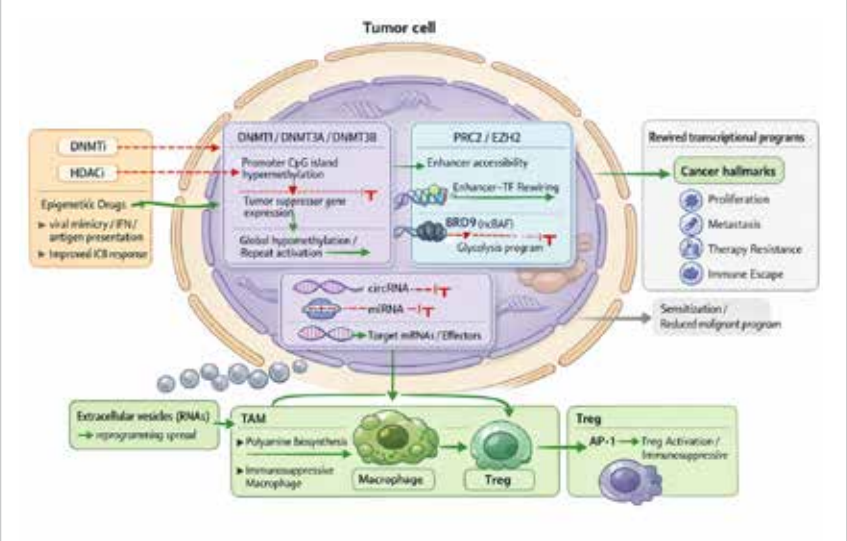
Epigenetic and gene regulatory landscapes in cancer: mechanisms, plasticity and therapeutic opportunities

Noah Favre[1], Liam von Escher[1,*]

1 Department of Biomedicine, University of Basel, Basel, Switzerland

* Address for Correspondences:
Liam von Escher
Department of Biomedicine, University of Basel, Basel, Switzerland
E-mail: liam12vonescher@gmail.com



Epigenetic and gene-regulatory rewiring drives cancer plasticity and creates therapeutic vulnerabilities.

Aberrant DNA methylation mediated by DNMT1/3A/3B promotes promoter CpG island hypermethylation and tumor-suppressor silencing, while global hypomethylation can activate repeats. Altered chromatin regulation (e.g. PRC2/EZH2 and remodelers such as BRD9/ncBAF) modulates enhancer accessibility, TF wiring, and metabolic programs (including glycolysis). Regulatory RNAs (miRNAs and circRNAs) further tune target mRNAs/effectors. These coordinated changes generate rewired transcriptional states

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that support cancer hallmarks (proliferation, metastasis, therapy resistance, immune escape). Epigenetic drugs (DNMT inhibitors and HDAC inhibitors) can partially reverse malignant programs and enhance immunogenicity through viral mimicry/interferon signaling and improved antigen presentation, thereby sensitizing tumors to immune checkpoint blockade. Crosstalk with the microenvironment is illustrated by RNA-containing extracellular vesicles that spread reprogramming and by immunometabolic circuits that promote TAM polarization (e.g. polyamine biosynthesis) and Treg activation (e.g. AP-1-linked programs), reinforcing immunosuppression.

Abstract

Cancer development and progression reflect not only the accumulation of genetic alterations but also pervasive rewiring of gene regulatory programs. Epigenetic mechanisms provide the molecular infrastructure that interprets genetic potential, shaping chromatin accessibility, transcriptional output, cellular plasticity, and phenotypic heterogeneity without altering DNA sequence. Aberrant DNA methylation, distorted histone modification landscapes, dysfunctional chromatin remodeling, and regulatory RNA networks cooperatively establish malignant states that support proliferation, immune evasion, metabolic adaptation, metastasis, and therapy resistance. Importantly, these regulatory alterations can drive profound cell-state transitions even in the absence of additional mutations, underscoring the limits of mutation-centric models of cancer. This review synthesizes current understanding of core epigenetic mechanisms dysregulated in cancer, spanning DNA methylation dynamics, histone modifications, chromatin remodelers, and non-coding RNA-mediated control. It focuses on how these layers intersect with transcription factor networks and three-dimensional genome organization to encode stable yet adaptable regulatory states. Particular emphasis is placed on epigenetic contributions to canonical cancer hallmarks, tumor microenvironment remodeling, and immunometabolic coupling that reinforces immune suppression. Furthermore, the review discusses the latest advances in epigenetic targeted therapy, including DNA methyltransferase and histone deacetylase inhibitors, emerging chromatin reader and remodeler dependencies, and the rationale for combination strategies with chemotherapy, radiotherapy, immunotherapy, or metabolic intervention. Finally, the translational applications of epigenetic biomarkers (especially DNA methylation signatures detectable via liquid biopsy) are explored, which inform early detection, molecular subtyping, prognosis, and therapeutic stratification. Collectively, this review positions epigenetic and gene regulatory landscapes as central determinants of cancer behavior and as actionable leverage points for precision oncology.

KEYWORDS

Epigenetic regulation, Gene regulatory networks, Cancer, Chromatin remodeling

Introduction

Cancer is increasingly recognized as a disease of dual causality, arising from the interplay between genetic lesions and pervasive epigenetic dysregulation. Somatic mutations, copy number changes, and structural variants are necessary components of tumorigenesis(1). However, a genome alone does not specify tumor behavior. Malignant phenotypes emerge when gene regulation is rewired, enabling sustained proliferation, evasion of growth suppressors, invasion and metastasis, altered metabolism, immune escape, and therapy resistance(2). Epigenetic control systems provide the molecular infrastructure for such rewiring because they shape chromatin accessibility, transcription factor (TF) occupancy, enhancer–promoter communication, and transcript fate without altering DNA sequence(3). The classical mutation-centric framework has been indispensable for identifying oncogenes, tumor suppressors, and actionable driver alterations; however, it provides an incomplete explanation for several defining features of malignancy(4).

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Tumors with comparable mutational burdens can display strikingly different phenotypes, clinical trajectories, and therapeutic vulnerabilities. Conversely, profound shifts in cell state may emerge in the absence of new DNA sequence changes, reflecting regulatory reprogramming rather than additional mutational events(5). These observations underscore a central limitation of purely genetic models: DNA mutations specify potential, yet the epigenetic and transcriptional architecture determines how that potential is interpreted in a given cellular context.

Building on this dual genetic–epigenetic view, it is useful to outline the core architecture of epigenetic control that governs transcriptional output in cancer. At the level of DNA, cytosine methylation and its oxidation derivatives provide a stable yet editable layer of information that influences promoter competency, enhancer activity, imprinting, and genome stability(6). In parallel, histone tails carry a diverse repertoire of post-translational modifications—acetylation, methylation, phosphorylation, ubiquitination—that tune nucleosome dynamics, recruit effector proteins, and partition chromatin into transcriptionally permissive or repressive states (7). Beyond covalent modifications, ATP-dependent chromatin remodeling complexes actively reposition, evict, or restructure nucleosomes to regulate accessibility of transcription factor binding sites(8). Such remodeling events are tightly coupled to the deployment of lineage-determining factors and oncogenic transcriptional programs, thereby shaping enhancer repertoires and altering promoter–enhancer communication. Non-coding RNAs add a complementary dimension. MicroRNAs modulate mRNA stability and translation, long non-coding RNAs scaffold chromatin regulators or guide them to specific genomic loci, while emerging classes of regulatory RNAs participate in nuclear organization and transcriptional control(9-11). Together, these layers operate within the spatial constraints of three-dimensional genome folding, in which topologically associating domains, chromatin loops, and nuclear compartments constrain regulatory reach and coordinate co-regulated gene sets.

Crucially, epigenetic regulation cannot be separated from transcriptional control. Transcription factors recruit chromatin modifiers, remodelers, and co-regulators to establish active enhancers or silence alternative programs(12). Conversely, chromatin state determines which transcription factor motifs are accessible, which promoter architectures are competent, and which enhancer-promoter contacts are productive(13). The result is an interdependent regulatory network in which epigenetic mechanisms act as both the substrate and the consequence of transcription. In cancer, perturbations at any node—enzymes, remodelers, regulatory RNAs, or higher-order chromatin organization—can reverberate across this network, rewiring gene expression landscapes to enable plasticity, stress adaptation, and malignant progression. Therefore, epigenetic pathways are appealing targets clinically because they can be pharmacologically modulated and may re-sensitize tumors to existing therapies(14). Yet epi-drug responses remain heterogeneous, and adaptive resistance is common, underscoring the need for mechanistic biomarkers and rational combinations(15). This review synthesizes the mechanistic landscape, highlights immunometabolic epigenetics in the TME, and outlines translational strategies grounded primarily in your curated evidence base.

Core epigenetic mechanisms dysregulated in cancer

DNA methylation abnormalities

DNMT/TET families and CpG island dynamics

DNA methylation patterns are established and maintained by DNA methyltransferases (DNMTs) and can be remodeled by TET-dependent oxidation pathways(16). DNMT/TET dysregulation is both a marker and a driver of malignant progression(17, 18). Importantly, methylation changes are not uniform; they can be locus-specific (e.g., promoter CpG islands) or global, affecting repetitive elements and genome stability. DNMT1 maintains the methylation pattern during DNA replication, while DNMT3A and DNMT3B establish de novo methylation during development and cell state transitions(19). Methylcytosine is actively remodeled by TET1-3, which repeatedly oxidize 5-methylcytosine to

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5-hydroxymethylcytosine and its derivatives, thereby achieving replication-dependent dilution or downstream repair-coupled demethylation(20). In normal tissues, CpG islands (typically located in CpG-dense regions near gene promoters) are generally unmethylated, thus maintaining basic accessibility to transcription initiation(21). In colorectal cancer (CRC), DNMT3A is associated with malignant progression through promoter methylation-mediated tumor suppressor signaling pathways, supporting the role of methylation-modifying enzymes in maintaining oncogenic pathway output(22). Furthermore, TET-related regulation is involved in aberrant methylation states in various cancers, further demonstrating that "writing" and "erasure/oxidation" mechanisms jointly shape the tumor regulatory landscape.

Promoter hypermethylation and tumor suppressor silencing

Promoter hypermethylation remains one of the most interpretable mechanisms connecting epigenetics to gene expression. A prominent hallmark is focal CpG island hypermethylation at promoters of tumor suppressor genes, which enforces stable transcriptional repression. This silencing can phenocopy genetic loss by extinguishing expression of regulators of cell-cycle control, DNA repair, apoptosis, and lineage fidelity(23). CpG island hypermethylation has been shown to directly suppress the expression of tumor suppressor genes, preventing them from functioning normally and promoting disordered cell proliferation(24). Promoter hypermethylation also cooperates with repressive histone marks to lock chromatin into a closed configuration, reducing responsiveness to differentiation cues or stress signals(25). In parallel, many tumors exhibit global DNA hypomethylation across intergenic regions, gene bodies, and repetitive elements. Loss of methylation at transposable elements can permit their transcriptional reactivation, increasing the risk of insertional mutagenesis, aberrant transcript formation, or double-strand breaks during attempted mobilization(26). In breast cancer, promoter hypermethylation of the BRCA1 and BRCA2 genes is commonly found in tumor tissue and patient blood samples, and is associated with malignant transformation and clinical progression of cancer; these epigenetic alterations can serve as markers of tumorigenesis(27). DNMT3A-driven promoter methylation suppresses a tumor suppressor, thereby enabling pathway activation and aggressive phenotypes(28). In exposure-linked carcinogenesis, methylation-dependent downregulation can similarly trigger EMT programs. In bladder cancer models associated with benzo[a]pyrene/BPDE exposure, epigenetically modified LOXL1 downregulation is linked to a SLUG/E-cadherin EMT axis, illustrating how environmental inputs can be written into stable regulatory programs(29).

Global hypomethylation, repeat activation, and genome instability

Whereas focal hypermethylation often represses tumor suppressors, global hypomethylation can destabilize the genome and derepress repetitive elements(30). Although many studies emphasize promoter-level effects, regulatory activity and tissue-origin patterns can be inferred from pan-tissue methylation mapping, further highlighting the relevance of global methylation structure to cancer classification and mechanistic explanation. Global hypomethylation further compromises genome integrity by weakening heterochromatin structure at pericentromeric repeats, which contributes to chromosomal segregation errors and aneuploidy(31). These apparently opposing trends—local hypermethylation with widespread hypomethylation—reflect a reallocation of methylation rather than a uniform gain or loss. Functionally, the consequence is a methylation landscape that simultaneously suppresses protective programs and destabilizes the genome, thereby accelerating malignant evolution. Within this framework, altered DNMT or TET activity becomes a powerful driver of epigenetic plasticity, shaping both transcriptional states and the tempo of genomic change in cancer.

Histone modifications and chromatin remodeling

Histone acetylation often marks active enhancers and promoters, enabling high transcriptional throughput at lineage and oncogenic loci. In basal-like pancreatic ductal adenocarcinoma, an enhancer network involving AP-1/RUNX2 is presented as a driver of aggressive behavior, consistent with acetylation-supported enhancer accessibility as a determinant of subtype identity(32). In parallel, deacetylase-associated regulation emerges in mechanistic studies that link specific HDACs to proliferation programs, suggesting that altered acetylation dynamics can either support or restrain malignant growth depending on the circuit context(33). From a translational angle, acetylation-centric states are attractive

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because they can be modulated pharmacologically, yet responses will likely depend on whether the tumor relies on enhancer output versus alternative regulatory routes(34).

Polycomb repressive complex 2 (PRC2) and its catalytic component EZH2 frequently appear as central hubs linking chromatin repression to cancer phenotypes(35). Numerous mechanistic studies on PRC2/EZH2 support its role in regulating lineage identity, proliferation, and immune-related programs. An emerging motif is that histone methylation intersects with stemness. For example, an oncohistone-driven H3.3K27M axis is reported to maintain stemness and malignancy in diffuse intrinsic pontine glioma, illustrating how chromatin mutations can hard-wire a stem-like program(36). In liver cancer contexts, non-coding RNA-based mechanisms are also reported to drive self-renewal, providing a complementary route to stemness maintenance that may converge on chromatin control(37).

ATP-dependent chromatin remodelers shape nucleosome positioning and can create context-specific vulnerabilities. In colon adenocarcinoma, BRD9—a component of non-canonical BAF complexes—is reported as an essential regulator of glycolysis that creates an epigenetic vulnerability, linking remodeling-associated factors to metabolic dependency(38). Such studies highlight an important conceptual shift: chromatin regulators may be most actionable when they support a tumor's metabolic constraints or when they gate access to oncogenic enhancers. By contrast, other remodeling complexes such as NuRD are less directly covered in this curated set, suggesting that future evidence mapping could expand to capture the full diversity of remodeling machinery across tumor types.

Non-coding RNAs and post-transcriptional epigenetic regulation

Non-coding RNAs (ncRNAs) provide versatile regulatory control at multiple levels: post-transcriptional repression, modulation of transcription factor circuits, recruitment of chromatin regulators, and intercellular communication through extracellular vesicles. lncRNAs are particularly prominent, spanning mechanistic tumor suppressive roles, oncogenic transcriptional activation, and immune-related risk signatures(39). circRNAs and miRNAs appear as both functional regulators and biomarker candidates.

miRNAs can reshape cancer signaling by rewiring target networks, often converging on proliferation, apoptosis, EMT, and immune modulation(40). Several studies frame miRNA-mediated circuits within broader regulatory programs, including axes that couple miRNAs to pathway effectors or to epigenetic enzymes(41, 42). For translational purposes, miRNA signatures can be informative when linked to mechanistic targets or when embedded within multi-omics models that account for cell composition and tumor heterogeneity.

Rather than serving as isolated biomarkers, lncRNAs often function as circuit components that influence transcription factor activity, chromatin accessibility, or recruitment of epigenetic complexes. In gastric cancer, a newly described lncRNA is reported to suppress tumor growth through inhibition of MEK/ERK signaling, offering a mechanistically interpretable example of lncRNA-mediated pathway control(43). In lung adenocarcinoma and hepatocellular carcinoma contexts, additional lncRNAs are presented as regulators of transcriptional activation and malignant phenotypes, supporting the view that lncRNAs can modulate transcriptional programs at scale(44, 45).

CircRNAs are increasingly recognized as stable regulatory molecules with potential clinical utility. Related research includes regulatory programs associated with circRNAs in the context of cancer, including the circRNA-related axis intersecting with miRNA regulation and pathway output. circRNAs contain miRNA binding sites and can competitively bind to miRNAs, thereby inhibiting the regulatory effects of miRNAs on target genes. This is known as the competitive endogenous RNA (ceRNA) mechanism, which can affect downstream gene expression and promote or inhibit tumor-related signaling pathways(46). For example, circRNAs, through sponge miRNAs, regulate genes related to cell proliferation, apoptosis, and metastasis, playing a crucial role in tumorigenesis. In non-small cell lung cancer (NSCLC), circRNAs have been identified as potential biomarkers, and sequencing technology has revealed their regulation of miRNA-mRNA networks, affecting tumor-related signaling pathways(47). Circ-FAT3 is upregulated as an oncogene in lung cancer and is closely associated with tumor progression(48). From a translational standpoint, circRNAs are attractive candidates for liquid biopsy due to stability(49). tumors.

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Epigenetic dysregulation as a driver of cancer hallmarks

Silencing of tumor suppressor pathways can occur through promoter methylation, Polycomb repression, or chromatin compaction that prevents transcription factor access. In CRC, DNMT3A-associated regulation is reported to facilitate progression via repression of a tumor-suppressive axis coupled to downstream signaling activation, offering a mechanistic model that links methylation writing to pathway output and phenotype(22). Additional studies describe tumor suppressor function as methylation-sensitive across distinct cancer settings, supporting the generality of methylation-mediated silencing. Importantly, epigenetic silencing often interacts with genetic lesions. For example, loss of DNA repair capacity can be reinforced by methylation states that attenuate checkpoint function, thereby amplifying genomic instability and therapy resistance(50-52).

Oncogene activation frequently reflects enhancer rewiring and chromatin state changes that elevate transcriptional throughput. The basal-like pancreatic cancer study through an AP-1/RUNX2 enhancer network associated with aggressive behavior, suggesting that enhancer control can specify malignant subtype identity(32). In parallel, viral oncogenesis provides an instructive case of epigenetic hijacking: Epstein-Barr virus is reported to exploit histone demethylase machinery to promote epithelial malignancy progression, highlighting how external genomic elements can impose chromatin rewiring(53). Finally, post-transcriptional control via m6A adds another layer of oncogenic program tuning, supporting the view that transcriptional rewriting spans chromatin and RNA(54).

Therapy resistance and metastasis often depend on plasticity: the ability to shift into alternative cell states that tolerate stress. Exposure-linked methylation changes associated with EMT provide a mechanistic bridge from environmental pressure to stable state transitions(29). Oncohistone-driven chromatin programs demonstrate that epigenetic alterations can hard-wire stemness in aggressive tumors, while non-coding RNA axes in liver cancer support self-renewal of cancer stem-like populations(36). Several studies also describe protein modification states that connect metabolism to stemness maintenance, indicating that plasticity is frequently reinforced by metabolic-epigenetic coupling. From a therapeutic perspective, these observations argue for interventions that block state transitions or destabilize resistant states rather than merely increasing cytotoxic stress(55-57).

Epigenetic reprogramming in the tumor microenvironment

A recurring concept is that tumor-exposed immune cells acquire stable regulatory programs that resemble ‘trained’ or imprinted states. In hepatocellular carcinoma, integrative epigenetic analysis reveals that AP-1 supports activation of tumor-infiltrating Treg cells, implying enhancer and accessibility remodeling that stabilizes immunosuppressive function(58). Such data caution against viewing immune dysfunction as purely cytokine-driven or transient. Instead, chromatin-level remodeling may lock in suppressive states, thereby limiting the durability of checkpoint blockade when deployed alone. Additional studies explore immune infiltration and prognostic associations for epigenetic regulators in HCC and other tumor types, offering candidate biomarkers for immune context stratification(59, 60).

Cancer cell-derived arginine fuels polyamine biosynthesis in tumor-associated macrophages, driving an immunosuppressive macrophage program that promotes immune evasion. This work establishes a cross-compartment axis: tumor nutrient export or consumption reshapes myeloid metabolism, which in turn engages epigenetic regulation to stabilize cell fate(61). More broadly, enhancer-centered frameworks suggest that metabolism and chromatin are reciprocally coupled, because super-enhancer programs can

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direct metabolic reprogramming while metabolite availability modulates chromatin enzyme activity(62, 63). These observations motivate combination strategies that target both metabolic nodes and epigenetic regulators to break reinforcing feedback loops.

Furthermore, extracellular vesicles provide a mechanism for transferring regulatory molecules—RNAs, proteins, or DNA fragments—that can reshape gene regulation in recipient cells. Existing research has considered exosomal RNAs as a component of EZH2-associated tumor promotion, suggesting that RNA cargo can influence chromatin states across cell types(64). Although exosome studies often focus on biomarker discovery, the most informative translational view is that exosomal signaling may propagate immunosuppressive programs and can contribute to resistance by reprogramming stromal or immune compartments(65, 66). Future work will benefit from perturbation experiments that block vesicle biogenesis or specific RNA cargo to clarify causality.

A multi-omics view: constructing cancer epigenetic gene-regulatory maps

Understanding causality in epigenetics requires integrative maps linking chromatin state, TF activity, transcript output, and phenotype. First, atlas and integrative resources enable inference beyond single-gene effects. A pan-tissue DNA methylation atlas supports activity inference and cross-tissue comparisons, useful for classification and tissue-of-origin analyses(67). Second, single-cell multi-omics approaches expose heterogeneity that is invisible in bulk assays. Single-cell multi-omics analyses of cancer cell lines reveal intra-line heterogeneity, cautioning against interpreting "cell line epigenetics" as uniform and underscoring why drug response variability can arise even in controlled systems(68). Third, enhancer network approaches are increasingly common. Integrated enhancer regulatory network analyses highlight how enhancer states and TF relationships can be inferred and connected to tumor biology(69). Fourth, immune epigenomics in patient samples provides direct evidence of TME-induced rewiring; the HCC Treg study illustrates how chromatin accessibility and enhancer landscapes can be integrated to explain impaired antitumor immunity(58). Finally, drug response mapping from epigenomic datasets illustrates a pragmatic direction: predicting therapeutic sensitivity and synergy from chromatin context. Epigenetic landscape analyses using large-scale ChIP-seq data provide examples of computational inference of drug modes of action, supporting a move from descriptive epigenomics to functional pharmacogenomics(70). Therefore, multi-omics can overfit without perturbation. The strongest mechanistic conclusions typically require a perturbation axis—genetic (CRISPR), pharmacologic inhibition, or epigenome editing—and validation in vivo.

Epigenetic-targeted therapy

Epigenetic drugs

In most studies, actionable epigenetic interventions are most clearly supported in contexts where chromatin regulators create pathway vulnerabilities or where low-dose epigenetic modifiers reshape immune context. For gastrointestinal

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cancers, low-dose epigenetic modifiers combined with TIC10 are reported to enhance antitumor immunity while inhibiting tumor growth, providing a direct translational link between epigenetic modulation and immune remodeling(71). In colon adenocarcinoma, BRD9 is described as a regulator of glycolysis that creates an epigenetic vulnerability, suggesting that chromatin remodeler dependencies can be targeted in metabolism-constrained tumors(38). DNA methyltransferase inhibitors (DNMTi) reverse the abnormal hypermethylation silencing of tumor suppressor genes and restore their expression by inhibiting DNA methyltransferase activity and blocking methylation at cytosine 5-site(72). Low doses activate the silenced genes, while high doses produce cytotoxicity. Multiple studies have shown that DNMTi has been used in hematologic malignancies (such as leukemia) and has demonstrated anti-tumor activity in solid tumors such as HCC and head and neck squamous cell carcinoma(73). However, its efficacy as a monotherapy for solid tumors is poor, and it is often used in combination with other regimens for synergistic effects. Unlike DNMTi, HDAC inhibitors (HDACi) affect chromatin structure and gene transcription by regulating histone acetylation status, and can also acetylate non-histone proteins, thus playing an important role in cancer treatment. In breast cancer, HDACi exhibit potent antiproliferative effects, regulating the cell cycle, modulating immune responses, triggering apoptosis, inhibiting tumor growth, and reducing angiogenesis(74). Furthermore, HDACi, when combined with radiotherapy for the treatment of solid malignancies, show potential as a novel anticancer therapy, especially through epigenetic modification and radiosensitization(75).

Rational combinations

The reversible nature of epigenetic dysregulation provides a compelling rationale for combinatorial strategies that integrate epigenetic agents with established or emerging anticancer modalities. Rather than acting as potent cytotoxins per se, many epigenetic drugs function by reprogramming transcriptional states, restoring lineage fidelity, or reshaping stress-response pathways(76). These properties position them as effective sensitizers that enhance the depth, durability, and breadth of responses to other therapies. One well-established strategy involves combining epigenetic modulators with chemotherapy or radiotherapy. Aberrant DNA methylation patterns and histone modifications frequently underlie chemoresistance through silencing of pro-apoptotic genes, DNA damage sensors, or cell-cycle checkpoints(77). In this context, DNMT inhibitors or histone deacetylase inhibitors can restore the expression of genes involved in apoptosis and DNA repair, thereby lowering the threshold for chemotherapy-induced cell death. In cholangiocarcinoma (CCA) models, the combination of DNMT inhibitors (such as decitabine) and PARP inhibitors significantly inhibited tumor growth (cell lines, organoids, and mouse xenograft models) and induced senescence in cancer cells(78). Similarly, epigenetic reprogramming has been shown to impair efficient DNA damage repair, rendering tumor cells more vulnerable to ionizing radiation(79). Importantly, such combinations often allow dose de-escalation of cytotoxic agents, potentially reducing systemic toxicity while preserving antitumor efficacy. Studies in NSCLC have also shown that DNMT inhibitors combined with iRT can overcome radiotherapy resistance, and further combination with immunotherapy may improve prognosis(80). Importantly, such combinations often allow dose de-escalation of cytotoxic agents, potentially reducing systemic toxicity while preserving antitumor efficacy.

Another rapidly advancing area is the integration of epigenetic therapy with immune checkpoint blockade. Tumor immune evasion is closely linked to epigenetic silencing of antigen presentation machinery, interferon signaling components, and chemokines required for immune cell recruitment(81). Epigenetic drugs can reinstate the expression of endogenous retroelements and tumor-associated antigens, inducing a viral mimicry state that enhances type I interferon responses. This transcriptional rewiring promotes T-cell infiltration and converts immunologically “cold” tumors into “hot” ones, thereby improving responsiveness to PD-1/PD-L1 or CTLA-4 inhibitors. Studies have found that ALKBH5 (an RNA demethylase) drives immunosuppression, and targeting its epigenetic pathway can enhance the efficacy of immune checkpoint blockade(82). The SIX4 gene has also been identified as a key regulator, which, by regulating STING expression, can serve as a biomarker for predicting or enhancing treatment response(83). In metastatic breast cancer, the combination of HDAC inhibitors and immune checkpoint blockade can improve the immune response rate,

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especially in response to the heterogeneity of the immune microenvironment(84). In parallel, epigenetic regulation of immune checkpoint ligand expression and T-cell exhaustion programs further supports the mechanistic complementarity of these combinations.

Beyond immunotherapy, rational pairing of epigenetic agents with targeted or metabolic interventions offers opportunities for precision oncology. Oncogenic signaling pathways frequently converge on chromatin modifiers to establish stable transcriptional programs that sustain tumor growth(85). Targeted inhibition of driver kinases or transcription factors can be undermined by adaptive epigenetic plasticity, leading to drug tolerance. Oncogenic signaling pathways frequently converge on chromatin modifiers to establish stable transcriptional programs that sustain tumor growth. Targeted inhibition of driver kinases or transcription factors can be undermined by adaptive epigenetic plasticity, leading to drug tolerance. Likewise, cancer cell metabolism is tightly coupled to the epigenetic landscape through metabolite-dependent chromatin modifications(86, 87). Combining epigenetic drugs with metabolic inhibitors may therefore disrupt feed-forward circuits that reinforce malignant states.

Resistance mechanisms

Resistance to epigenetic therapies frequently emerges through transcriptional escape rather than through target mutation. A clear example in uveal melanoma shows that YAP upregulation contributes to acquired resistance to BET inhibitors, indicating that tumors can reconstitute oncogenic transcription through alternative regulators when bromodomain-dependent enhancer function is constrained(88). This pattern aligns with broader regulatory logic: if tumors are addicted to high-output transcription at key loci, they can rewire enhancer usage, switch transcription factor usage, or exploit metabolic support to restore expression. Therefore, resistance-aware design should prioritize combinations that simultaneously restrict primary enhancer output and block the most plausible escape routes (e.g. Hippo/YAP signaling, metabolic one-carbon support, or parallel kinase pathways).

Biomarkers and clinical translation

Biomarker translation is a major opportunity because epigenetic states are measurable in tissue and, potentially, liquid biopsies. Because epigenetic alterations arise early during tumorigenesis and remain detectable throughout disease evolution, they provide unique opportunities for cancer detection, classification, and therapeutic stratification. Unlike genetic mutations, epigenetic changes are often tissue- and context-specific, allowing them to capture both tumor origin and functional state.

DNA methylation–based biomarkers have emerged as particularly powerful tools for early cancer detection and molecular subtyping. Aberrant CpG island hypermethylation at gene promoters frequently precedes overt malignant transformation, enabling discrimination between premalignant lesions and benign conditions(89). Advances in liquid biopsy technologies have further expanded the clinical utility of methylation markers. Changes in DNA methylation can be detected early in plasma, even in the early stages of cancer development, making it a promising candidate for early screening(90). For example, in breast cancer, DNA methylation biomarkers can be used for non-invasive early detection(91). Similarly, in CRC, altered DNA methylation has been identified as a promising biomarker for early diagnosis and disease management(92). Liquid biopsy enables real-time, minimally invasive cancer monitoring by analyzing methylation biomarkers in ctDNA.

DNA methylation signatures not only play a crucial role in early detection but also in cancer molecular subtyping, helping to differentiate tumor subtypes, predict prognosis, and guide treatment. DNA methylation signatures are cancer subtype-specific biomarkers that can be used for molecular subtyping to provide more accurate diagnoses. For example, in gastric cancer, subtype classification based on RNA sequencing, copy number variation, and DNA methylation data helps identify prognostic lncRNA biomarkers(93). Similarly, the meth-SemiCancer framework utilizes DNA methylome datasets for semi-supervised cancer subtype classification, addressing the challenges of high dimensionality and insufficient sample size(94). In invasive lobular breast cancer (ILBC), genome-wide DNA methylation analysis reveals variability among tumors and correlates methylation levels with clinical characteristics for disease subtyping and prognostic prediction(95).

Histone modification landscapes and chromatin regulator

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expression levels further enrich the epigenetic biomarker repertoire. Alterations in histone acetylation or methylation states often reflect transcriptional dependencies that can be therapeutically exploited(96). Expression of epigenetic enzymes, including writers, erasers, and readers, has been linked to sensitivity or resistance to targeted inhibitors, supporting their use as companion diagnostics(97). Integration of these features with transcriptomic and metabolic readouts provides a multidimensional view of tumor behavior that surpasses single-marker approaches. Despite these advances, several challenges remain before widespread clinical adoption. Standardization of assay platforms, harmonization of analytical pipelines, and prospective validation in large, well-annotated cohorts are essential to ensure reproducibility and clinical reliability(98). Moreover, dynamic changes in epigenetic states under therapeutic pressure necessitate longitudinal sampling strategies. Collectively, continued refinement of epigenetic biomarkers will be pivotal for translating gene regulatory knowledge into actionable clinical tools that support early diagnosis, personalized therapy, and improved patient outcomes.

Conclusion

Cancer is a disease of regulatory states. DNA methylation, histone modifications, chromatin remodeling, enhancer architecture, and RNA modifications converge to encode transcriptional programs that enable tumor growth, metastasis, immune escape, and therapy resistance. Mechanistically strong examples illustrate how methylation writing can silence tumor suppressor pathways and drive progression, how enhancer networks specify aggressive subtypes, and how metabolic–epigenetic coupling reprograms immune cells toward suppressive fates. Clinically, epigenetic regulation is attractive because it is in principle reversible, yet reversibility does not guarantee therapeutic durability. Adaptive rewiring, including transcriptional escape from chromatin-reader inhibition, underscores the need for combination strategies grounded in regulatory circuitry and resistance forecasting. Three axes appear decisive for progress. First, cell-type resolved mapping of epigenetic programs within tumors will enable mechanistic biomarkers and patient stratification. Second, circuit-informed combination therapy will likely outperform empirical stacking of agents. Third, locus-specific intervention strategies, including epigenome editing, may eventually enable selective reactivation of tumor suppressor networks or dismantling of oncogenic enhancer hubs. Together, these approaches position epigenetic regulation as a central leverage point for precision oncology, particularly in immunometabolic contexts where tumor ecology and gene regulation are tightly coupled.

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