Am J Stem Cells 2025;14(3):98-133
www.AJSC.us /ISSN:2160-4150/AJSC0167215

Review Article

Epigenetic crosstalk between stem cells and tumors: mechanisms and emerging perspectives

Wenli Zhou[1], Xuehai Liu[1], Zhaoyu Li[2], Binkui Jia[1], Xilin Lei[1], Kai Sun[3], Pengfei Yang[1], Shiye He[1], Di Wang[4], Haoling Zhang[4], Sinong Wang[1]

[1]School of Clinical Chinese Medicine, Gansu University of Chinese Medicine, Affiliated Hospital of Gansu University of Chinese Medicine, Lanzhou 730000, Gansu, China; [2]College of Acupuncture-Moxibustion and Tuina, Gansu University of Chinese Medicine, Gansu University of Chinese Medicine, Lanzhou 730000, Gansu, China; [3]College of Acupuncture-Moxibustion and Tuina, Henan University of Chinese Medicine, No. 156 Jinshui East Road, Zhengzhou 450000, Henan, China; [4]Department of Biomedical Sciences, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Penang 13200, Malaysia

Received July 4, 2025; Accepted August 16, 2025; Epub August 25, 2025; Published August 30, 2025

Abstract: Stem cells possess self-renewal and multipotent differentiation capabilities, exhibiting broad applications in regenerative medicine and tissue homeostasis maintenance. Their fate regulation relies heavily on precise epigenetic mechanisms. Cancer stem cells (CSCs), as key drivers of tumor heterogeneity, recurrence, and drug resistance, share extensive epigenetic features with normal stem cells, forming a complex and dynamic regulatory network. Mechanisms including DNA methylation, histone modification, chromatin remodeling, and ncRNAs collectively sustain stem cell pluripotency and tumor stemness, while aberrant epigenetic alterations serve as core drivers of tumor initiation and progression. In recent years, with the advent of single-cell omics and CRISPR-dCas9 epigenetic editing technologies, epigenetic "crosstalk" between stem cells and tumor cells has been progressively uncovered, especially the multidimensional epigenetic reprogramming induced by the tumor microenvironment (TME) that promotes CSC traits and drug resistance. This review systematically summarizes the epigenetic regulatory mechanisms of stem cells, epigenetic abnormalities in tumors, their interactions, and translational potential in therapeutic strategies, focusing on frontier topics such as reversible epigenetic plasticity, metabolic-epigenetic interplay, and liquid biopsy epigenetic biomarkers. Looking forward, artificial intelligence (AI) and big data analysis are expected to deepen the understanding of epigenetic heterogeneity, driving integrative innovations in precision medicine and regenerative interventions. Comprehensive understanding of the epigenetic crosstalk between stem cells and tumors will provide solid theoretical support and technical pathways for CSC-targeted therapies, epigenetic drug development, and stem cell fate manipulation.

Keywords: Stem cells, epigenetics, crosstalk mechanisms, DNA methylation, histone modification, non-coding RNA

Introduction

Stem cells, owing to their unique capacities for self-renewal and multilineage differentiation, have demonstrated broad clinical translational potential in regenerative medicine and tissue repair. Promising advances have already been made in treating hematological disorders, neurodegenerative diseases, and organ injuries. However, the success of clinical applications remains highly dependent on the precise regulation of stem cell differentiation fate. Meanwhile, cancer remains a leading global health burden, characterized by high heterogeneity, recurrence, and metastatic potential - features that remain inadequately explained by conventional research frameworks. The CSC theory posits that within tumors exists a subpopulation of cells with stem-like properties, capable of sustaining tumor heterogeneity, progression, and therapeutic resistance through asymmetric division. This suggests that CSCs may share critical epigenetic regulatory programs with normal stem cells.

In recent years, epigenetic mechanisms have emerged as a pivotal link bridging stem cell biology and tumor development. Processes

https://doi.org/10.62347/GQZH3508

such as DNA methylation, histone modifications, and non-coding RNA regulation reshape gene expression landscapes without altering the underlying DNA sequence. In stem cells, for example, TET family enzymes mediate the oxidation of 5-methylcytosine (5 mC) to facilitate gene activation [1, 2]; histone acetylation mediated by p300 plays essential roles in maintaining pluripotency or inducing lineage-specific differentiation [3]; and ncRNAs such as miR-34a contribute to fate determination [4]. In tumors, however, dysregulated epigenetic control acts as a major driving force. Aberrant promoter hypermethylation can silence tumor suppressor genes, histone deacetylation may enhance invasiveness, and disruption of non-coding RNA networks can promote therapeutic resistance. Moreover, key regulators such as EZH2 exert complex and often bidirectional roles in both stem cells and cancer cells [5, 6], underscoring a profound epigenetic overlap between these two cellular contexts.

Emerging technologies such as single-cell omics and CRISPR-dCas9-mediated epigenetic editing have provided powerful tools for dissecting stem cell differentiation trajectories, tumor heterogeneity, and the fine-tuned regulatory mechanisms underlying both processes [7]. Nevertheless, how environmental factors influence stem cell homeostasis and tumor evolution through epigenetic reprogramming remains largely unexplored and requires systematic investigation. Future research should focus on integrating clinical specimens, animal models, and precise intervention tools to elucidate the translational potential of epigenetic mechanisms - both in enhancing the safety and efficacy of stem cell-based therapies and in overcoming therapeutic resistance in cancer.

A comprehensive understanding of the epigenetic interconnections between stem cells and tumors holds great promise for unveiling novel mechanisms of disease pathogenesis and advancing breakthroughs in regenerative medicine and precision oncology. With the continued maturation of multi-omics integration and epigenetic intervention technologies, this interdisciplinary field is poised to drive biomedicine toward a new era of individualized and precision-based healthcare.

Epigenetic regulation of stem cells

Epigenetic features of embryonic stem cells (ESCs)

ESCs, derived from early-stage embryos, exhibit unlimited proliferative potential and pluripotency, enabling differentiation into diverse cell types of all three germ layers. These properties confer fundamental significance to ESCs in the fields of developmental biology and regenerative medicine. The maintenance of pluripotency in ESCs is governed by a highly coordinated molecular regulatory network. The core transcription factors Oct4, Sox2, and Nanog form an interconnected regulatory circuit that sustains self-renewal while repressing differentiation, with Oct4 and Sox2 functioning as indispensable components [8, 9].

At the epigenetic level, pluripotency-associated genomic regions generally retain a hypomethylated state accompanied by activating histone modifications, such as H3K4me3, which collectively facilitate robust transcription of pluripotency genes [10]. In addition, several signaling pathways are critically involved in preserving pluripotency. The Wnt/β-catenin pathway enhances stemness through the activation of downstream targets [10]; the Notch pathway regulates cell fate determination and prevents premature differentiation [11, 12], and the TGF-β pathway contributes to the stabilization of the pluripotent state.

Long non-coding RNAs (lncRNAs) further participate in this regulatory network and demonstrate dual functional roles. While certain lncRNAs positively support pluripotency, aberrant expression can disrupt homeostasis. For example, overexpression of linc-NSC has been shown to induce apoptosis in ESCs and reduce their tumorigenic capacity [13]. Taken together, pluripotency in ESCs is maintained through the integrated action of transcription factors, epigenetic modifications, and multiple signaling pathways. These mechanisms not only ensure the stability of ESC identity but also provide molecular insights into tumorigenesis and reveal potential therapeutic targets.

The pluripotency and self-renewal capacity of ESCs are governed by multilayered epigene-

tic mechanisms that orchestrate chromatin remodeling and transcriptional network coupling. In the H1-hESC model, high levels of DNA methylation cooperate with core pluripotency transcription factors such as Oct4, Sox2, and Nanog to maintain an open chromatin configuration and precisely control the temporal expression of key genes [14]. This central regulatory axis operates in concert with the histone modification system, forming a functionally complementary framework: H3K4me1, catalyzed by KMT2B, enhances enhancer-promoter interactions and facilitates transcriptional activation. Meanwhile, the bivalent domains marked by H3K4me3 and H3K27me3 at promoters of developmental genes establish a reversible balance between gene silencing and activation, endowing ESCs with both plasticity and responsiveness [15].

In recent years, increasing evidence has highlighted the critical role of RNA modifications in regulating stem cell fate. Epigenetic crosstalk between N6-methyladenosine (m^6A) and 5mC not only modulates transposable element activity but also plays a pivotal role in cell fate decisions, thereby expanding the conceptual boundaries of epigenetic regulation [16]. The plasticity of chromatin architecture is also fundamental to the maintenance of stemness. For example, Dppa3 induces a 2-cell embryo-like chromatin state, which is essential for zygotic genome activation [17]. At the same time, the DNA methylation machinery exhibits spatiotemporally specific regulatory patterns: DNMT1 controls the timing of de novo methylation by DNMT3 through both catalytic activity-dependent and independent pathways, ensuring the precise inheritance of epigenetic information [18].

The non-coding RNA regulatory network is also deeply embedded within the chromatin regulation system. For instance, Lnc530 modulates local chromatin states by forming a complex with DDX5 and TDP-43 proteins [19]. At the level of differentiation regulation, epigenetic factors exhibit marked functional heterogeneity: miR-146a directs the differentiation trajectory of vascular smooth muscle cells by targeting KLF4 [20], whereas TET-mediated active DNA demethylation influences mitotic fidelity in ESCs via regulation of KHDC3 expression, a process closely linked to tumorigenesis [21]. Notably, the enzymatic activity of TET proteins is finely modulated by the Idax/Rinf signaling axis, ensuring the precise execution of differentiation programs [22]. Dysregulation of such epigenetic regulatory networks is particularly prominent in cancer. For example, BRD9 not only sustains self-renewal in stem cells but also participates in the epigenetic reprogramming associated with pancreatic and breast cancer pathogenesis, underscoring a deep homology between stem cell epigenetic regulation and oncogenic mechanisms [23]. **Figure 1** illustrates the key epigenetic features of ESCs, including low DNA methylation levels, enrichment of active histone marks, and distinct chromatin configurations, which together establish the foundational framework for maintaining pluripotency and enabling lineage-specific differentiation.

Epigenetic regulation of adult stem cells

The epigenetic regulatory network precisely governs fate decisions in adult stem cells through mechanisms including DNA methylation, histone modifications (such as H3K27me3), and non-coding RNAs, thereby maintaining a dynamic balance between their quiescent state and differentiation potential. Environmental stimuli or pathological factors can reshape stem cell behavior by altering chromatin accessibility. Mechanistic studies have shown that Wedelolactone promotes chondrogenesis in mesenchymal stem cells (MSCs) by activating the transcription factor FOXO1, which in turn suppresses the activity of EZH2, the catalytic subunit of polycomb repressive complex 2 (PRC2), thereby lifting the epigenetic silencing of chondrogenesis-related genes [24]. In contrast, CTR9 deletion disrupts the bone morphogenetic protein 2 (BMP-2) signaling pathway and impairs the functional integrity of MSCs [25]. In a cardiac injury repair model, inhibition of EZH2 markedly attenuates the cardioprotective effects of MSC-derived exosomes (MSC-EXOs) and accelerates myocardial fibrosis. Interestingly, high mobility group protein A2 (HMGA2) can counteract this pathological effect. Further mechanistic exploration revealed that MSC-EXOs mitigate post-infarction fibrosis by inhibiting EZH2 activity, a process involving EZH2-mediated repression of HMGA2 expression and downstream damage to the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway [26].

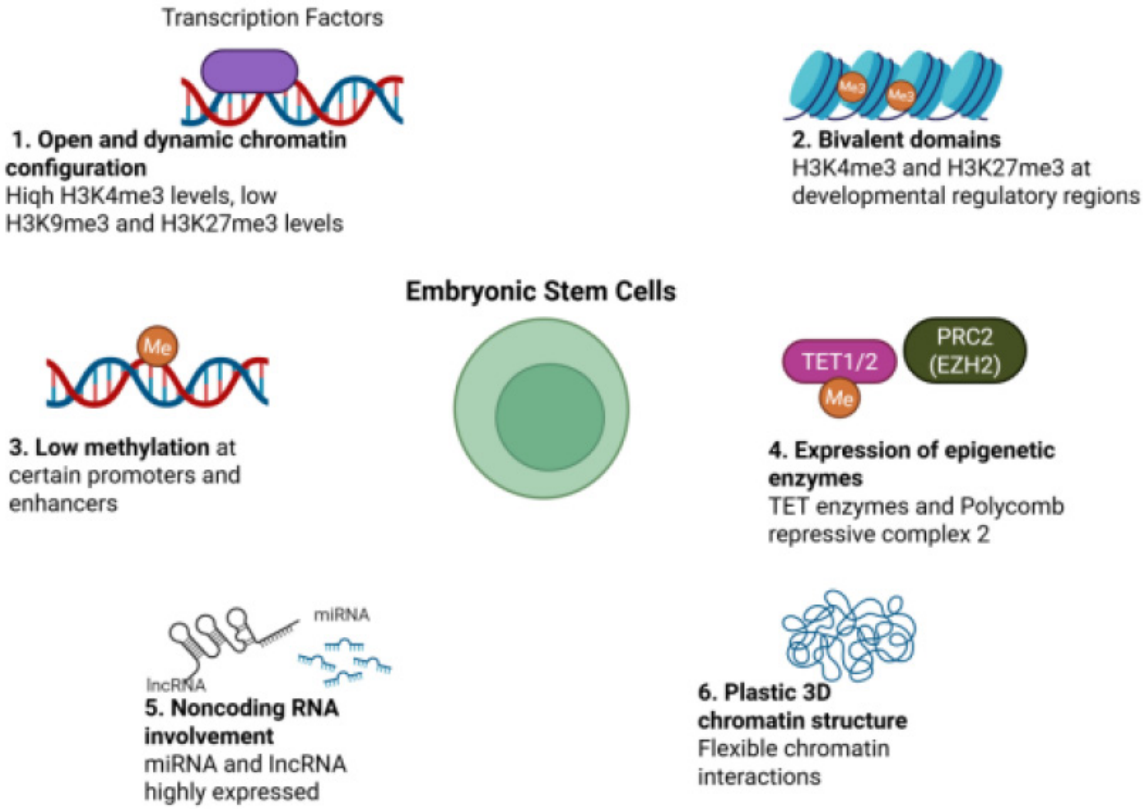

Figure 1. Illustrates the key epigenetic features of ESCs.

Aberrant epigenetic regulation can lead to impaired stem cell differentiation and contribute to the onset and progression of various diseases. For instance, the long non-coding RNA CIR inhibits the expression of ATOH8, thereby blocking the chondrogenic differentiation of human umbilical cord-derived MSCs (hUC-MSCs). Interestingly, ATOH8 itself positively regulates chondrogenesis via the EZH2/H3K27me3 axis, suggesting a feedback mechanism involving both transcriptional and epigenetic layers [27]. Similarly, in a pathological pregnancy model, exosomes derived from adipose-derived MSCs (AD-MSCs) mediate EZH2-dependent inactivation of the mammalian target of rapamycin (mTOR) signaling pathway, which plays a pivotal role in inducing protective autophagy in hypoxic trophoblasts [28].

The above studies have systematically demonstrated the central role of the EZH2/H3K27me3 axis in regulating stem cell differentiation and revealed how its dysregulation disrupts key signaling pathways such as BMP-SMAD, PI3K/AKT, and mTOR, thereby affecting tissue regeneration and repair (e.g., in the heart and cartilage) or mediating pathological processes (e.g., fibrosis, trophoblast dysfunction). These findings not only deepen our understanding of the molecular mechanisms underlying complex diseases such as tumorigenesis but also provide a critical theoretical foundation for developing precise therapeutic strategies based on exosome delivery systems or epigenetic inhibitors. Adult stem cells play essential roles in maintaining tissue homeostasis and driving regeneration, and their fate decisions are likewise governed by complex epigenetic mechanisms. Compared to ESCs, adult stem cells are generally maintained in a relatively stable yet reversible quiescent state. NcRNAs also contribute to the regulation of adult stem cell activation, proliferation, and differentiation. **Table 1** summarizes the major epigenetic features of various adult stem cell types and highlights their critical roles in functional maintenance and fate determination, providing valuable insights into their underlying regulatory networks.

Epigenetic reprogramming of induced pluripotent stem cells

Induced pluripotent stem cells (iPSCs) achieve somatic cell fate reversal through the system-

Table 1. Epigenetic regulatory mechanisms of adult stem cells

Stem Cell Type	Epigenetic Mechanism	Key Regulatory Factors/Enzymes	Target Genes or Pathways	Functional Impact	References
Hepatic Stellate Cells (HSCs)	Regulation via MIR4435-2HG/miR-506-3p axis; Regulation by miR-500a-3p transported through HCC-derived exosomes	CXCL1, TGF-β1; TGF-β1, IL-10, PD-L1	TGF-β signaling pathway; SOCS2/JAK3/STAT5A/STAT5B signaling pathway	Exacerbates the malignant behavior of HCC cells; Promotes HCC growth, migration, and regulation of the immune microenvironment	[214, 215]
Breast CSCs (BCSCs)	LINC00115 mediates SETDB1-driven methylation of PLK3; lncROPM regulates the mRNA stability of PLA2G16	SETDB1, PLK3, HIF1α, ALKBH5; lncROPM and PLA2G16	LINC00115-SETDB1-PLK3-HIF1α-ALKBH5 positive feedback loop; PLA2G16 and PI3K/AKT signaling pathways	Induces the BCSC phenotype, enhancing chemoresistance and metastasis; Maintains BCSC stemness, promoting chemoresistance and tumorigenesis	[108, 216]
Colorectal CSCs (CRCSC)	Epigenetic regulation of miR-8063; miR-210-3p-mediated targeting of STMN1	miR-8063 and its target hnRNPAB; miR-210-3p and STMN1	The hnRNPAB gene and the Wnt/β-catenin signaling pathway regulate microtubule stability via STMN1	Regulates the self-renewal capacity of colorectal CSCs; Promotes the migratory and deformability potential of CRCSC cells	[217, 218]
Prostate CSCs (PCSCs)	lncRNA MBNL1-AS1 competitively binds to miR-221-3p; miR-34a targets and regulates cancer-associated molecules	lncRNA MBNL1-AS1 and miR-221-3p; miR-34a and folate receptor alpha (FOLR1)	Targets CDKN1B to inhibit the Wnt signaling pathway; Targets molecules such as folate receptor alpha (FOLR1)	Regulates PCSC stemness and tumor proliferation and invasion; Inhibits prostate cancer cell growth and stemness	[219, 220]
Pancreatic CSCs (PCSCs)	lncRNA NORAD competitively binds to miR-202-5p; miR-630 targets and regulates PRKC	lncRNA NORAD, miR-202-5p, ANP32E; miR-630	ANP32E gene; PRKCI-Hedgehog signaling axis	Promotes PCSC proliferation and self-renewal; Inhibits PCSC self-renewal and tumorigenicity	[221, 222]
GSCs	lncRNA INHEG regulates rRNA 2'-O-methylation; EZH2-mediated enhancement of ZNF596/STAT3 signaling	lncRNA INHEG, SUMO2 E3 ligase TAF15, and NOP58; LINC00115 and EZH2	rRNA 2'-O-methylation pathway mediated by SUMOylation of NOP58; ZEB1 gene and the ZNF596/EZH2/STAT3 pathway	Promotes GSC self-renewal and tumorigenicity	[223, 224]
Esophageal CSCs (ECSCs)	SNHG16 functions as a miR-802 sponge to regulate gene expression; SNHG12 acts as a sponge for miR-6835-3p and regulates mRNA stability	miR-802, PTCH1; miR-6835-3p, BMI1, IGF2BP2, β-catenin	Hedgehog signaling pathway and PTCH1 gene; BMI1 and CTNNB1 (β-catenin)-related pathways	Promotes esophageal cancer cell proliferation and self-renewal; Enhances cell proliferation, migration, EMT transition, and maintenance of stemness	[225, 226]
Bladder CSCs (BCSCs) (CSCs)	DNMT3A mediates hypermethylation of the miR-129-2 promoter; LUCAT1 enhances mRNA stability in an m6A-dependent manner	DNMT3A, SNHG1; LUCAT1, IGF2BP2, HMGA1	SNHG1/DNMT3A/miR-129-2-5p/Rac1 signaling pathway; LUCAT1/IGF2BP2/HMGA1 axis	Induces stem-like behavior and cellular invasion; Enhances stem cell phenotype, chemoresistance, and malignant tumor progression	[227, 228]
Thyroid CSCs (TCSCs)	CDKN2B-AS1 regulates by sponging miR-122-5p; DOCK9-AS2 regulates gene expression by sponging miR-1972	miR-122-5p and P4HA1; SP1 and β-catenin (CTNNB1)	miR-122-5p/P4HA1 axis; Wnt/β-catenin pathway	Promotes thyroid cancer cell growth, migration, and invasion; Promotes tumor proliferation, migration, invasion, EMT, and stemness	[229, 230]
Endometrial CSCs (CSCs)	miR-326 targets and regulates gene expression; miR-137 is upregulated and suppresses PITX2 expression through targeted inhibition	GPR91, STAT3, VEGF; miR-137, PITX2	GPR91/STAT3/VEGF signaling pathway; miR-137/PITX2/MyoD regulatory axis	Inhibits HuECSC proliferation, invasion, angiogenesis, and tumorigenicity; Suppresses the myogenic differentiation capacity of EN-MSCs	[231, 232]

atic remodeling of the epigenetic landscape. The core mechanisms involve dynamic regulation of DNA methylation, reconfiguration of histone modifications, and decondensation of higher-order chromatin structures. This process relies on the targeted erasure of genomic imprints by DNA demethylases (e.g., the TET family), chromatin opening mediated by histone acetyltransferases (e.g., p300), and the overcoming of epigenetic barriers such as X chromosome reactivation, ultimately reconstructing an embryonic stem cell-like gene regulatory network. However, residual epigenetic memory - such as donor cell-specific DNA methylation heterogeneity - may impair the differentiation potential of iPSCs and increase their tumorigenic risk. Recent single-cell multi-omics studies have shed light on the molecular characteristics of such residual signatures: in iPSCs with homozygous deletions of different exons in DNMT3A, near-complete loss of DNA methylation is observed, yet the cells retain the capacity for mesenchymal and hematopoietic differentiation. Notably, exon 23-deleted iPSC-derived hematopoietic progenitor cells (iHPCs) partially recapitulate the methylation features of DNMT3A-mutant acute myeloid leukemia (AML) [29]. This phenomenon suggests that functional redundancy among epigenetic enzymes may buffer the consequences of global methylation loss.

Further studies have revealed that histone modification regulation plays a pivotal role in cell fate determination. For instance, HDAC2 modulates the expression of Endophilin-B1 in neuronal subtypes, serving not only as a marker of differentiated neurons but also directly influencing neuronal and mitochondrial metabolic pathways [30].

Moreover, epigenetic reprogramming can be precisely modulated through signaling pathways. Interferon-γ (IFNγ) stimulation enhances the activity of TET enzymes via activation of the STAT3 signaling pathway, thereby promoting X chromosome reactivation - a process directly associated with TET-mediated DNA demethylation [31]. Current research is increasingly focused on integrating CRISPR-based screening technologies with epigenetic editing tools - such as dCas9-TET1 fusion proteins - to explore novel strategies for eliminating epigenetic noise, with the ultimate goal of enabling precise control over iPSC reprogramming trajectories and enhancing their clinical safety.

Similar to ESCs, iPSCs exhibit various "bivalent" epigenetic states during early reprogramming. The interplay between ncRNAs and epigenetic regulators plays a pivotal role in shaping their phenotypic characteristics. **Table 2** summarizes the major molecular events and regulatory mechanisms involved in the epigenetic reprogramming of iPSCs, providing critical insights into the principles of reprogramming and its potential links to epigenetic abnormalities in cancer.

Epigenetic aberrations in cancer

Aberrant DNA methylation in tumorigenesis

Aberrant DNA methylation profoundly influences tumor initiation and progression through dual-layered epigenetic mechanisms. On a global scale, hypomethylation can induce chromosomal instability (CIN) and aberrant activation of repetitive genomic elements, thereby significantly enhancing the genomic mutational potential of cancer cells. Concurrently, hypermethylation of CpG islands in the promoter regions of specific tumor suppressor genes (e.g., p16, BRCA1) and DNA damage repair genes leads to transcriptional silencing, collectively forming a core oncogenic mechanism that drives cancer progression. Epidemiological studies indicate that approximately 70% of tumor-associated genes exhibit aberrant methylation. This epigenetic alteration is implicated in the maintenance of CSC properties and clonal evolution, and has emerged as a critical therapeutic target in the field of epigenetic therapy. In solid tumors, global hypomethylation is significantly associated with tumor aggressiveness and clinical prognosis. In pancreatic cancer, clinical studies have demonstrated that DNA hypomethylation can serve as a biomarker for predicting occult metastasis risk [32]. In hepatocellular carcinoma (HCC), gastric cancer, and colorectal cancer, hypomethylation within intragenic regions of the SMAD3 gene suggests dysregulation of the TGF-β signaling pathway [33]. Additionally, hypomethylation of the S100P gene has been identified as a driver of malignant transformation in the serrated adenoma-carcinoma sequence [34]. Notably, in ovarian cancer, hypermethylation of the BRCA1 promoter detectable in patient serum

Table 2. Epigenetic reprogramming mechanisms of iPSCs

Reprogramming Stage	Epigenetic Mechanism	Key Regulatory Factors/Enzymes	Target Sites or Regions	Biological Effects	Experimental Model or Cell Type	References
Early Stage	DNA demethylation	TET1/2/3; miR-29a/b	Genome-wide CpG islands; Promoter region	Early transcriptional reprogramming; Silencing of tumor suppressor genes	Mouse pulmonary epithelial premalignant cells; TET2-knockout RWPE-1 cells	[233, 234]
Early Stage	Histone modification	H3K4 methyltransferase, BRD4	Transgene promoter	Pro-metastatic phenotype	Primary PDAC cells; PLC	[235, 236]
Intermediate Stage	Non-coding RNA	LncRNA; BMP7	BMP7 promoter	BMP7 expression	Oct4/JDP2-induced iPS-like cells; Human ESCC cell line	[237, 238]
Intermediate Stage	Non-coding RNA	miRNA; miR-155	Pluripotency gene promoter; Ship1 mRNA 3' untranslated region (3'UTR)	Phenotypic reversibility; Inhibition of terminal differentiation	Genome-wide miRNA microarray; Antigen-specific $CD8^+$ T cells	[239, 240]
Intermediate Stage	Chromatin remodeling	Core driver factors; BRG1	MYC promoter; FASN promoter	Epigenetic heterogeneity; Proliferation dependence	Patient-derived organoids (PDOs); TNBC cell lines TNBC	[241, 242]
Maturation Stage	Gene expression activation	SOX2; Ezh2	Super-enhancer-associated oncogenes; Neuroendocrine gene promoters	Tumor dependency; Heterogeneous tumor	Mouse xenograft model; Patient-derived xenograft (PDX) model	[243, 244]
Maturation Stage	Transcription factor regulation	GLI2-NANOG positive feedback loop; NANOG-MYC positive feedback loop	Metastasis-specific enhancer regions; MYC target gene promoters	Distant organ colonization; Therapeutic resistance (castration/chemotherapy)	Clonosphere-derived tumor model; CRPC xenograft tumor (LAPC9) CRPC	[245, 246]
Late Stage	Histone modification	OCT4	OCT4 promoter region	Promotes cellular phenotype transformation	MCF7 breast cancer cell line	[247, 248]
Late Stage	Inhibits the Wnt/β-catenin signaling pathway	DNMTs, TET	Wnt/β-catenin signaling pathway	Enhances antitumor and antimetastatic effects	Breast CSCs; LUAD mouse model (LUAD: Lung Adenocarcinoma)	[233, 249]
Early Stage	Histone modification	EZH2, miR-490-3p	Host gene of miR-490-3p; Gene regulatory region of GC B cells (GC B cells: Germinal Center B cells)	Affects the expression of its target genes; Inhibits proliferation	GBM cell lines (GBM Multiforme cell lines); FL cell lines (Follicular Lymphoma cell lines)	[250, 251]

has demonstrated promising potential as a non-invasive diagnostic marker [35].

At the molecular level, aberrant methylation is primarily mediated by the DNA methyltransferase (DNMT) family. In breast cancer, the cooperative action of DNMT1 and DNMT3a induces hypermethylation of the RGMA gene, which subsequently activates the FAK/Src/PI3K/AKT signaling pathway [36]. In endometrial carcinoma, the long non-coding RNA FAM83H-AS1 has been shown to epigenetically regulate ferroptosis by recruiting DNMT1 to enhance methylation of the CDO1 gene [37]. Cancer type-specific methylation landscapes further underscore the complexity of this regulatory network. In gallbladder cancer, hypermethylation of the DLC1 gene directly contributes to oncogenic transformation [38]; in gastric cancer, hypomethylation of LIN28B is independently associated with poor prognosis [39]. In HCC, PDE7B promoter methylation modulates epithelial-mesenchymal transition (EMT) via the PI3K/AKT pathway [40], while in colorectal cancer, hypomethylation of SLCO4A1-AS1 activates the Hsp90/Cdk2/c-Myc axis to promote tumor progression [41]. In glioblastoma (GBM), FOSL2 hypomethylation has been found to drive M2 polarization of tumor-associated macrophages [42]. In hematological malignancies, BCL7A gene silencing via promoter methylation has been implicated in the regulation of leukemic cell proliferation [43], and in colorectal cancer, CXCL14 hypermethylation reveals a novel epigenetic mechanism for TME modulation [43].

Epigenetic therapeutic strategies are making breakthroughs in clinical translation. DNMT inhibitors have shown promising effects in restoring target gene expression and enhancing the sensitivity of tumors to immunotherapy. For example, decitabine combined with PAS1-30nt-RNA effectively suppresses breast cancer metastasis by reactivating silenced genes [44]. Additionally, the regulation of DNMT3A by the SYNCRIP protein has identified a novel therapeutic target for reversing aberrant p16 gene methylation [45]. These advances strongly support the notion that DNA methylation abnormalities are not only hallmark epigenetic features of cancer, but also highly actionable targets in the era of precision medicine. Their clinical potential warrants further in-depth exploration and development.

Aberrant histone modifications in cancer

Aberrant histone modifications play a central role in tumor initiation and progression by altering chromatin accessibility and gene expression patterns. Dysregulated modifications - such as acetylation, methylation, and ubiquitination - can disrupt the dynamic balance of chromatin structure, leading to oncogene activation or tumor suppressor gene silencing. For example, hypoxia promotes sustained EMT in pancreatic ductal adenocarcinoma (PDAC) via the histone methylation-MAPL axis, which is targetable by multidrug therapy, offering a potential strategy to overcome chemoresistance [46]. Further studies have shown that hyperactivation of histone deacetylases (HDACs) induces chromatin condensation and suppresses tumor suppressor gene expression. Meanwhile, aberrant overexpression of the histone methyltransferase EZH2 promotes cancer cell proliferation by catalyzing H3K27me3-mediated gene silencing [47]. In addition, mutations in histone-modifying enzymes - such as MLL gene rearrangements - can lead to abnormal methylation patterns, driving the progression of hematologic malignancies such as leukemia [48]. These epigenetic disruptions not only act as independent oncogenic drivers but also interact with other mechanisms, including DNA methylation and non-coding RNAs, collectively shaping the epigenomic landscape of cancer.

In colorectal cancer (CRC), methylation of H3R117 promotes the citrullination of histone H3 (H3cit), which in turn increases methylation of the IGFBP1 promoter. This process enhances the enrichment of H3K9me2, heterochromatin protein 1 (HP1), and DNMT1 at the promoter region. IGFBP1 is believed to function as a tumor suppressor gene, while MARylation of H3R117 may facilitate CRC progression [49]. Mechanistically, HBO1 acetylates H3K14, H4K8, and H4K12, thereby upregulating CTNNB1 expression and activating the Wnt/β-catenin signaling pathway. A novel small-molecule HBO1 inhibitor, WM-3835, has been shown to effectively suppress the progression of B-cell acute lymphoblastic leukemia (B-ALL) [50]. Similarly, in gastric cancer, hesperetin modulates the activity of CBP, affecting the stability of the DOT1L protein, which leads to a significant reduction in H3K79 methylation and

the expression of metastasis-related genes [51].

Key nodes within the epigenetic regulatory network have further revealed potential therapeutic targets in cancer. ASH2L, through its interaction with COMPASS components and specific genomic loci, promotes invasion and migration in triple-negative breast cancer (TNBC) cells, likely via H3K4 methylation at inflammation- and immune response-related genes [52]. Elevated nuclear levels of SREBF1 and histone H2A lysine 130 acetylation (H2A-K130ac) are directly associated with advanced prostate cancer. Reversal of these epigenetic changes can sensitize castration-resistant prostate cancer (CRPC) to abiraterone treatment [53]. In addition, HMGCL-mediated metabolic regulation of histone acetylation activates the FOXM1/β-catenin pathway in GBM, and targeting HMGCL with JIB-04 has been shown to effectively inhibit tumor growth [54].

The synergistic interaction between ncRNAs and histone modifications also warrants significant attention. The transcription factor NONO directly interacts with nuclear PKM2, guiding PKM2-mediated phosphorylation of histone H3 at threonine 11 (H3T11ph) to promote metastasis in TNBC. H3T11ph, in cooperation with TIP60-mediated H3K27 acetylation (H3K27ac), jointly activates SERPINE1 expression, thereby enhancing tumor invasiveness [55]. In ovarian cancer, high expression of PRMT1 facilitates BRD4 methylation, which promotes its phosphorylation. Silencing PRMT1 significantly inhibits tumor progression, highlighting its potential as a therapeutic target [56].

Epigenetic-targeted therapeutic strategies have made breakthrough advances. HDACi alleviate the suppression of PRELP mRNA expression in bladder cancer cells by promoting histone acetylation, and several HDAC is have already entered clinical application [57]. Belinostat effectively kills KRAS-mutant lung cancer cells by modulating mitochondrial metabolism, while Panobinostat exerts anticancer effects via the Nrf2 signaling pathway [58]. Moreover, the combination of HDACi with ferroptosis inducers has been shown to enhance the ferroptotic sensitivity of colorectal cancer cells [59]. In prostate cancer, reversing the SREBF1/H2A-K130ac axis can resensitize CRPC to abiraterone [53], and NIT2, by inhibiting HBO1-mediated H3K14 acetylation and oxidative phosphorylation gene expression, is positively correlated with favorable prognosis in gastric cancer [60].

In summary, aberrant histone modifications reshape the epigenomic landscape of tumors through multilayered regulatory networks, providing a solid theoretical foundation for the development of targeted therapies, such as HDACi, EZH2is, and PRMT1 antagonists. Future research should focus on elucidating the crosstalk mechanisms among different histone modifications to enable precise epigenetic intervention strategies.

Dysregulation of non-coding RNA in cancer

Dysregulated non-coding RNAs (ncRNAs) have become a central component of epigenetic disruption in cancer, playing critical roles in tumor initiation, progression, and therapeutic resistance through multilayered regulatory networks involving epigenetic modifications, post-transcriptional regulation, and protein interactions. As key regulatory hubs of gene expression, different classes of ncRNAs exhibit distinct molecular mechanisms: MicroRNAs (miRNAs) can simultaneously regulate tumor suppressor genes and oncogenes via bidirectional control, influencing tumor behavior in a context-dependent manner; Long non-coding RNAs (lncRNAs) function both by recruiting chromatin-modifying complexes (such as PRC2) to mediate histone methylation, and by acting as competing endogenous RNAs (ceRNAs) to construct intricate epigenetic regulatory networks; Circular RNAs (circRNAs) typically participate in the fine-tuning of oncogenic signaling pathways by functioning as miRNA sponges, thereby modulating downstream gene expression.

Mechanistic studies have revealed the specific roles of ncRNAs in tumor regulation. At the level of microRNA-mediated control, miR-204-3p significantly suppresses pancreatic cancer metastasis by targeting the MGAT1 gene [61], while miR-1269b modulates the malignant behavior of gastric cancer cells by regulating METTL3 expression [62]. The lncRNA MALAT1 promotes breast cancer progression via the miR-561-3p/TOP2A signaling axis [63], whereas miR-488 [64] and miR-432 [65] exert tumor-suppre-

ssive effects in breast cancer by targeting FSCN1 and AXL, respectively. In colorectal cancer, miR-330 inhibits tumor cell proliferation by downregulating TYMS expression [66], and miR-195-5p affects metabolic reprogramming in TNBC through the regulation of PSAT1 [67].

The regulatory network of lncRNAs exhibits multidimensional characteristics in tumor biology. SNHG1 promotes breast cancer growth and angiogenesis by regulating STAT6 phosphorylation [68], and also facilitates oral squamous cell carcinoma progression via the RUNX2/GDF10 signaling axis [69]. SNHG14 drives gastric cancer metastasis by activating the EMT program [70], while MYO16-AS1 enhances invasive capacity of bladder cancer cells, contributing to disease progression [71]. In contrast, NBR2 suppresses breast cancer cell proliferation by inhibiting the autophagy pathway [72].

In the field of circRNA regulation, circ_0007379 promotes the maturation of miR-320a, thereby negatively regulating RUNX1 expression [73]. Exosome-derived circPLEKHM1 drives tumor metastasis by upregulating OSMR protein translation [74], while circNEIL3 suppresses colorectal cancer metastasis by binding to and promoting the degradation of the YBX1 protein [75]. These studies highlight how ncRNAs construct intricate interactive regulatory networks, forming complex hierarchical layers of control throughout the entire course of tumor development and therapeutic resistance.

In summary, ncRNA-mediated epigenetic regulatory networks offer a novel perspective for understanding the biological behavior of tumors. Their multilayered and multipathway regulatory characteristics not only deepen our understanding of the mechanisms underlying tumorigenesis but also open new avenues for the development of ncRNA-based precision diagnostic and therapeutic strategies.

Epigenetic interactions between stem cells and cancer

Epigenetic regulation of CSCS

Stem cells and somatic cells exhibit substantial convergence in their epigenetic regulatory mechanisms, encompassing DNA methylation, histone modifications, and non-coding RNA-mediated control. In stem cells, global hypomethylation serves to preserve pluripotency and self-renewal, whereas differentiated cells rely on selective gene silencing through DNA methylation to ensure phenotypic stability. CSC-associated surface markers are similarly subject to methylation-dependent regulation; for example, methylation of Lgr5 has been correlated with favorable prognosis in CRC, highlighting the pivotal role of DNA methylation in both cell fate determination and tumor progression, albeit not as the sole regulatory mechanism [76, 77]. Histone modifications further contribute to the plasticity of epigenetic states. The coexistence of the “bivalent” marks H3K4me3 and H3K27me3, enriched at promoters of ESCs and developmental regulators, establishes a poised configuration that facilitates transcriptional activation upon differentiation cues. Although the functional implications of UTX-mediated H3K27 demethylation remain under debate, accumulating evidence indicates its essential contribution to the regulation of these state transitions [78, 79]. Moreover, non-coding RNAs, particularly miRNAs and lncRNAs, exert multilayered regulatory effects by modulating translational repression, chromatin remodeling, and transcriptional control, thereby maintaining cellular homeostasis and directing lineage commitment. A notable example is HOTAIR, which activates core stemness factors through the NF-κB pathway, thereby sustaining ovarian CSC self-renewal and driving tumor progression. Therapeutic approaches that integrate epigenetic modulators with strategies targeting HOTAIR have been proposed as promising avenues to mitigate recurrence risk [6].

The maintenance of CSCs and their role in driving tumor heterogeneity and treatment resistance are fundamentally governed by a dynamic regulatory network formed through the interplay between epigenetic mechanisms and non-coding RNA signaling. At the epigenetic level, DNA methylation contributes to oncogenesis by silencing tumor suppressor genes (such as CDKN2A and APC) and activating stemness-associated pathways, notably Wnt/β-catenin, thereby establishing a persistent pro-oncogenic epigenetic memory. Of particular interest is the role of PRMT9 in regulating leukemia stem

cell survival and immune evasion, suggesting its potential as a therapeutic target [80-82]. Histone-modifying enzymes, including EZH2, HDACs, and KDM1A/LSD1, dynamically modulate chromatin accessibility to fine-tune the expression thresholds of key stemness genes such as SOX2, OCT4, and LGR5. Representative examples include BEX1, which maintains liver CSC properties via the Wnt/β-catenin pathway, and SLC25A22, which reprograms succinate metabolism to activate the same pathway and induce 5-fluorouracil resistance in colorectal cancer [81, 83-87]. Moreover, the cooperative interaction between H3K4 methyltransferases (KMT2B/KMT2D) and DNA methylation has opened new avenues for understanding breast CSC dormancy mechanisms. Interventions targeting UHRF1 or disrupting the DNA methylation-progesterone signaling axis have also demonstrated clinical potential in attenuating CSC phenotypes in both HCC and leukemia [82, 85, 88].

NcRNAs play a pivotal role in reinforcing epigenetic regulatory effects by establishing multilayered control networks. At the axis level, HotairM1 promotes CSC self-renewal via the HOXA1-Nanog signaling axis, while m6A modification mediated by METTL14/IGF2BP2 regulates malignant transformation of lung cancer stem-like cells through lncRNA AC026356.1 [89, 90]. In breast cancer, the lncROPM-PLA2G16 axis has been shown to maintain stem cell pluripotency, while lnc408 supports the stem-like phenotype via the CBY1-β-catenin axis; HOTAIR significantly enhances breast CSC activity by activating the NF-κB pathway [91-93]. In prostate cancer, lncRNA NORAD accelerates CSC proliferation via the miR-202-5p/ANP32E axis. In gastric cancer, WT1-AS suppresses stemness through downregulation of WT1 or hsa-miR-15a-5p via the ONECUT2/β-catenin axis [94-96].

In esophageal squamous cell carcinoma (ESCC), the UPF1/LINC00963/miR-508-5p/SOX2 axis, along with SOX2OT, forms an integrated regulatory network mediating chemoresistance and tumorigenesis. In oral squamous cell carcinoma, miR-146a maintains CSC survival via the CD24-AKT-β-catenin axis, while LSD1 promotes stemness through the KPNA2/PI3K/AKT pathway [87, 97, 98]. In HCC, TINCR maintains stem-like properties through autophagy regulation, while the DIO3OS-NONO-ZEB1 axis exhibits tumor-suppressive activity. Moreover, m6A modification of MIR4435-2HG/NOP58 drives maintenance of the CSC phenotype [99-101]. In glioma, lncRNA INHEG supports CSC characteristics by linking rRNA methylation to protein translation, and GAS5 suppresses GBM proliferation through epigenetic regulation [102, 103]. In ovarian cancer, combining HOTAIR inhibition with epigenetic drugs can reverse platinum resistance, while in breast cancer, LINC00115 has been implicated in chemoresistance via SETDB1-mediated epigenetic regulation [91, 104, 105].

Epigenetic reprogramming endows CSCs with unique properties of drug resistance and dormancy, enabling them to evade therapy through reversible shifts in epigenetic states under microenvironmental stress. This forms the biological foundation for tumor recurrence and metastasis. Systematic dissection and precise targeting of these regulatory networks hold significant translational potential for the development of innovative combination therapies aimed at overcoming drug resistance, eradicating CSCs, and preventing tumor relapse.

Epigenetic mechanisms underlying the transformation of stem cells into tumor cells

In recent years, advances in stem cell engineering and epigenetic research have highlighted the pivotal role of stem cells in tumor initiation, progression, and therapeutic intervention. MSCs and iPSCs, owing to their tumor-tropic properties, have been utilized as vehicles for targeted drug delivery. By carrying anti-tumor agents or gene-editing tools, they enable precise targeting of the tumor microenvironment, thereby enhancing therapeutic efficacy while minimizing adverse effects. Evidence indicates that MSCs can promote fatty acid oxidation (FAO), which in turn enhances GC cell stemness and chemoresistance; conversely, the combination of FAO inhibitors with chemotherapy has been proposed as a promising strategy to overcome this resistance. Furthermore, the MSC-associated long non-coding RNA HCP5 has been shown to aggravate chemoresistance through specific signaling axes [106, 107].

Beyond drug delivery, stem cells contribute to immunotherapy by secreting cytokines or serving as carriers for tumor vaccines to potentiate

immune responses. They also participate in epigenetic regulation and gene repair delivery strategies designed to reverse drug resistance. Notably, the LINC00115/SETDB1 axis and the lncROPM-PLA2G16 signaling pathway have been identified as key mediators of chemoresistance in breast CSCs [108, 109]. Collectively, these findings underscore that stem cells not only exert essential regulatory functions in tumorigenesis but also provide novel strategies for drug delivery, immunotherapeutic enhancement, and the reversal of therapeutic resistance.

In EpCAM-positive hepatic progenitor stem cells (HpSCs), aberrant epigenetic regulatory networks drive tumorigenesis through multilayered synergistic interactions. The DNA methylation landscape exhibits a paradoxical pattern characterized by global hypomethylation alongside localized hypermethylation, resulting in oncogene activation and transcriptional silencing of key tumor suppressor genes such as p16 and BRCA1. This bidirectional epigenetic dysregulation disrupts the threshold of cell fate determination and acts as a crucial molecular switch for the malignant transformation of HpSCs into CSCs, contributing to the development of hepatoblastoma (HB) and HCC [110].

Aberrant regulation at the level of histone modifications also constitutes a core mechanism in malignant transformation. The histone demethylase KDM5B remodels chromatin architecture by specifically removing H3K4me3 marks, while functional inactivation of its negative regulator, hsa-miR-448, further lifts the repression of the KDM5B-MALAT1 signaling axis, forming a positive feedback loop that sustains tumor cell stemness. Notably, this mechanism has been experimentally validated in a TNBC metastasis model [111]. Non-coding RNA-mediated epigenetic reprogramming also plays a pivotal role. The long non-coding RNA DUXAP10, by recruiting PRC2, induces local CpG island hypermethylation and reshapes chromatin accessibility landscapes during cadmium-induced carcinogenesis [112]. In HCC, m6A methylation serves as an upstream driver of lncRNA MIR4435-2HG expression, which - through recognition by the YTHDF protein family - initiates a NOP58-dependent stemness maintenance program [101].

The epigenetic hub protein SATB2 exhibits a unique dual regulatory function: by integrating DNMT activity with histone acetylation, it simultaneously silences differentiation-related gene expression and activates the Wnt/β-catenin signaling pathway. This dual mode of regulation directly drives the malignant transformation of prostate epithelial progenitor cells (PrECs) into a CSC-like phenotype [113]. In ESCC, miR-191-3p regulates the CXCR4/PI3K/AKT signaling axis by targeting and suppressing RGS1 expression. Its stemness-regulating effect shows a strong correlation with HDAC activity [114]. The histone demethylase KDM1A establishes a cross-regulatory network between the histone code and non-histone modifications by coordinately removing H3K4me1/2 marks and stabilizing HIF-1α protein via deubiquitination. This leads to transcriptional repression of the Wnt pathway antagonist APC2 and aberrant activation of DKK1, a mechanism identified as a central molecular event in maintaining thyroid cancer stemness [86].

Of particular interest is the TET1/FOXO4 transcriptional regulatory axis, which modulates β-catenin nuclear translocation via 5-hydroxymethylcytosine (5hmC) modification. During gastric cancer metastasis, this axis forms a positive feedback loop with the canonical Wnt signaling pathway, revealing the dual functional nature of TET family enzymes as key executors of epigenetic reprogramming [115]. Collectively, these studies outline a molecular landscape of epigenetic memory remodeling, wherein imbalanced DNA methylation, disrupted histone modifications, and non-coding RNA regulatory networks drive a cascade amplification effect that facilitates the phenotypic transformation of stem cells into tumor-initiating cells. This provides a novel epigenetic perspective for understanding tumor initiation and progression. The transformation of stem cells into cancer cells is typically accompanied by aberrant DNA methylation, dysregulated histone modifications, reorganization of higher-order chromatin structure, and perturbation of non-coding RNA networks - all of which collectively promote the aberrant activation of stemness-associated genes and silencing of tumor suppressor genes. **Figure 2** provides a systematic overview of the key epigenetic events, molecular pathways, and their interactions involved in the transformation of stem cells into tumor cells, offering a

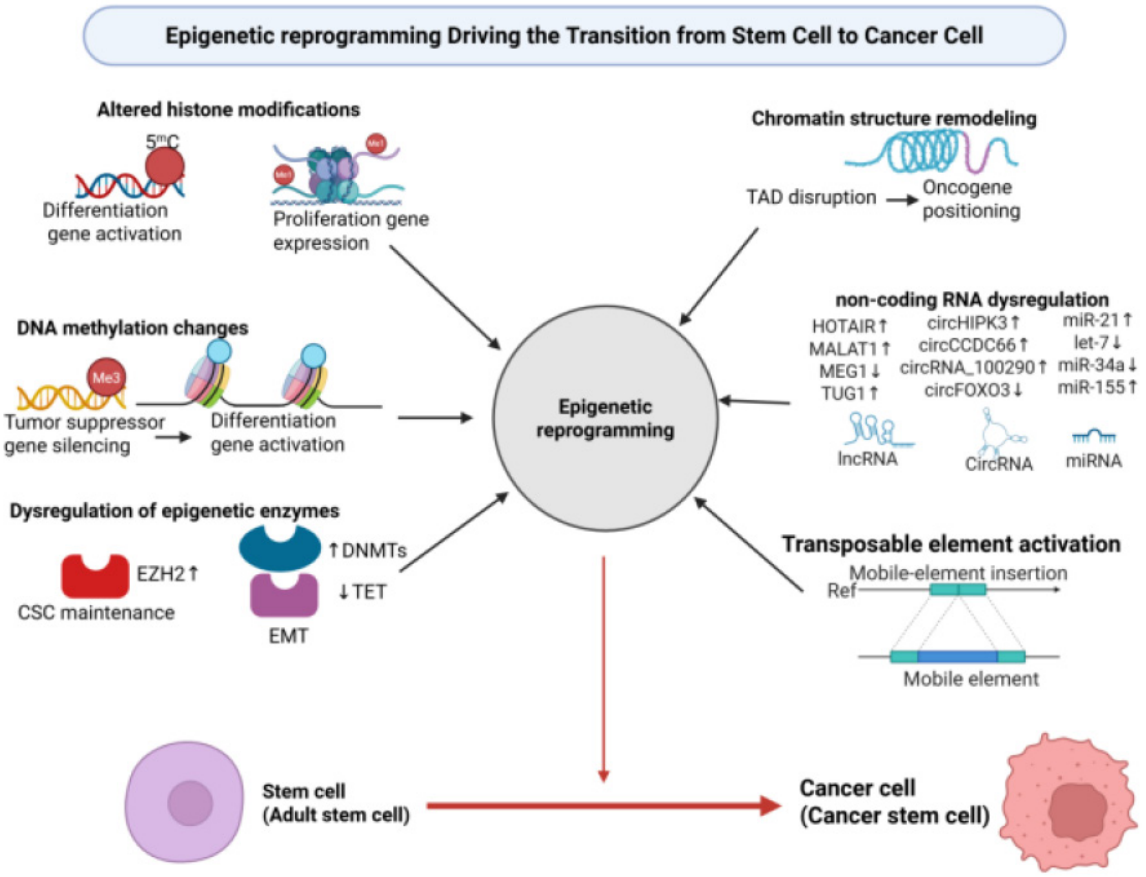

Figure 2. A comprehensive schematic of critical epigenetic events.

visual framework for deciphering the mechanisms of stem cell malignant conversion and identifying potential intervention strategies.

Epigenetic influence of the TME on stem cells and cancer cells

The epigenetic interplay between stem cells and tumors is reflected not only in their shared gene regulatory mechanisms but also in the establishment of complex multilayered networks mediated by DNA methylation, histone modifications, and non-coding RNAs. These networks play critical roles in sustaining the characteristics of CSCs and in driving therapeutic resistance [116]. Although stem cells exhibit considerable potential in drug delivery and immune modulation, their genomic instability and epigenetic plasticity remain major challenges to clinical application. Emerging epigenetic editing technologies, such as CRISPR/Cas9, offer promising opportunities to target key regulatory modifications, optimize stem cell-based therapies, and enhance immune responses [117, 118].

In addition, stem cells actively remodel the tumor epigenetic landscape within the tumor microenvironment (TME) by modulating immune cells, fibroblasts, and cytokine networks. For example, exosomal H19 derived from cancer-associated fibroblasts (CAFs) has been shown to promote stemness and drug resistance in CRC [119]. These findings underscore the necessity for future research to systematically dissect the stem cell-tumor epigenetic regulatory networks, while integrating epigenetic editing, immune modulation, and stem cell engineering to accelerate the clinical translation of precision medicine and personalized anticancer strategies.

The TME plays a critical role in driving malignant tumor progression through multidimensional epigenetic regulatory networks. Under hypoxic conditions, a central component of the

TME, the expression of DNA methyltransferase 3B (DNMT3B) is upregulated, leading to hypermethylation of the promoter region of microRNA-485-3p (miR-485-3p). This epigenetic alteration not only directly sustains CSC properties and chemoresistance in PDAC [120], but also reveals a key regulatory mechanism by which hypoxia suppresses TET dioxygenase activity, resulting in a global increase in DNA methylation. Further mechanistic analysis has shown that the hypoxia-activated spliced variant of XBP1 (XBP1s), independent of the hypoxia-inducible factor 1α (HIF1α) signaling pathway, forms a transcriptional regulatory complex with histone deacetylase 2 (HDAC2) and histone methyltransferase EZH2. This complex remodels the chromatin architecture associated with ΔNp63α, providing an epigenetic foundation for breast cancer metastasis [121].

This regulatory network exhibits dual epigenetic effects at the level of histone modifications. Hypoxia-induced histone H3 lysine 9 lactylation (H3K9la) enhances the invasive capacity of ESCC by activating the expression of laminin subunit gamma 2 (LAMC2) [122]. Meanwhile, E2F transcription factor 1 (E2F1) mediates the aberrant alternative splicing of serine/arginine-rich splicing factor 7 (SRSF7), providing novel insight into how epigenetic plasticity influences breast cancer progression through alternative splicing regulation [123].

The cytokines secreted by stromal fibroblasts, such as transforming growth factor-β (TGF-β) and interleukin-6 (IL-6), constitute another crucial regulatory axis. Pan-cancer analysis of the long non-coding RNA MIR210HG has shown a significant positive correlation between its expression levels and both tumor hypoxia and immune cell infiltration [124], highlighting the synergistic role of microenvironmental factors in driving epigenetic imbalance. On the level of metabolic regulation, lactate dehydrogenase (LDH) activity between tumor and stromal cells leads to the accumulation of L-2-hydroxyglutarate (L-2HG), which perpetuates a malignant cycle by maintaining CSC traits and promoting an immunosuppressive microenvironment [125]. Meanwhile, ALL1 fusion gene-associated protein 9 (AF9) bridges HIF1α and acetylated c-Myc to form a transcriptional complex, thereby revealing the central role of epigenetic regulators in HCC progression from a metabolic reprogramming perspective [126].

These dynamic interactions indicate that the TME orchestrates a multilayered epigenetic reprogramming system -comprising DNA methylation, histone modifications, and non-coding RNA regulation - which not only intensifies molecular heterogeneity but also confers drug resistance and metastatic potential to tumor cells. This theoretical framework provides a critical scientific basis for the development of therapeutic strategies targeting the epigenetic-microenvironmental interaction axis and underscores the need for future interventions to consider the synergistic regulatory network involving metabolism, epigenetics, and the immune microenvironment. Components of the TME - such as inflammatory cytokines, hypoxic conditions, tumor-associated fibroblasts, and immune cells - can modulate the activity of DNMTs and histone-modifying enzymes, thereby influencing chromatin accessibility and non-coding RNA expression. These changes, in turn, promote the maintenance of stemness, drug resistance, and invasive phenotypes. **Figure 3** summarizes the key molecular pathways and mechanisms by which the TME regulates the epigenetic states of stem and tumor cells, offering a visual reference for understanding their dynamic interactions.

Epigenetic therapy strategies targeting stem cells and tumors

Application of epigenetic drugs in cancer treatment

DNA methylation inhibitors such as 5-aza-2'-deoxycytidine (5-Aza-CdR, decitabine), 5-azacytidine (5-AzaC, Vidaza), and 5'-fluoro-2'-deoxycytidine (FdCyd) can suppress DNMT1 activity, thereby reactivating the INK4a/ARF and CIP/KIP families, significantly inhibiting the growth of colorectal cancer HCT-116 cells and inducing apoptosis [127]. The DNA demethylating agent 5-azacytidine (5-aza) has been shown to reduce cell proliferation and increase the expression of glial fibrillary acidic protein (GFAP). Additionally, 5-aza can enhance the therapeutic efficacy of the DNA-damaging agent temozolomide (TMZ) in both subcutaneous and orthotopic PDX models of IDH1 R132H-mutant gliomas. As a monotherapy, 5-Aza offers survival benefits, but its combination with TMZ demonstrates optimal efficacy in two distinct IDH1 R132H-mutant glioma models [128]. The combination of nivolumab and 5-aza has shown acceptable safety,

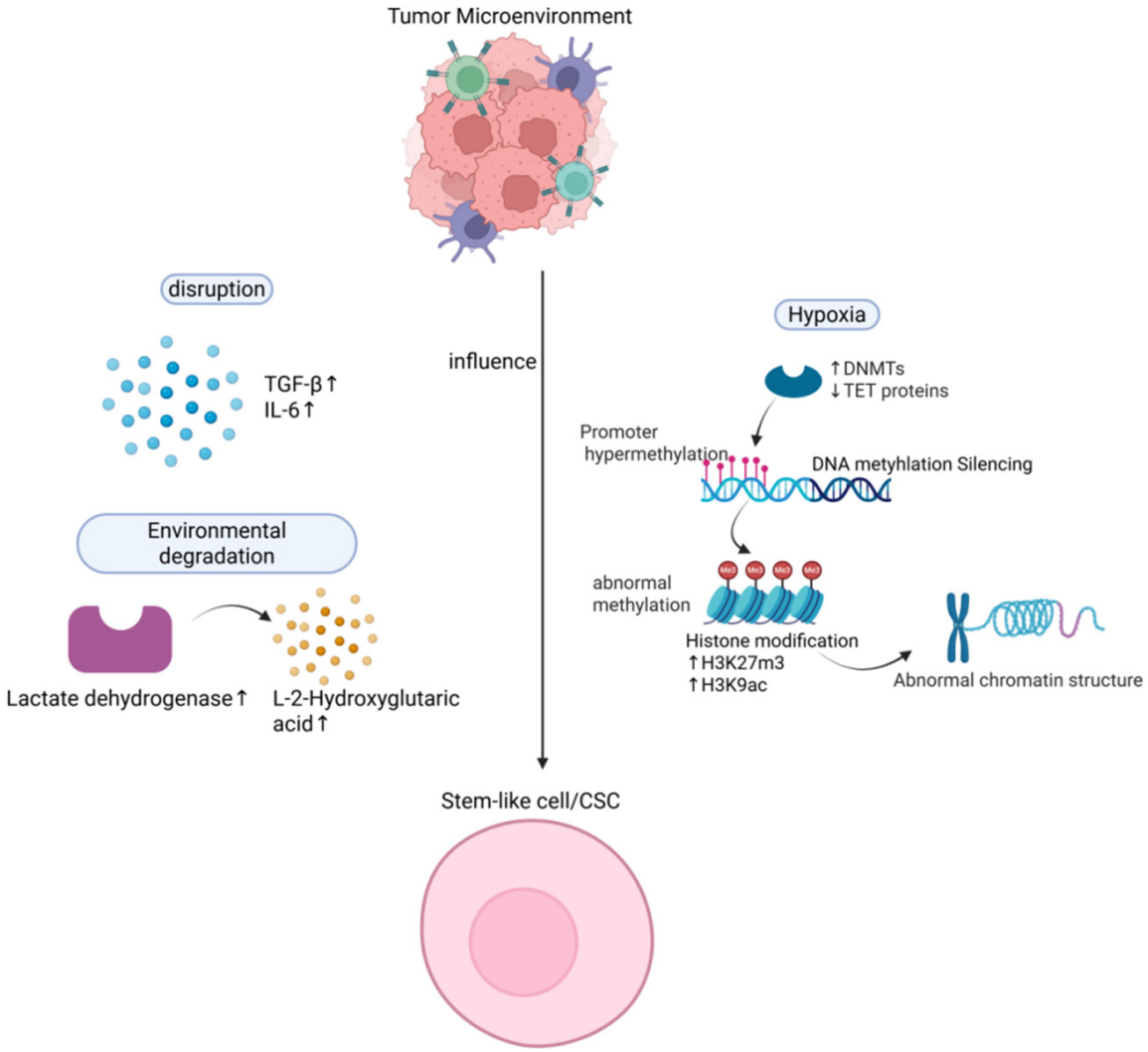

Figure 3. Effects of the TME on the epigenetics and metabolism of stem cells and tumor cells.

increased CD3+ and CD8+ T cell infiltration, and good tolerability in heavily pretreated pediatric patients with relapsed/refractory acute myeloid leukemia (R/R AML) at the RP2D (3 mg/kg/dose) [129]. PTEN-deficient GBMs evade immune surveillance through inhibition of the ERV-MAVS-IFN axis. Combined treatment with an EZH2i and 5-Aza epigenetically reactivates viral mimicry pathways, overcoming this resistance and offering a promising strategy to enhance antitumor immunity and improve prognosis in patients with PTEN-deficient GBM [130]. Epigenetic priming with oral azacitidine (CC-486) prior to R-CHOP chemotherapy shows acceptable safety in previously untreated patients with intermediate- to high-risk diffuse large B-cell lymphoma (DLBCL) or grade 3B/transformed follicular lymphoma. Moreover, CC-486 combined with vincristine and prednisone (R-CHOP) demonstrates initial signs of safety and antitumor activity in this patient group [131]. In human breast cancer cell lines, decitabine induces transcriptome reprogramming mediated by DNA methylation [132]. Vitamin C enhances DNA hydroxymethylation induced by decitabine or azacytidine in colon cancer cells and subsequently reactivates the epigenetically silenced tumor suppressor CDKN1A [133]. Furthermore, 5-aza-2'-deoxycytidine (decitabine) increases the expression of cancer-testis antigens and alters immune checkpoint expression in head and neck squamous cell carcinoma, particularly in CD39-positive CD8 and CD4 T cells [134].

HDAC inhibitors, either as monotherapy or in combination with other agents, can reactivate silenced genes by remodeling tightly con-

densed chromatin structures. This reactivation subsequently induces differentiation, cell cycle arrest, or apoptosis [135]. The HDAC inhibitor Vorinostat exerts anticancer effects in TNBC cells by preventing nitric oxide-driven histone deacetylation [136]. Small molecules that bind G-quadruplex DNA structures synergize with the HDAC inhibitor SAHA (Vorinostat) to enhance antitumor efficacy in both gemcitabine-sensitive and gemcitabine-resistant pancreatic cancer cells [137]. The combination of Vorinostat and isotretinoin (13-cis-retinoic acid) is safe and tolerable in patients with advanced renal cell carcinoma and has shown response in refractory metastatic cases [138]. Vorinostat also inhibits the expression of small-cell transcription factors and induces cell death in giant congenital melanocytic nevus cells [139]. The combination of 5-Aza-CdR and SAHA can induce growth arrest and apoptosis via the JAK/STAT signaling pathway [140]. HDACi such as valproic acid (VPA) and SAHA enhance both trastuzumab-mediated phagocytosis and trastuzumab-independent cytotoxicity. The immunomodulatory properties of these HDACis support their rational combination with monoclonal antibodies for cancer therapy [141]. The combination of SAHA and cisplatin synergistically induces apoptosis in hepatic-like adenocarcinoma cells that produce alpha-fetoprotein [142]. In lung adenocarcinoma, SAHA enhances antitumor immunity through the HDAC1/JAK1/FGL1 axis, affecting CD8+ T cell-mediated cytotoxicity [143]. The HDAC inhibitor Romidepsin (FK228) inhibits the proliferation of endometrial cancer (EC) cells and induces apoptosis via activation of the p53/p21-caspase/PARP signaling cascade [144]. FK228 also modulates the expression of the immune checkpoint ligand PD-L1 in colorectal cancer and suppresses immune cell function [145]. Furthermore, combination therapy with FK228 and radiotherapy sensitizes fusion-positive rhabdomyosarcoma cells to radiation [146].

Panobinostat (LBH589), another HDAC inhibitor, shows potent anti-myeloma activity both in vitro and in vivo when combined with the β-catenin inhibitor Tegavivint (BC2059) [147]. Panobinostat also inhibits the Wnt/β-catenin signaling pathway by upregulating APCL expression in breast cancer cells [148]. More broadly, pan-HDAC inhibitors can reverse breast cancer metastasis induced by NEDD9 overexpression [149].

In the treatment of CSCS via epigenetic regulation, specific DNA methylation sites play pivotal roles. iDNMT-induced DNMT1 inhibition enhances the expression of miR-27-3p in lung squamous cell carcinoma (LSCC), thereby suppressing activation of the Notch pathway. Furthermore, the combination of iDNMT and radiofrequency ablation (RFA) shows promise as a potential therapeutic strategy for LSCC [150]. SOX17, a tumor-suppressive transcription factor, is downregulated in ESCC due to promoter hypermethylation. Dysregulation of the SOX17/NRF2 axis contributes to resistance to radiochemotherapy, positioning it as a novel therapeutic target in ESCC [151]. Targeting DNMT1 reshapes the global DNA hypomethylation pattern, enhancing anticancer efficacy while minimizing potential toxicity through balanced signaling synergy. DNMT1 thus acts as a key gatekeeper of fate and treatment outcomes in oral squamous cell carcinoma [152]. Overexpression of SOX17 increases radiosensitivity and chemosensitivity in esophageal cancer by transcriptionally downregulating DNA repair and damage response genes [153]. SOX7 contributes to apoptosis regulation via control of the MAPK/ERK-BIM signaling pathway [154, 155]. PARP inhibitors enhance the antitumor effects of DNMT inhibitors in cholangiocarcinoma by promoting tumor cell senescence [156]. ARID1A modulates transcription and the epigenetic landscape through POLE and DMAP1; its deficiency or pharmacologic inhibition renders germ cell tumor cells sensitive to ATR inhibitors [157]. The methylation status of the Nanog promoter determines the transition between cancer cells and CSCS [158]. piRNA-823 contributes to the regulation of CSCS by altering DNA methylation associated with luminal breast cancer [159]. BEX1, regulated by DNMT1, is essential for the self-renewal and maintenance of liver CSCS via activation of Wnt/β-catenin signaling, making it a potentially valuable therapeutic target in HB and CSC-driven hepatocellular carcinoma (CSC-HCC) [160]. ABI2 has been identified as a novel therapeutic target for liver CSCS, promoting CSC activity and tumor recurrence through the MEOX2/KLF4-NANOG axis [161]. DNA methylation-mediated silencing of miR-7-5p enhances the invasiveness of gastric CSCS by upregulating Smo and Hes expression [162]. Lastly, DNMT3b-mediated hypermethylation of the SPAG6 promoter influences LSCC progression via the JAK/STAT signaling pathway [163].

Histone-Modifying Enzymes and ncRNAs in CSC Epigenetic Therapy EZH2, a key histone methyltransferase, has been identified as a CSC marker in clear cell renal cell carcinoma and a target of the antitumor effects of epigallocatechin gallate (EGCG) [164]. As a core component of the polycomb repressive complex, EZH2 plays a crucial role in maintaining CSC traits. In ovarian cancer, EZH2 activates CHK1 signaling, thereby sustaining CSC characteristics and contributing to chemoresistance [165]. UTMD-mediated shEZH2 silencing suppresses stemness and EMT of hepatic CSCs in vitro and in vivo by modulating the STAT3/PI3K/AKT pathway [166]. Capsaicin significantly inhibits stemness expression and metastatic potential in osteosarcoma. It suppresses stem-like properties and migration by downregulating SOX2 and EZH2, positioning capsaicin as a promising therapeutic agent against osteosarcoma metastasis [167]. lncRNA TUG1 inhibits the CSC-like properties of temozolomide-resistant glioma cells via interaction with EZH2 [168]. Downregulation of KDM2B and EZH2 reduces stemness in colorectal cancer cells, and their interaction may serve as a novel prognostic marker and therapeutic target in colorectal cancer [169]. In squamous cell carcinoma, EZH2 promotes the CSC phenotype by regulating the SETDB1/ΔNp63α axis through RUNX3 [170]. In HCC, inhibiting EZH2 mitigates sorafenib resistance by targeting NOTCH1-dependent CSCs via NOTCH1-associated miRNAs [171]. In PDAC, lncRNA HOTAIR promotes invasion and migration by sponging miR-34a and activating the JAK2/STAT3 pathway, thereby enhancing CSC-like features [172]. Ectopic expression of miR-34a/-328 sensitizes breast CSCs to γ-irradiation or doxorubicin by targeting BCL2/ABCG2, with miR-34a and miR-328 respectively downregulating Bcl-2 or ABCG2 to enhance apoptosis [173]. The DNMT1/miR-34a/FOXM1 axis contributes to hepatic CSC maintenance; thus, inhibiting DNMT1/miR-34a-mediated FOXM1 upregulation may suppress HCC via CSC targeting [174]. Cancer-associated fibroblasts promote CSC traits and chemoresistance in colorectal cancer by transferring exosomal lncRNA H19. H19 acts as a ceRNA for miR-141, thereby activating the β-catenin pathway, whereas miR-141 inhibits CSC properties in colorectal cancer cells [119]. Extracellular vesicles rich in lncRNA H19 derived from gastric CSCs promote tumorigenesis and metastasis by mediating intratumoral communication [175]. miR-675-3p, derived from lncRNA H19, directly targets SOCS5 to activate the STAT3 pathway, promoting EMT and stemness in human pancreatic cancer cells [176].

Stem cell-mediated tumor therapy and epigenetic regulation

Human endometrial MSCs (eMSCs) have emerged as novel anticancer agents targeting breast CSCS [177]. MSCs are promising cellular vehicles for delivering anticancer agents into malignant tumors. For instance, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has been site-specifically integrated into iPSC-derived MSCs for targeted cancer therapy [178]. Tumor-intrinsic signals have also been utilized to induce MSC-mediated suicide gene therapy to combat malignant gliomas [179]. Glioma-associated MSCs (GA-MSCs) play a critical role in shaping the immunosuppressive microenvironment. As amplifiers of exosome-mediated immunosuppressive signaling in GBM, MSCs enhance the immunosuppressive activity of myeloid-derived suppressor cells (MDSCs) through a positive feedback loop involving miR-21/SP1/DNMT1 [180]. Extracellular vesicle (EV) mimetics derived from iPSC-MSCs have shown therapeutic benefits in metastatic prostate cancer. These EV-like nanovesicles, with theoretically unlimited scalability and consistent biological activity, represent a promising platform for targeted anticancer drug delivery [181]. Similarly, iPSC-derived neural stem cells (NSCs) have been used as cellular vehicles for treating gliomas and breast cancer [182]. Differentiation of MSCs from human iPSCs results in downregulation of c-Myc and DNA replication pathways and immunomodulation of CD4+ and CD8+ cells. iPSC-MSCs exhibit low tumorigenicity and strong immunomodulatory capacity, making them attractive therapeutic candidates regardless of the reprogramming method or original cell source [183]. PTEN, a frequently mutated tumor suppressor in various cancers, plays a pivotal role in stem cell transformation. PTEN deficiency reprograms human NSCs into GBM stem-like cells by interacting with CREB/CBP and repressing PAX7 transcription via promoter binding. PTEN loss leads to PAX7 upregulation, which in turn drives the oncogenic transformation of NSCs and restores the invasive pheno-

type of human GBM stem cells (GSCs). Notably, PTEN disruption transforms NSCs but not MSCs into tumorigenic cells [184]. Adipose-derived stem cell (ADSC) exosomes are effective carriers for in vivo small molecule delivery. miR-138-5p-loaded exosomes show therapeutic potential for prostate cancer by inhibiting migration, invasion, and proliferation of bladder cancer cells in vitro, and by penetrating tumor tissue and suppressing xenograft tumor growth in vivo [185]. Exosomes derived from MSCs have also been used as nano-carriers for vincristine sulfate (VCR) in treating breast CSCs Loading VCR into these exosomes enhances targeted delivery and reduces side effects [186]. The ExoDS platform, based on exosomes, serves as a multifunctional drug delivery system targeting both cancer cells and CSCs [187]. MSC-derived EVs delivering microRNA-34a-5p suppress colorectal tumorigenesis through the c-MYC/DNMT3a/PTEN axis [188]. In summary, stem cells offer multifaceted advantages in cancer therapy - not only enabling targeted delivery of antitumor agents but also modulating the epigenetic landscape of tumor cells to affect their proliferation, differentiation, and drug resistance. These strategies, combined with gene editing and epigenetic regulation, expand new avenues for precision oncology. **Table 3** systematically summarizes the major stem cell-mediated therapeutic approaches and their corresponding epigenetic regulatory mechanisms, providing a reference for comparative analysis and future research.

Stem cells have garnered increasing attention in recent years as a promising therapeutic strategy in cancer treatment. Owing to their self-renewal capacity and multipotent differentiation potential, stem cells have been employed not only in targeted and gene therapy for tumors but also show significant promise in cancer immunotherapy. Among them, MSCs and iPSCs have been extensively studied due to their tumor-tropic properties within the TME. These cells can serve as carriers for drugs and genes, enabling targeted delivery of anti-tumor agents, therapeutic genes, or immune cells directly to tumor sites, thereby enhancing therapeutic efficacy while minimizing damage to normal tissues. MSCs, for instance, can carry anticancer genes or immunomodulatory factors and migrate autonomously to tumor regions for precise therapeutic action [189].

Moreover, stem cells exhibit great potential in tumor immunotherapy by homing to tumor sites and activating immune cells such as T cells and macrophages, thus amplifying the anti-tumor immune response [190]. They may also serve as vehicles for tumor vaccines to induce tumor-specific immune clearance. Beyond these applications, stem cells have shown the ability to reverse tumor drug resistance by modulating the epigenetic landscape of tumor cells or secreting cytokines, thereby alleviating chemoresistance [191].

Despite the multiple advantages of stem cells in cancer therapy, several challenges remain in their clinical translation. Notably, iPSCs may carry a risk of tumorigenicity due to genomic instability, and the long-term efficacy and safety of stem cell-based therapies require further extensive validation. Nevertheless, advancements in gene-editing technologies (e.g., CRISPR/Cas9) and immunomodulatory strategies are expected to significantly enhance the safety and precision of stem cell therapies. These developments position stem cell-based interventions as promising candidates for future applications in personalized medicine and multimodal combination therapies [192].

Frontier research and future perspectives

Application of single-cell epigenetic analysis technologies in stem cell and tumor research

In recent years, breakthroughs in single-cell epigenomics have opened up new dimensions for dissecting the heterogeneity of the TME and the mechanisms of dynamic cellular interactions. By constructing frameworks for intercellular differences in DNA methylation landscapes, chromatin accessibility maps, and histone modification profiles, researchers have systematically unveiled the epigenetic regulatory networks governing heterogeneous self-renewing populations in GBM. Single-cell analysis of primary human GBM samples has revealed significant epigenetic diversity within patient-derived GSC populations. Invasive subpopulations acquire heightened therapeutic resistance through epigenetic reprogramming, and this phenotype is strongly associated with poor patient prognosis [193]. In AML, the integration of multi-omics at the single-cell level - such as scTEM-seq - has demonstrated that decitabine treatment induces global DNA me-

Table 3. Stem cell-mediated tumor therapy and epigenetic regulatory mechanisms

Stem Cell Type	Tumor Type	Epigenetic Regulatory Mechanism	Key Factors/Targets	Pathways or Signaling Mechanisms	Application Strategy	References
MSCs	Gastric Cancer	LncHCP5 sponges miR-3619-5p; lncRNA MACC1-AS1 antagonizes and regulates miR-145-5p	lncHCP5; lncRNA MACC1-AS1	HCP5/miR-3619-5p/PPARGC1A/PGC1α/CEBPB axis drives FAO; TGF-β1/SMAD2/3-induced MACC1-AS1 promotes FAO (FAO: Fatty Acid Oxidation)	Targeting lncRNA HCP5 enhances chemotherapy efficacy; FAO inhibitors combined with chemotherapy overcome gastric cancer drug resistance	[106, 107]
CSCs	Colorectal Cancer	lncTUG1 enhances GATA6 protein stability; lncRNA HOTAIR sponges miR-211-5p to regulate gene expression	lncTUG1, GATA6; HOTAIR, miR-211-5p, FLT-1	GATA6-BMP signaling pathway; HOTAIR/miR-211-5p/FLT-1 axis regulates cell stemness	Targeting the TUG1/GATA6-BMP pathway for CRC treatment; Targeting the HOTAIR/miR-211-5p/FLT-1 axis as a potential therapeutic approach	[252, 253]
CSCs	Breast Cancer	XIST sponges let-7a-2-3p; LINC00589 acts as a ceRNA to sponge miR-100/452	XIST, let-7a-2-3p, IL-6, STAT3; LINC00589, miR-100, miR-452, DLG5, PRDM16	IL-6/STAT3 signaling pathway promotes CSC self-renewal; LINC00589-miR-100-DLG5 and LINC00589-miR-452-PRDM16-mucin4 axes	Targeting the XIST/let-7a-2-3p/IL-6 axis inhibits breast CSCs; Serves as a diagnostic, prognostic biomarker and therapeutic target for HER2-positive breast cancer	[254, 255]
CSCs	Liver Cancer	miR-22 inhibits CBL and indirectly upregulates SPRY2; lncRNA DIO3OS post-transcriptionally suppresses ZEB1 expression	miR-22, CBL, SPRY2; DIO3OS, NONO, ZEB1	miR-22-3p/CBL/SPRY2/ERK axis inhibits EMT and related processes; DIO3OS-NONO-ZEB1 axis	Targeting the miR-22/SPRY2/ERK axis for liver cancer treatment; Targeting the DIO3OS-NONO-ZEB1 axis for HCC therapy HCC	[256, 257]
PCSC	Prostate Cancer	NUMB targets and inhibits the oncogenic effects of miR-9-5p; miR-34a mediates post-transcriptional suppression of target genes	NUMB, miR-9-5p; miR-34a	NUMB/miR-9-5p axis regulates PCSC characteristics; TP53-miR-34a axis regulates PCSC-associated genes (PCSC: Prostate CSCs)	Inhibiting miR-9-5p or overexpressing NUMB for prostate cancer (PCa) treatment; Developing ligand-conjugated miR-34a for targeted therapy of PCa	[220, 258]
CSCs	Pancreatic Cancer	LINC00909 reduces SMAD4 mRNA stability; LncMIR4435-2HG sponges miR-1252-5p	LINC00909 and SMAD4; LncMIR4435-2HG, miR-1252-5p, STAT1	MAPK/JNK signaling pathway is activated; MIR4435-2HG/miR-1252-5p/STAT1 axis	Targeting LINC00909 inhibits pancreatic cancer metastasis; targeting MIR4435-2HG suppresses CSCs and enhances chemosensitivity.	[259, 260]
CSCs	Lung Cancer	lncMir100hg enhances H3K14 lactylation modification; lncRNA PGM5-AS1 acts as a molecular sponge for miR-1247-5p	Mir100hg, HNRNPF, HNRNPA2B1, ALDOA; PGM5-AS1, miR-1247-5p, RSPO1	ALDOA drives glycolysis and histone lactylation; PGM5-AS1/miR-1247-5p/RSPO1 regulatory axis	Targeting HNRNPF/HNRNPA2B1 or the histone lactylation pathway; Targeting the PGM5-AS1-miR-1247-5p-RSPO1 axis to inhibit tumor progression	[261, 262]
CSCs	Melanoma	Exosomal miR-1268a regulation; HotairM1-mediated histone methylation and acetylation	miR-1268a; lncRNA HotairM1, HOXA1, Nanog	Inhibits the autophagy pathway; HOXA1-Nanog signaling loop	Block exosomal miR-1268a transfer or activate autophagy; Target HotairM1 or the HOXA1-Nanog loop to enhance HotairM1 expression	[263, 264]
GSCs	GBM	lncCASCADES regulates SOX2 epigenetically; miR-370-3p targets and regulates associated genes	lncCASCADES, SOX2; miR-370-3p, NEAT1, HMGA2, HIF1A	Promotes GSC stemness maintenance and inhibits neuronal differentiation; Inhibits EMT and hypoxia signaling pathways	Targeting CASCADES to disrupt GSC stemness for GBM treatment; Restoring miR-370-3p expression to inhibit GBM progression	[265, 266]
OCSCs	Ovarian Cancer	lncHOTAIR recruits EZH2 to catalyze H3K27 trimethylation; LINC00665 targets CNBP mRNA for degradation	lncHOTAIR; lncRNA LINC00665, CNBP	HOTAIR-EZH2-mediated chromatin modification and NF-κB pathway; Wnt/Notch signaling pathways	HOTAIR inhibitors combined with EZH2 is and platinum-based chemotherapy; Targeting LINC00665 to suppress ovarian cancer stemness	[6, 267]

thylation heterogeneity, which in turn directly mediates the remodeling of immune-related gene expression. A significant inverse correlation between the expression of transposable elements and DNA methylation levels further highlights the subclonal specificity of epigenetic regulation, offering novel epigenetic insights into the mechanisms underlying chemotherapy resistance [194].

The innovative integration of epigenetic clocks with lineage-tracing technologies has significantly enhanced our capacity for spatiotemporal dynamic analysis. The EpiTrace analytical framework, developed based on scATAC-seq data, reconstructs developmental trajectories across multi-lineage cell populations by quantifying the proportion of open chromatin sites. Its strong concordance with DNA methylation clocks confirms the central role of epigenetic regulation in determining cellular age. In GBM studies, this analytical system revealed that neural progenitor-like cells and outer radial glia-like cells share a common epigenetic regulatory compartment. Their dynamic chromatin accessibility patterns recapitulate gene regulatory features characteristic of early neurodevelopment, despite pronounced epigenetic heterogeneity among individual tumors [195, 196]. Of particular interest, single-nucleus epigenetic profiling (snATAC-seq) of IDH1-mutant gliomas has, for the first time, identified non-coding RNA regions as major sources of epigenetic heterogeneity. Rare nuclear subpopulations exhibiting features of both IDHmut-codel and IDHmut-noncodel subtypes were discovered, and their distinct epigenetic signatures may serve as novel biomarkers for predicting treatment response [197].

Significant progress has been made in elucidating the mechanisms linking epigenetic dysregulation to tumor aggressiveness. In invasive GBM, regions of locally elevated DNA methylation abnormalities are strongly associated with transcriptomic disruption and aberrant activation of environmental stress response pathways. In vitro functional assays have confirmed that epigenetic instability accelerates disease progression by promoting cellular state plasticity. This phenomenon of genetic-epigenetic synergistic dysregulation has been validated in longitudinal clinical cohorts, providing critical theoretical support for targeting epigenetic vulnerabilities [198]. In GSC models, heterogeneous epigenomic features show strong correlations with aberrant activation of DNA damage repair pathways and cell proliferation regulatory networks. Dysregulated expression of TET enzymes leads to failure in enhancer landscape remodeling, directly accounting for the defective epigenetic reprogramming observed in GSCs compared to normal NSCs. Furthermore, imbalanced dynamic regulation of chromatin accessibility persists throughout the differentiation process [199]. Looking forward, the integration of spatial omics with single-cell epigenetic analysis is expected to enable in situ dissection of epigenetic regulatory mechanisms within stem cell-tumor cell interaction networks. This advancement holds promise for developing novel, precision-targeted therapeutic strategies.

Application of AI and big data in stem cell and tumor epigenetics research

The deep integration of AI and big data is reshaping the research paradigm of stem cell and tumor epigenetics, enabling full-spectrum breakthroughs from molecular mechanism exploration to clinical translation through multidimensional technological integration. In the field of single-cell multi-omics analysis, a global-local dual-layer interpretability framework based on the random forest algorithm has successfully decoded pan-cancer DNA methylation landscapes, accurately pinpointing the hypomethylated promoter region of the CHD8 gene characteristic of GBM [200]. The EpiTrace method integrates temporal dynamics of chromatin accessibility with convolutional neural network models, enabling - for the first time - cross-species developmental trajectory analysis. This approach has validated the functional conservation of H3K4me3 histone modifications during evolution [195]. To address the challenge of data heterogeneity in tumor epigenomics, the crossNN deep learning framework employs transfer learning strategies to harmonize datasets across different sequencing platforms. This model has achieved breakthrough diagnostic performance in the molecular subtyping of lung adenocarcinoma, while simultaneously identifying IDH1 mutation-associated methylation anomalies [201]. The scMeFormer model, which innovatively incorporates a Transformer architecture, effectively alleviates the sparsity

of single-cell sequencing data and has uncovered heterogeneous methylation patterns at the SOX2 enhancer region in glioma stem cell research [202].

At the level of multimodal data integration, the MGRL framework has pioneered the fusion of DNA methylation profiles, chromatin accessibility maps, and protein-protein interaction network data. Using graph attention network modeling, it quantitatively elucidated the regulatory relationship between methylation levels at ribosomal protein gene promoters and stem cell proliferation capacity [203]. These technological breakthroughs have already demonstrated significant clinical translational value. For example, the stemness index (mDNAsi), constructed using the OCLR algorithm, successfully enabled prognostic stratification of GBM patients and systematically elucidated the synergistic mechanisms of epigenetic regulatory drugs [204]. Additionally, a prognostic model based on random forest integration of single-cell multi-omics data has provided a clinical decision-support system for combination cancer therapies, incorporating novel biomarkers such as POU5F1B [205].

Looking ahead, the deep integration of federated learning frameworks with multimodal knowledge graphs is expected to effectively overcome the challenge of data silos. Recent studies have demonstrated that combining dynamic features of H3K4me3 modifications with AI-driven causal inference models enables the systematic construction of epigenetic regulatory networks underlying CSC stemness maintenance [206]. This technological convergence not only promises to accelerate the clinical validation of epigenetic biomarkers but also holds great potential for advancing epigenetic drug discovery through virtual screening platforms. Ultimately, it paves the way for a new era of precision medicine and opens intelligent and innovative pathways for both stem cell therapy and tumor immunotherapy.

Future directions and challenges in stem cell and tumor epigenetics research

Combined analyses of single-cell and spatial transcriptomics have revealed that SCs drive tumor initiation and maintain stemness through interaction networks with inflammation-associated cancer-associated fibroblasts (iCAFs), highlighting the pivotal role of this crosstalk in tumor progression [207]. Multi-omics integration has further clarified the pathways linking genomic variation to phenotypic regulation: integrating genomic and transcriptomic data enables causal inference between genotype and tumor-associated phenotypes, while joint analysis of epigenomic and transcriptomic data systematically reveals regulatory networks by which epigenetic modifications modulate target gene expression [208, 209]. Technological innovations are propelling the field toward a deeper integration of dynamic regulatory mechanism analysis and clinical translation. Single-cell multi-omics approaches - by integrating DNA, RNA, and proteomics data - have significantly improved the resolution of tumor heterogeneity. However, the bisulfite treatment commonly used for methylome sequencing still induces DNA damage, limiting accuracy [209]. Recently developed enzyme-based base conversion combined with nanopore sequencing (ONT) now enables long-read, phased epigenetic analysis at single-molecule resolution, offering a new paradigm for studying epigenetic heterogeneity [210]. A representative application is the nanoNOMe platform, which combines GpC methyltransferase labeling with nanopore sequencing to simultaneously detect genomic DNA methylation and chromatin accessibility - substantially improving data quality while reducing DNA damage [211]. This technology has been successfully applied in human cancer cell line studies, where integration with scRNA-seq and scATAC-seq revealed that dynamic changes in chromatin accessibility and extrachromosomal DNA (ecDNA) jointly drive intracellular heterogeneity [212].

However, current technological approaches still face limitations in accurately analyzing protein phosphorylation modifications and controlling biases introduced by cell fixation. Future research must focus on three major breakthrough directions: ① Optimizing experimental protocols or developing novel multi-omics combinations (such as integrated genome-proteome analyses) to improve detection sensitivity; ② Combining CRISPR-dCas9-based epigenetic editing tools with organoid models to enable precise validation of therapeutic targets in tumor stem cells; ③ Constructing multidimensional data integration models (e.g., the

TMODINET framework) to address the challenge of therapy resistance driven by epigenetic heterogeneity [213]. Although real-time in vivo monitoring of epigenetic dynamics presents ethical challenges, interdisciplinary collaboration and long-term clinical follow-up will be essential for elucidating the mechanisms of stem cell-tumor epigenetic interactions. Current technological advances mark a transition in epigenetic research - from static correlation analysis toward the dissection of dynamic regulatory networks - ultimately paving the way for clinical translation based on epigenetic reprogramming.

Conclusion

Stem cells, with their unique self-renewal and multipotent differentiation capabilities, hold broad application prospects in regenerative medicine and tissue repair. CSCs maintain heterogeneity and drive tumor progression and drug resistance through epigenetic mechanisms. DNA methylation, histone modifications, and non-coding RNA regulation form the core link between stem cells and tumorigenesis. Embryonic and adult stem cells regulate fate decisions via dynamic epigenetic networks, while iPSCs achieve epigenetic reprogramming. Epigenetic abnormalities in tumors promote genomic instability and treatment resistance, and the TME exacerbates tumor heterogeneity and drug resistance through multidimensional regulation. Epigenetic memory and non-coding RNA networks confer dormancy and resistance traits to CSCs, providing a molecular basis for recurrence and metastasis. DNA methylation inhibitors and HDACi demonstrate clinical potential, and precise regulation combined with stem cell carriers and exosomes expands novel anti-tumor therapeutic avenues. Single-cell omics, spatial omics, and AI technologies drive in-depth analysis of regulatory networks. Future integration of CRISPR editing and multimodal data promises to overcome therapeutic bottlenecks, advancing regenerative medicine and precision oncology toward a new level of personalized medicine.

Acknowledgements

The project title: Construction and Practice of the Theoretical System of “New Blood Syndrome Theory” for Psoriasis, Key Special Project of “Research on Modernization of Traditional Chinese Medicine” under the National Key Research and Development Program, 2023-ZD-219. Gansu Province University Teachers’ Innovation Fund Project (2025A-110) in 2025.

Disclosure of conflict of interest

None.

Address correspondence to: Di Wang and Haoling Zhang, Department of Biomedical Sciences, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Penang 13200, Malaysia. E-mail: wangdi2024@student.usm.my (DW); zhanghaolingedu@163.com (HLZ); Sinong Wang, School of Clinical Chinese Medicine, Gansu University of Chinese Medicine, Affiliated Hospital of Gansu University of Chinese Medicine, Lanzhou 730000, Gansu, China. E-mail: 15095319507@163.com

References

[1] Alrehaili AA, Gharib AF, Alghamdi SA, Alhazmi A, Al-Shehri SS, Hagag HM, Alsaeedi FA, Alhuthali HM, Raafat N, Etewa RL and Elsawy WH. Evaluation of TET family gene expression and 5-hydroxymethylcytosine as potential epigenetic markers in non-small cell lung cancer. In Vivo 2023; 37: 445-453.

[2] Lopez-Bertoni H, Johnson A, Rui Y, Lal B, Sall S, Malloy M, Coulter JB, Lugo-Fagundo M, Shudir S, Khela H, Caputo C, Green JJ and Laterra J. Sox2 induces glioblastoma cell stemness and tumor propagation by repressing TET2 and deregulating 5hmC and 5mC DNA modifications. Signal Transduct Target Ther 2022; 7: 37.

[3] Waddell A, Mahmud I, Ding H, Huo Z and Liao D. Pharmacological inhibition of cbp/p300 blocks estrogen receptor alpha (Erα) function through suppressing enhancer h3k27 acetylation in luminal breast cancer. Cancers (Basel) 2021; 13: 2799.

[4] Ibrahim N, Alsadi N, Yasavoli-Sharahi H, Shahbazi R, Hebbo MJ, Kambli D, Balcells F and Matar C. Berberine inhibits breast cancer stem cell development and decreases inflammation: involvement of miRNAs and IL-6. Curr Dev Nutr 2024; 9: 104532.

[5] Singh AK, Verma A, Singh A, Arya RK, Maheshwari S, Chaturvedi P, Nengroo MA, Saini KK, Vishwakarma AL, Singh K, Sarkar J and Datta D. Salinomycin inhibits epigenetic modulator EZH2 to enhance death receptors in colon cancer stem cells. Epigenetics 2021; 16: 144-161.

[6] Cai L, Liu Y, Li Y, Liu B, Cao Y, Yang W, Wang B and Sun T. TRIM37 interacts with EZH2 to epi-

genetically suppress PTCH1 and regulate stemness in glioma stem cells through sonic hedgehog pathway. J Neurooncol 2024; 169: 269-279.
[7] Saunderson EA, Encabo HH, Devis J, Rouault-Pierre K, Piganeau M, Bell CG, Gribben JG, Bonnet D and Ficz G. CRISPR/dCas9 DNA methylation editing is heritable during human hematopoiesis and shapes immune progeny. Proc Natl Acad Sci U S A 2023; 120: e2300224120.
[8] Yang Y, Wang F, Huang H, Zhang Y, Xie H and Men T. lncRNA SLCO4A1-AS1 promotes growthand invasion of bladder cancer through spong-ing miR-335-5p to upregulate OCT4. Onco Targets Ther 2019; 12: 1351-1358.
[9] Gao Y, Zhang N, Zeng Z, Wu Q, Jiang X, Li S, Sun W, Zhang J, Li Y, Li J, He F, Huang Z, Zhang J, Gong Y and Xie C. LncRNA PCAT1activates SOX2 and suppresses radioimmuneresponses via regulating cGAS/STINGsignalling in non-small cell lung cancer. ClinTransl Med 2022; 12: e792.
[10] Chen L, Wu X, Xie H, Yao N, Xia Y, Ma G, Qian M, Ge H, Cui Y, Huang Y, Wang S and Zheng M. ZFP57 suppress proliferation of breastcancer cells through down-regulation of MEST-mediated Wnt/β-catenin signalling pathway. Cell Death Dis 2019; 10: 169.
[11] Wang Y, Cheng Y, Yang Q, Kuang L and Liu G. Overexpression of FOXD2-AS1 enhances proliferation and impairs differentiation of gliomastem cells by activating the NOTCH pathwayvia TAF-1. J Cell Mol Med 2022; 26: 2620-2632.
[12] Song H, Zhang Y, Liu N, Zhao S, Kong Y and Yuan L. miR-92a-3p exerts various effects inglioma and glioma stem-like cells specifically-targeting CDH1/β-catenin and Notch-1/Aktsignaling pathways. Int J Mol Sci 2016; 17: 1799.
[13] Guo L, Zou D, Qiu W, Fei F, Chen L, Chen W, Xiong H, Li X, Wang Y, Gao M, Zhu J, Zhang J, He Y, Gao M and Xu R. Linc-NSC affects celldifferentiation, apoptosis and proliferation inmouse neural stem cells and embryonic stemcells in vitro and in vivo. Cell Mol Life Sci 2024; 81: 182.
[14] Luo X, Zhang T, Zhai Y, Wang F, Zhang S and Wang G. Effects of DNA methylation on TFs in human embryonic stem cells. Front Genet 2021; 12: 639461.
[15] Kubo N, Chen PB, Hu R, Ye Z, Sasaki H and Ren B. H3K4me1 facilitates promoter-enhancer interactions and gene activation during embryonic stem cell differentiation. Mol Cell 2024; 84: 1742-1752, e5.
[16] Sun T, Xu Y, Xiang Y, Ou J, Soderblom EJ and Diao Y. Crosstalk between RNA m6A and DNA methylation regulates transposable element chromatin activation and cell fate in human pluripotent stem cells. Nat Genet 2023; 55: 1324-1335.
[17] Zhang C, Wen H, Liu S, Fu E, Yu L, Chen S, Han Q, Li Z and Liu N. Maternal factor Dppa3 activates 2C-like genes and depresses DNA methylation in mouse embryonic stem cells. Front Cell Dev Biol 2022; 10: 882671.
[18] Ito T, Kubiura-Ichimaru M, Murakami Y, Bogutz AB, Lefebvre L, Suetake I, Tajima S and Tada M. DNMT1 regulates the timing of DNA methylation by DNMT3 in an enzymatic activity-dependent manner in mouse embryonic stem cells. PLoS One 2022; 17: e0262277.
[19] Gong D, Wang L, Zhou H, Gao J, Zhang W and Zheng P. Long noncoding RNA Lnc530 localizes on R-loops and regulates R-loop formation and genomic stability in mouse embryonic stem cells. Stem Cell Reports 2023; 18: 952-968.
[20] Zhang Q, Pan RR, Wu YT and Wei YM. MicroRNA-146a promotes embryonic stem cell differentiation towards vascular smooth muscle cells through regulation of Kruppel-like factor 4. Curr Med Sci 2023; 43: 223-231.
[21] Georges RO, Sepulveda H, Angel JC, Johnson E, Palomino S, Nowak RB, Desai A, López-Moyado IF and Rao A. Acute deletion of TET enzymes results in aneuploidy in mouse embryonic stem cells through decreased expression of Khdc3. Nat Commun 2022; 13: 6230.
[22] Abou-Jaoude A, Huang CY, Flores JC, Ravichandran M, Lei R, Chrysanthou S and Dawlaty MM. Idax and Rinf facilitate expression of Tet enzymes to promote neural and suppress trophectodermal programs during differentiation of embryonic stem cells. Stem Cell Res 2022; 61: 102770.
[23] Wang X, Song C, Ye Y, Gu Y, Li X, Chen P, Leng D, Xiao J, Wu H, Xie S, Liu W, Zhao Q, Chen D, Chen X, Wu Q, Chen G and Zhang W. BRD9-mediated control of the TGF-β/Activin/Nodal pathway regulates self-renewal and differentiation of human embryonic stem cells and progression of cancer cells. Nucleic Acids Res 2023; 51: 11634-11651.
[24] Qin W, Yang L, Chen X, Ye S, Liu A, Chen D and Hu K. Wedelolactone promotes the chondrogenic differentiation of mesenchymal stem cells by suppressing EZH2. Int J Stem Cells 2023; 16: 326-341.
[25] Chan NT, Lee MS, Wang Y, Galipeau J, Li WJ and Xu W. CTR9 drives osteochondral lineage differentiation of human mesenchymal stem cells via epigenetic regulation of BMP-2 signaling. Sci Adv 2022; 8: eadc9222.
[26] Jiao W, Hao J, Xie Y, Meng M and Gao W. EZH2 mitigates the cardioprotective effects of mesenchymal stem cell-secreted exosomes ag-

ainst infarction via HMGA2-mediated PI3K/AKT signaling. BMC Cardiovasc Disord 2022; 22: 95.
[27] Liu F, Song DY, Huang J, Yang HQ, You D and Ni JD. Long non-coding RNA CIR inhibits chondrogenic differentiation of mesenchymal stem cells by epigenetically suppressing ATOH8 via methyltransferase EZH2. Mol Med 2021; 27: 12.
[28] Chu Y, Chen W, Peng W, Liu Y, Xu L, Zuo J, Zhou J, Zhang Y, Zhang N, Li J, Liu L, Yao K, Gao G, Wang X, Han R, Liu C, Li Y, Zhou H, Huang Y and Ye Y. Amnion-derived mesenchymal stem cell exosomes-mediated autophagy promotes the survival of trophoblasts under hypoxia through mTOR pathway by the downregulation of EZH2. Front Cell Dev Bio 2020; 8: 545852.
[29] Cypris O, Franzen J, Frobel J, Glück P, Kuo CC, Schmitz S, Nüchtern S, Zenke M and Wagner W. Hematopoietic differentiation persists in human iPSCs defective in de novo DNA methylation. BMC Biol 2022; 20: 141.
[30] Frankowski H, Yeboah F, Berry BJ, Kinoshita C, Lee M, Evitts K, Davis J, Kinoshita Y, Morrison RS and Young JE. Knock-down of HDAC2 in human induced pluripotent stem cell derived neurons improves neuronal mitochondrial dynamics, neuronal maturation and reduces amyloid beta peptides. Int J Mol Sci 2021; 22: 2526.
[31] Barrero M, Lazarenkov A, Blanco E, Palma LG, López-Rubio AV, Bauer M, Bigas A, Di Croce L, Sardina JL and Payer B. The interferon γ pathway enhances pluripotency and X-chromosome reactivation in iPSC reprogramming. Sci Adv 2024; 10: eadj8862.
[32] Endo Y, Suzuki K, Kimura Y, Tamaki S, Aizawa H, Abe I, Watanabe F, Kato T, Saito M, Futsuhara K, Noda H, Konishi F and Rikiyama T. Genome-wide DNA hypomethylation drives a more invasive pancreatic cancer phenotype and has predictive occult distant metastasis and prognosis potential. Int J Oncol 2022; 60: 61.
[33] Ansar M, Wang CJ, Wang YH, Shen TH, Hung CS, Chang SC and Lin RK. SMAD3 hypomethylation as a biomarker for early prediction of colorectal cancer. Int J Mol Sci 2020; 21: 7395.
[34] Takahashi S, Okamoto K, Tanahashi T, Fujimoto S, Nakagawa T, Bando M, Ma B, Kawaguchi T, Fujino Y, Mitsui Y, Kitamura S, Miyamoto H, Sato Y, Muguruma N, Bando Y, Sato T, Fujimori T and Takayama T. S100P expression via DNA Hypomethylation promotes cell growth in the sessile serrated adenoma/polyp-cancer sequence. Digestion 2021; 102: 789-802.
[35] Das J, Chandra L, Gandhi G, Amle DB, Patnayak RL, Khurana N and Saxena A. Evaluation of promoter hypermethylation of tumor suppressor gene BRCA1 in epithelial ovarian cancer. J Cancer Res Ther 2022; 18: 1578-1582.
[36] Li Y, Liu HT, Chen X, Wang YW, Tian YR, Ma RR, Song L, Zou YX and Gao P. Aberrant promoter hypermethylation inhibits RGMA expression and contributes to tumor progression in breast cancer. Oncogene 2022; 41: 361-371.
[37] Wang R, Yu X, Ye H, Ao M, Xi M and Hou M. LncRNA FAM83H-AS1 inhibits ferroptosis of endometrial cancer by promoting DNMT1-mediated CDO1 promoter hypermethylation. J Biol Chem 2024; 300: 107680.
[38] Singh D, Bharti A, Biswas D, Tewari M, Kar AG, Ansari MA, Singh S and Narayan G. Frequent downregulation and promoter hypermethylation of DLC1: relationship with clinical outcome in gallbladder cancer. J Gastrointest Cancer 2022; 53: 237-244.
[39] Xu J, Zhou Y, Yang J, Gu Y, Zhang E, Yuan W, Wang C, Jin G, Ma H and Hu Z. Hypomethylation-activated cancer-testis gene LIN28B promotes cell proliferation and metastasis in gastric cancer. Gene 2022; 813: 146115.
[40] Du Y, Xu Y, Guo X, Tan C, Zhu X, Liu G, Lyu X and Bei C. Methylation-regulated tumor suppressor gene PDE7B promotes HCC invasion and metastasis through the PI3K/AKT signaling pathway. BMC Cancer 2024; 24: 624.
[41] Zhang J, Cui K, Huang L, Yang F, Sun S, Bian Z, Wang X, Li C, Yin Y, Huang S, Zhou L, Fei B and Huang Z. SLCO4A1-AS1 promotes colorectal tumourigenesis by regulating Cdk2/c-Myc signalling. J Biomed Sci 2022; 29: 4.
[42] Du H, Sun J, Wang X, Zhao L, Liu X, Zhang C, Wang F and Wu J. FOSL2-mediated transcription of ISG20 induces M2 polarization of macrophages and enhances tumorigenic ability of glioblastoma cells. J Neurooncol 2024; 169: 659-670.
[43] Patiño-Mercau JR, Baliñas-Gavira C, Andrades A, Benitez-Cantos MS, Rot AE, Rodriguez MI, Álvarez-Pérez JC, Cuadros M and Medina PP. BCL7A is silenced by hypermethylation to promote acute myeloid leukemia. Biomark Res 2023; 11: 32.
[44] Fu Y, Zhang X, Liu X, Wang P, Chu W, Zhao W, Wang Y, Zhou G, Yu Y and Zhang H. The DNMT1-PAS1-PH20 axis drives breast cancer growth and metastasis. Signal Transduct Target Ther 2022; 7: 81.
[45] Li C, Lu T, Chen H, Yu Z and Chen C. The upregulation of SYNCRIP promotes the proliferation and tumorigenesis via DNMT3A/p16 in colorectal cancer. Sci Rep 2024; 14: 21570.
[46] Brown BA, Myers PJ, Adair SJ, Pitarresi JR, Sah-Teli SK, Campbell LA, Hart WS, Barbeau MC,

Leong K, Seyler N, Kane W, Lee KE, Stelow E, Jones M, Simon MC, Koivunen P, Bauer TW, Stanger BZ and Lazzara MJ. A histone methylation-MAPK signaling axis drives durable epithelial-mesenchymal transition in hypoxic pancreatic cancer. Cancer Res 2024; 84: 1764-1780.

[47] Zhang Y, Zheng B, Lou K, Xu X and Xu Y. Methylation patterns of Lys9 and Lys27 on histone H3 correlate with patient outcome and tumor progression in lung cancer. Ann Diagn Pathol 2022; 61: 152045.

[48] Zhou C, Zhu X, Liu N, Dong X, Zhang X, Huang H, Tang Y, Liu S, Hu M, Wang M, Deng X, Li S, Zhang R, Huang Y, Lyu H, Xiao S, Luo S, Ali DW, Michalak M, Chen XZ, Wang Z and Tang J. B-lymphoid tyrosine kinase-mediated FAM83A phosphorylation elevates pancreatic tumorigenesis through interacting with β-catenin. Signal Transduct Target Ther 2023; 8: 66.

[49] Wang C, Tang Y, Zhang S, Li M, Li Q, Xiao M, Yang L and Wang Y. Histone MARylation regulates lipid metabolism in colorectal cancer by promoting IGFBP1 methylation. Exp Cell Res 2024; 443: 114308.

[50] Wang H, Qiu Y, Zhang H, Chang N, Hu Y, Chen J, Hu R, Liao P, Li Z, Yang Y, Cen Q, Ding X, Li M, Xie X and Li Y. Histone acetylation by HBO1 (KAT7) activates Wnt/β-catenin signaling to promote leukemogenesis in B-cell acute lymphoblastic leukemia. Cell Death Dis 2023; 14: 498.

[51] Wang SW, Sheng H, Zheng F and Zhang F. Hesperetin promotes DOT1L degradation and reduces histone H3K79 methylation to inhibit gastric cancer metastasis. Phytomedicine 2021; 84: 153499.

[52] Batbayar G, Ishimura A, Lyu H, Wanna-Udom S, Meguro-Horike M, Terashima M, Horike SI, Takino T and Suzuki T. ASH2L, a COMPASS core subunit, is involved in the cell invasion and migration of triple-negative breast cancer cells through the epigenetic control of histone H3 lysine 4 methylation. Biochem Biophys Res Commun 2023; 669: 19-29.

[53] Nguyen T, Sridaran D, Chouhan S, Weimholt C, Wilson A, Luo J, Li T, Koomen J, Fang B, Putluri N, Sreekumar A, Feng FY, Mahajan K and Mahajan NP. Histone H2A Lys130 acetylation epigenetically regulates androgen production in prostate cancer. Nat Commun 2023; 14: 3357.

[54] Sun Y, Mu G, Zhang X, Wu Y, Wang S, Wang X, Xue Z, Wang C, Liu J, Li W, Zhang L, Guo Y, Zhao F, Liu X, Xue Z, Zhang Y, Ni S, Wang J, Li X, Han M and Huang B. Metabolic modulation of histone acetylation mediated by HMGCL activates the FOXM1/β-catenin pathway in glioblastoma. Neuro Oncol 2024; 26: 653-669.

[55] Li Q, Ci H, Zhao P, Yang D, Zou Y, Chen P, Wu D, Shangguan W, Li W, Meng X, Xing M, Chen Y, Zhang M, Chen B, Kong L, Zen K, Huang DCS, Jiang ZW and Zhao Q. NONO interacts with nuclear PKM2 and directs histone H3 phosphorylation to promote triple-negative breast cancer metastasis. J Exp Clin Cancer Res 2025; 44: 90.

[56] Liu Y, Liu H, Ye M, Jiang M, Chen X, Song G, Ji H, Wang ZW and Zhu X. Methylation of BRD4 by PRMT1 regulates BRD4 phosphorylation and promotes ovarian cancer invasion. Cell Death Dis 2023; 14: 624.

[57] Shozu K, Kaneko S, Shinkai N, Dozen A, Kosuge H, Nakakido M, Machino H, Takasawa K, Asada K, Komatsu M, Tsumoto K, Ohnuma SI and Hamamoto R. Repression of the PRELP gene is relieved by histone deacetylase inhibitors through acetylation of histone H2B lysine 5 in bladder cancer. Clin Epigenetics 2022; 14: 147.

[58] Peter RM, Sarwar MS, Mostafa SZ, Wang Y, Su X and Kong AN. Histone deacetylase inhibitor belinostat regulates metabolic reprogramming in killing KRAS-mutant human lung cancer cells. Mol Carcinog 2023; 62: 1136-1146.

[59] Yang Z, Su W, Zhang Q, Niu L, Feng B, Zhang Y, Huang F, He J, Zhou Q, Zhou X, Ma L, Zhou J, Wang Y, Xiong W, Xiang J, Hu Z, Zhan Q and Yao B. Lactylation of HDAC1 confers resistance to ferroptosis in colorectal cancer. Adv Sci (Weinh) 2025; 12: e2408845.

[60] Wang Z, Di Y, Wen X, Liu Y, Ye L, Zhang X, Qin J, Wang Y, Chu H, Li G, Zhang W, Wang X and He W. NIT2 dampens BRD1 phase separation and restrains oxidative phosphorylation to enhance chemosensitivity in gastric cancer. Sci Transl Med 2024; 16: eado8333.

[61] Liu W, Li X, Tan X, Huang X and Tian B. MicroRNA-204-3p inhibits metastasis of pancreatic cancer via downregulating MGAT1. J BUON 2021; 26: 2149-2156.

[62] Kang J, Huang X, Dong W, Zhu X, Li M and Cui N. MicroRNA-1269b inhibits gastric cancer development through regulating methyltransferase-like 3 (METTL3). Bioengineered 2021; 12: 1150-1160.

[63] Hajibabaei S, Nafissi N, Azimi Y, Mahdian R, Rahimi-Jamnani F, Valizadeh V, Rafiee MH and Azizi M. Targeting long non-coding RNA MALAT1 reverses cancerous phenotypes of breast cancer cells through microRNA-561-3p/TOP2A axis. Sci Rep 2023; 13: 8652.

[64] Wu Y, Yuan MH, Wu HT, Chen WJ, Zhang ML, Ye QQ, Liu J and Zhang GJ. MicroRNA-488 inhibits proliferation and motility of tumor cells via downregulating FSCN1, modulated by Notch3 in breast carcinomas. Cell Death Dis 2020; 11: 912.

[65] Wu J and Zhou Z. MicroRNA-432 acts as a prognostic biomarker and an inhibitor of cell proliferation, migration, and invasion in breast cancer. Clin Breast Cancer 2021; 21: e462-e470.
[66] Karimi L, Jaberi M, Asadi M, Zarredar H, Zafari V, Bornehdeli S, Niknam S and Kermani TA. Significance of microRNA-330-5p/TYMS expression axis in the pathogenesis of colorectal tumorigenesis. J Gastrointest Cancer 2022; 53: 965-970.
[67] Wang H, Fang Q, You S, Wu Y and Zhang C. miRNA-195-5p/PSAT1 feedback loop in human triple-negative breast cancer cells. Genes Genomics 2023; 45: 39-47.
[68] Zong S, Dai W, Guo X and Wang K. LncRNA-SNHG1 promotes macrophage M2-like polarization and contributes to breast cancer growth and metastasis. Aging (Albany NY) 2021; 13: 23169.
[69] Zhang D, Song Y, Li D, Liu X, Pan Y, Ding L, Shi G, Wang Y, Ni Y and Hou Y. Cancer-associated fibroblasts promote tumor progression by lncRNA-mediated RUNX2/GDF10 signaling in oral squamous cell carcinoma. Mol Oncol 2022; 16: 780-794.
[70] Dai ZT, Wu YL, Xu T, Li XR and Ji T. The role of lncRNA SNHG14 in gastric cancer: enhancing tumor cell proliferation and migration, and mechanisms of CDH2 expression. Cell Cycle 2023; 22: 2522-2537.
[71] Shen D, Zhang Y, Zheng Q, Yu S, Xia L, Cheng S and Li G. A competing endogenous RNA network and an 8-lncRNA prognostic signature identify MYO16-AS1 as an oncogenic lncRNA in bladder cancer. DNA Cell Biol 2021; 40: 26-35.
[72] Yang J, Gao L, Wang Z, Xu Y, Jin X, Jin Q and Yu L. Effects of the lncRNA NBR2 on the proliferation and autophagy of breast cancer cells under starvation conditions. Sci Rep 2024; 14: 22624.
[73] Long F, Li L, Xie C, Ma M, Wu Z, Lu Z, Liu B, Yang M, Zhang F, Ning Z, Zhong C, Yu B, Liu S, Wan L, Tian B, Yang K, Guo Y, Chen M, Chou J, Li X, Hu G, Lin C and Zhang Y. Intergenic circRNA circ_0007379 inhibits colorectal cancer progression by modulating miR-320a biogenesis in a KSRP-dependent manner. Int J Biol Sci 2023; 19: 3781-3803.
[74] Wang D, Wang S, Jin M, Zuo Y, Wang J, Niu Y, Zhou Q, Chen J, Tang X, Tang W, Liu X, Yu H, Yan W, Wei HH, Huang G, Song S and Tang S. Hypoxic exosomal circPLEKHM1-mediated crosstalk between tumor cells and macrophages drives lung cancer metastasis. Adv Sci (Weinh) 2024; 11: e2309857.
[75] Chen S, Li K, Guo J, Chen HN, Ming Y, Jin Y, Xu F, Zhang T, Yang Y, Ye Z, Liu W, Ma H, Cheng J, Zhou JK, Li Z, Shen S, Dai L, Zhou ZG, Xu H and Peng Y. circNEIL3 inhibits tumor metastasis through recruiting the E3 ubiquitin ligase Nedd4L to degrade YBX1. Proc Natl Acad Sci U S A 2023; 120: e2215132120.
[76] Su S, Hong F, Liang Y, Zhou J, Liang Y, Chen K, Wang X, Wang Z, Wang Z, Chang C, Han W, Gong W, Qin H, Jiang B, Xiong H and Peng L. Lgr5 methylation in cancer stem cell differentiation and prognosis-prediction in colorectal cancer. PLoS One 2015; 10: e0143513.
[77] Shah M, Cardenas R, Wang B, Persson J, Mongan NP, Grabowska A and Allegrucci C. HOXC8 regulates self-renewal, differentiation and transformation of breast cancer stem cells. Mol Cancer 2017; 16: 38.
[78] Sun W, Lee KL, Poellinger L, Masai H and Kato H. Catalytic domain-dependent and -independent transcriptional activities of the tumour suppressor histone H3K27 demethylase UTX/KDM6A in specific cancer types. Epigenetics 2023; 18: 2222245.
[79] Boileau RM, Chen KX and Blelloch R. Loss of MLL3/4 decouples enhancer H3K4 monomethylation, H3K27 acetylation, and gene activation during embryonic stem cell differentiation. Genome Biol 2023; 24: 41.
[80] Dong H, He X, Zhang L, Chen W, Lin YC, Liu SB, Wang H, Nguyen LXT, Li M, Zhu Y, Zhao D, Ghoda L, Serody J, Vincent B, Luznik L, Gojo I, Zeidner J, Su R, Chen J, Sharma R, Pirrotte P, Wu X, Hu W, Han W, Shen B, Kuo YH, Jin J, Salhotra A, Wang J, Marcucci G, Luo YL and Li L. Targeting PRMT9-mediated arginine methylation suppresses cancer stem cell maintenance and elicits cGAS-mediated anticancer immunity. Nat Cancer 2024; 5: 601-624.
[81] Wong CC, Xu J, Bian X, Wu JL, Kang W, Qian Y, Li W, Chen H, Gou H, Liu D, Yat Luk ST, Zhou Q, Ji F, Chan LS, Shirasawa S, Sung JJ and Yu J. In colorectal cancer cells with mutant KRAS, SLC25A22-mediated glutaminolysis reduces DNA demethylation to increase WNT signaling, stemness, and drug resistance. Gastroenterology 2020; 159: 2163-2180, e6.
[82] Liu S, Yin P, Xu J, Dotts AJ, Kujawa SA, Coon V JS, Zhao H, Dai Y and Bulun SE. Progesterone receptor-DNA methylation crosstalk regulates depletion of uterine leiomyoma stem cells: a potential therapeutic target. Stem Cell Reports 2021; 16: 2099-2106.
[83] Wang Q, Liang N, Yang T, Li Y, Li J, Huang Q, Wu C, Sun L, Zhou X, Cheng X, Zhao L, Wang G, Chen Z, He X and Liu C. DNMT1-mediated methylation of BEX1 regulates stemness and tumorigenicity in liver cancer. J Hepatol 2021; 75: 1142-1153.
[84] Wang W, Fang F, Ozes A and Nephew KP. Targeting ovarian cancer stem cells by dual inhibi-

tion of HOTAIR and DNA methylation. Mol Cancer Ther 2021; 20: 1092-1101.
[85] Wang Y, Hu P, Wang F, Xi S, Wu S, Sun L, Du Y, Zheng J, Yang H, Tang M, Gao H, Luo H, Lv Y, Yan J, Ou X and Li Y. UHRF1 inhibition epigenetically reprograms cancer stem cells to suppress the tumorigenic phenotype of hepatocellular carcinoma. Cell Death Dis 2023; 14: 381.
[86] Zhang W, Ruan X, Li Y, Zhi J, Hu L, Hou X, Shi X, Wang X, Wang J, Ma W, Gu P, Zheng X and Gao M. KDM1A promotes thyroid cancer progression and maintains stemness through the Wnt/β-catenin signaling pathway. Theranostics 2022; 12: 1500-1517.
[87] Wangzhou K, Fu W, Li M, Lu Z, Lai Z, Liu C, Tan Y and Hao C. microRNA-17 is a tumor suppressor in oral squamous cell carcinoma and is repressed by LSD1. Oral Dis 2023; 29: 491-504.
[88] Ferrer-Diaz AI, Sinha G, Petryna A, et al. Role of KMT2B and KMT2D histone 3, lysine 4 methyltransferases and DNA oxidation status in circulating breast cancer cells provide insights into cell-autonomous regulation of cancer stem cells. 2024.
[89] Sweef O, Yang C and Wang Z. The oncogenic and tumor suppressive long non-coding RNA-microRNA-Messenger RNA regulatory Axes identified by analyzing multiple platform omics data from Cr(VI)-transformed cells and their implications in lung cancer. Biomedicines 2022; 10: 2334.
[90] Zhang Z, Tan X, Wu R, Deng T, Wang H, Jiang X, Zeng P and Tang J. m6A-mediated upregulation of lncRNA-AC026356.1 promotes cancer stem cell maintenance in lung adenocarcinoma via activating Wnt signaling pathway. Aging (Albany NY) 2023; 15: 3538-3548.
[91] Zhang S, Wang B, Xiao H, Dong J, Li Y, Zhu C, Jin Y, Li H, Cui M and Fan S. LncRNA HOTAIR enhances breast cancer radioresistance through facilitating HSPA1A expression via sequestering miR-449b-5p. Thorac Cancer 2020; 11: 1801-1816.
[92] Wen S, Qin Y, Wang R, Yang L, Zeng H, Zhu P, Li Q, Qiu Y, Chen S, Liu Y, Hou Y, Tang X, Liu M and Tu G. A novel Lnc408 maintains breast cancer stem cell stemness by recruiting SP3 to suppress CBY1 transcription and increasing nuclear β-catenin levels. Cell Death Dis 2021; 12: 437.
[93] Wang J, Liu X, Li P, Wang J, Shu Y, Zhong X, Gao Z, Yang J, Jiang Y, Zhou X and Yang G. Long noncoding RNA HOTAIR regulates the stemness of breast cancer cells via activation of the NF-κB signaling pathway. J Biol Chem 2022; 298: 102630.
[94] Zhang H and Guo H. Long non-coding RNA NORAD induces cell proliferation and migration in prostate cancer. J Int Med Res 2019; 47: 3898-3904.
[95] Zhang X, Jin M, Liu S, Zang M, Hu L, Du T and Zhang B. The roles and molecular mechanisms of long non-coding RNA WT1-AS in the maintenance and development of gastric cancer stem cells. Heliyon 2023; 9: e1465.
[96] Shen C, Wang J, Xu Z, Zhang L, Gu W and Zhou X. ONECUT2 which is targeted by hsa-miR-15a-5p enhances stemness maintenance of gastric cancer stem cells. Exp Biol Med (Maywood) 2021; 246: 2645-2659.
[97] Chen H, Ma J, Kong F, Song N, Wang C and Ma X. UPF1 contributes to the maintenance of endometrial cancer stem cell phenotype by stabilizing LINC00963. Cell Death Dis 2022; 13: 257.
[98] Ghuwalewala S, Ghatak D, Das S, Roy S, Das P, Butti R, Gorain M, Nath S, Kundu GC and Roychoudhury S. MiRNA-146a/AKT/β-catenin activation regulates cancer stem cell phenotype in oral squamous cell carcinoma by targeting CD24. Front Oncol 2021; 11: 651692.
[99] Shi J, Guo C, Li Y and Ma J. The long noncoding RNA TINCR promotes self-renewal of human liver cancer stem cells through autophagy activation. Cell Death Dis 2022; 13: 961.
[100] Bartucci M, Hussein MS, Huselid E, Flaherty K, Patrizii M, Laddha SV, Kui C, Bigos RA, Gilleran JA, El Ansary MMS, Awad MAM, Kimball SD, Augeri DJ and Sabaawy HE. Synthesis and characterization of novel BMI1 inhibitors targeting cellular self-renewal in hepatocellular carcinoma. Target Oncol 2017; 12: 449-462.
[101] Zhu Y, Xiao B, Liu M, Chen M, Xia N, Guo H, Huang J, Liu Z and Wang F. N6-methyladenosine-modified oncofetal lncRNA MIR4435-2HG contributed to stemness features of hepatocellular carcinoma cells by regulating rRNA 2'-O methylation. Cell Mol Biol Lett 2023; 28: 89.
[102] Wang S, Ming H, Wang Z, Zhai X, Zhang X, Wu D, Bo Y, Wang H, Luo Y, Han Z, Hao L, Xiang Y, Han X, Wang Z and Wang Y. NON-HSAT141192.2 facilitates the stemness and radioresistance of glioma stem cells via the regulation of PIK3R3 and SOX2. CNS Neurosci Ther 2025; 31: e70279.
[103] Wu S, Ren K, Zhao J, Li J, Jia B, Wu X, Dou Y, Fei X, Huan Y, He X, Wang T, Lv W, Wang L, Wang Y, Zhao J, Fei Z and Li S. LncRNA GAS5 represses stemness and malignancy of gliomas via elevating the SPACA6-miR-125a/let-7e axis. Front Oncol 2022; 12: 803652.
[104] Wang W, Zhou Y, Wang J, Zhang S, Ozes A, Gao H, Fang F, Wang Y, Chu X, Liu Y, Wan J, Mitra AK, O'Hagan HM and Nephew KP. Targeting ovarian cancer stem cells by dual inhibition of the long noncoding RNA HOTAIR and lysine

methyltransferase EZH2. Mol Cancer Ther 2024; 23: 1666-1679.
[105] Luo F, Zhang M, Sun B, Xu C, Yang Y, Zhang Y, Li S, Chen G, Chen C, Li Y and Feng H. LINC00115 promotes chemoresistant breast cancer stem-like cell stemness and metastasis through SETDB1/PLK3/HIF1α signaling. Mol Cancer 2024; 23: 60.
[106] He W, Liang B, Wang C, Li S, Zhao Y, Huang Q, Liu Z, Yao Z, Wu Q, Liao W, Zhang S, Liu Y, Xiang Y, Liu J and Shi M. MSC-regulated lncRNA MACC1-AS1 promotes stemness and chemoresistance through fatty acid oxidation in gastric cancer. Oncogene 2019; 38: 4637-4654.
[107] Wu H, Liu B, Chen Z, Li G and Zhang Z. MSC-induced lncRNA HCP5 drove fatty acid oxidation through miR-3619-5p/AMPK/PGC1α/CEBPB axis to promote stemness and chemoresistance of gastric cancer. Cell Death Dis 2020; 11: 233.
[108] Fan Y, Gao Z, Xu J, Wang H, Guo Q, Li B, Li M, Xu H, Qi Y, Zhao S, Qiu W, Pan Z, Wang Q, Xue H, Zhao R, Guo X and Li G. SPI1-mediated MIR222HG transcription promotes proneural-to-mesenchymal transition of glioma stem cells and immunosuppressive polarization of macrophages. Theranostics 2023; 13: 3310-3329.
[109] Mazor G, Levin L, Picard D, Ahmadov U, Carén H, Borkhardt A, Reifenberger G, Leprivier G, Remke M and Rotblat B. The lncRNA TP73-AS1 is linked to aggressiveness in glioblastoma and promotes temozolomide resistance in glioblastoma cancer stem cells. Cell Death Dis 2019; 10: 246.
[110] Wu JF, Ho MC, Ni YH, Hsu HY, Lee PH and Chang MH. Dysregulation of liver developmental microRNA contribute to hepatic carcinogenesis. J Formos Med Assoc 2020; 119: 1041-1051.
[111] Bamodu OA, Huang WC, Lee WH, Wu A, Wang LS, Hsiao M, Yeh CT and Chao TY. Aberrant KDM5B expression promotes aggressive breast cancer through MALAT1 overexpression and downregulation of hsa-miR-448. BMC Cancer 2016; 16: 160.
[112] Lin HP, Wang Z and Yang C. LncRNA DUXAP10 upregulation and the hedgehog pathway activation are critically involved in chronic cadmium exposure-induced cancer stem cell-like property. Toxicol Sci 2021; 184: 33-45.
[113] Yu W, Srivastava R, Srivastava S, Ma Y, Shankar S and Srivastava RK. Oncogenic role of SATB2 in vitro: regulator of pluripotency, self-renewal, and epithelial-mesenchymal transition in prostate cancer. Cells 2024; 13: 962.
[114] Xun J, Ma Y, Wang B, Jiang X, Liu B, Gao R, Zhai Q, Cheng R, Wu X, Wu Y and Zhang Q. RGS1 targeted by miR-191-3p inhibited the stemness properties of esophageal cancer cells by suppressing CXCR4/PI3K/AKT signaling. Acta Histochem 2024; 126: 152190.
[115] Qi J, Cui D, Wu QN, Zhao Q, Chen ZH, Li L, Birchmeier W, Yu Y and Tao R. Targeting Wnt/β-catenin signaling by TET1/FOXO4 inhibits metastatic spreading and self-renewal of cancer stem cells in gastric cancer. Cancers (Basel) 2022; 14: 3232.
[116] Ma X, Zhou K, Yan T, Hu L, Xie S, Zheng H, Tong Y, Zhang H, Wang Y, Gong Z, Chen C, Tian Y, Guo L and Lu R. Calpain 2 promotes Lenvatinib resistance and cancer stem cell traits via both proteolysis-dependent and independent approach in hepatocellular carcinoma. Mol Biomed 2024; 5: 74.
[117] Li H, Song J, He Y, Liu Y, Liu Z, Sun W, Hu W, Lei QY, Hu X, Chen Z and He X. CRISPR/Cas9 screens reveal that hexokinase 2 enhances cancer stemness and tumorigenicity by activating the ACSL4-fatty acid β-oxidation pathway. Adv Sci (Weinh) 2022; 9: e2105126.
[118] Wang D, Prager BC, Gimple RC, Aguilar B, Alizadeh D, Tang H, Lv D, Starr R, Brito A, Wu Q, Kim LJY, Qiu Z, Lin P, Lorenzini MH, Badie B, Forman SJ, Xie Q, Brown CE and Rich JN. CRISPR screening of CAR T cells and cancer stem cells reveals critical dependencies for cell-based therapies. Cancer Discov 2021; 11: 1192-1211.
[119] Ren J, Ding L, Zhang D, Shi G, Xu Q, Shen S, Wang Y, Wang T and Hou Y. Carcinoma-associated fibroblasts promote the stemness and chemoresistance of colorectal cancer by transferring exosomal lncRNA H19. Theranostics 2018; 8: 3932-3948.
[120] Liu X, Huang Z, Chen Q, Chen K, Liu W, Liu G, Chu X, Li D, Ma Y, Tian X and Yang Y. Hypoxia-induced epigenetic regulation of miR-485-3p promotes stemness and chemoresistance in pancreatic ductal adenocarcinoma via SLC7A11-mediated ferroptosis. Cell Death Discov 2024; 10: 262.
[121] Chen H, Yu S, Ma R, Deng L, Yi Y, Niu M, Xu C and Xiao ZJ. Hypoxia-activated XBP1s recruits HDAC2-EZH2 to engage epigenetic suppression of ΔNp63α expression and promote breast cancer metastasis independent of HIF1α. Cell Death Differ 2024; 31: 447-459.
[122] Zang Y, Wang A, Zhang J, Xia M, Jiang Z, Jia B, Lu C, Chen C, Wang S, Zhang Y, Wang C, Cao X, Niu Z, He C, Bai X, Tian S, Zhai G, Cao H, Chen Y and Zhang K. Hypoxia promotes histone H3K9 lactylation to enhance LAMC2 transcription in esophageal squamous cell carcinoma. iScience 2024; 27: 110188.
[123] Ashok C, Ahuja N, Natua S, Mishra J, Samaiya A and Shukla S. E2F1 and epigenetic modifiers

orchestrate breast cancer progression by regulating oxygen-dependent ESRP1 expression. Oncogenesis 2021; 10: 58.
[124] Yadav G and Kulshreshtha R. Pan-cancer analyses identify MIR210HG overexpression, epigenetic regulation and oncogenic role in human tumors and its interaction with the tumor microenvironment. Life Sci 2024; 339: 122438.
[125] Gupta VK, Sharma NS, Durden B, Garrido VT, Kesh K, Edwards D, Wang D, Myer C, Mateo-Victoriano B, Kollala SS, Ban Y, Gao Z, Bhattacharya SK, Saluja A, Singh PK and Banerjee S. Hypoxia-driven oncometabolite L-2HG maintains stemness-differentiation balance and facilitates immune evasion in pancreatic cancer. Cancer Res 2021; 81: 4001-4013.
[126] Yu H, He J, Liu W, Feng S, Gao L, Xu Y, Zhang Y, Hou X, Zhou Y, Yang L and Wang X. The transcriptional coactivator, ALL1-fused gene from chromosome 9, simultaneously sustains hypoxia tolerance and metabolic advantages in liver cancer. Hepatology 2021; 74: 1952-1970.
[127] Sanaei M and Kavoosi F. Effect of 5'-fluoro-2'-deoxycytidine, 5-azacytidine, and 5-aza-2'-deoxycytidine on DNA methyltransferase 1, CIP/KIP family, and INK4a/ARF in colon cancer HCT-116 cell line. Int J Cancer Manag 2022; 14: e110419.
[128] Yamashita AS, da Costa Rosa M, Borodovsky A, Festuccia WT, Chan T and Riggins GJ. Demethylation and epigenetic modification with 5-azacytidine reduces IDH1 mutant glioma growth in combination with temozolomide. Neuro Oncol 2019; 21: 189-200.
[129] Verma A, Chi YY, Malvar J, Lamble A, Chaudhury S, Agarwal A, Li HT, Liang G, Leong R, Brown PA, Kaplan J, Schafer ES, Slone T, Pauly M, Chang BH, Stieglitz E, Wayne AS, Hijiya N and Bhojwani D. Nivolumab plus 5-azacitidine in pediatric relapsed/refractory acute myeloid leukemia (AML): phase I/II trial results from the therapeutic advances in childhood leukemia and lymphoma (TACL) consortium. Cancers (Basel) 2024; 16: 496.
[130] Zhu D, Li Z, Feng H, Zheng J, Xiao X, Huang Z, Zheng L, Guo J, Ling F, Li Y and Xing F. EZH2 inhibition and 5-azacytidine enhance antitumor immunity in PTEN-deficient glioblastoma by activation viral mimicry response. J Immunother Cancer 2025; 13: e011650.
[131] Martin P, Bartlett NL, Chavez JC, Reagan JL, Smith SM, LaCasce AS, Jones J, Drew J, Wu C, Mulvey E, Revuelta MV, Cerchietti L and Leonard JP. Phase 1 study of oral azacitidine (CC-486) plus R-CHOP in previously untreated intermediate- to high-risk DLBCL. Blood 2022; 139: 1147-1159.
[132] Buocikova V, Tyciakova S, Pilalis E, Mastrokalou C, Urbanova M, Matuskova M, Demkova L, Medova V, Longhin EM, Rundén-Pran E, Dusinska M, Rios-Mondragon I, Cimpan MR, Gabelova A, Soltysova A, Smolkova B and Chatziioannou A. Decitabine-induced DNA methylation-mediated transcriptomic reprogramming in human breast cancer cell lines; the impact of DCK overexpression. Front Pharmacol 2022; 13: 991751.
[133] Gerecke C, Schumacher F, Edlich A, Wetzel A, Yealland G, Neubert LK, Scholtka B, Homann T and Kleuser B. Vitamin C promotes decitabine or azacytidine induced DNA hydroxymethylation and subsequent reactivation of the epigenetically silenced tumour suppressor CDKN1A in colon cancer cells. Oncotarget 2018; 9: 32822-32840.
[134] Fehn A, von Witzleben A, Grages A, Kors TA, Ezić J, Betzler AC, Brunner C, Schuler PJ, Theodoraki MN, Hoffmann TK and Laban S. 5-Aza-2'-deoxycytidin (Decitabine) increases cancer-testis antigen expression in head and neck squamous cell carcinoma and modifies immune checkpoint expression, especially in CD39-positive CD8 and CD4 T cells. Neoplasia 2025; 59: 101086.
[135] Quinn DI, Tsao-Wei DD, Twardowski P, Aparicio AM, Frankel P, Chatta G, Wright JJ, Groshen SG, Khoo S, Lenz HJ, Lara PN, Gandara DR and Newman E. Phase II study of the histone deacetylase inhibitor vorinostat (Suberoylanilide Hydroxamic Acid; SAHA) in recurrent or metastatic transitional cell carcinoma of the urothelium - an NCI-CTEP sponsored: California Cancer Consortium trial, NCI 6879. Invest New Drugs 2021; 39: 812-820.
[136] Palczewski MB, Kuschman HP, Bovee R, Hickok JR and Thomas DD. Vorinostat exhibits anticancer effects in triple-negative breast cancer cells by preventing nitric oxide-driven histone deacetylation. Biol Chem 2021; 402: 501-512.
[137] Ahmed AA and Neidle S. A G-Quadruplex-binding small molecule and the HDAC inhibitor SAHA (Vorinostat) act synergistically in gemcitabine-sensitive and resistant pancreatic cancer cells. Molecules 2020; 25: 5407.
[138] Molina AM, van der Mijn JC, Christos P, Wright J, Thomas C, Dutcher JP, Nanus DM, Tagawa ST and Gudas LJ. NCI 6896: a phase I trial of vorinostat (SAHA) and isotretinoin (13-cis retinoic acid) in the treatment of patients with advanced renal cell carcinoma. Invest New Drugs 2020; 38: 1383-1389.
[139] Basu D, Salgado CM, Bauer B, Hoehl RM, Moscinski CN, Schmitt L and Reyes-Múgica M. Histone deacetylase inhibitor Vorinostat (SAHA) suppresses micropthalmia transcription factor

expression and induces cell death in nevocytes from large/giant congenital melanocytic nevi. Melanoma Res 2021; 31: 319-327.
[140] Sanaei M, Kavoosi F and Pourahmadi M. Effect of decitabine (5-aza-2'-deoxycytidine, 5-aza-CdR) in comparison with vorinostat (suberoylanilide hydroxamic acid, SAHA) on DNMT1, DNMT3a and DNMT3b, HDAC 1-3, SOCS 1, SOCS 3, JAK2, and STAT3 gene expression in hepatocellular carcinoma HLE and LCL-PI 11 cell lines. Asian Pac J Cancer Prev 2021; 22: 2089-2098.
[141] Yang Y, Yan Y, Chen Z, Hu J, Wang K, Tang N, Li X and Zhou Z. Histone deacetylase inhibitors romidepsin and vorinostat promote hepatitis B virus replication by inducing cell cycle arrest. J Clin Transl Hepatol 2021; 9: 160-168.
[142] Kyaw MTH, Yamaguchi Y, Choijookhuu N, Yano K, Takagi H, Takahashi N, Synn Oo P, Sato K and Hishikawa Y. The HDAC inhibitor, SAHA, combined with cisplatin synergistically induces apoptosis in alpha-fetoprotein-producing hepatoid adenocarcinoma cells. Acta Histochem Cytochem 2019; 52: 1-8.
[143] Xu T, Fang Y, Gu Y, Xu D, Hu T, Yu T, Xu YY, Shen HY, Ma P and Shu Y. HDAC inhibitor SAHA enhances antitumor immunity via the HDAC1/JAK1/FGL1 axis in lung adenocarcinoma. J Immunother Cancer 2024; 12: e010077.
[144] Li LH, Zhang PR, Cai PY and Li ZC. Histone deacetylase inhibitor, Romidepsin (FK228) inhibits endometrial cancer cell growth through augmentation of p53-p21 pathway. Biomed Pharmacother 2016; 82: 161-166.
[145] K ST, Joshi G, Arya P, Mahajan V, Chaturvedi A and Mishra RK. SUMO and SUMOylation pathway at the forefront of host immune response. Front Cell Dev Biol 2021; 9: 681057.
[146] Rossetti A, Petragnano F, Milazzo L, Vulcano F, Macioce G, Codenotti S, Cassandri M, Pomella S, Cicchetti F, Fasciani I, Antinozzi C, Di Luigi L, Festuccia C, De Felice F, Vergine M, Fanzani A, Rota R, Maggio R, Polimeni A, Tombolini V, Gravina GL and Marampon F. Romidepsin (FK228) fails in counteracting the transformed phenotype of rhabdomyosarcoma cells but efficiently radiosensitizes, in vitro and in vivo, the alveolar phenotype subtype. Int J Radiat Biol 2021; 97: 943-957.
[147] Savvidou I, Khong T, Whish S, Carmichael I, Sepehrizadeh T, Mithraprabhu S, Horrigan SK, de Veer M and Spencer A. Combination of histone deacetylase inhibitor panobinostat (LBH589) with β-Catenin Inhibitor Tegavivint (BC2059) exerts significant anti-myeloma activity both in vitro and in vivo. Cancers (Basel) 2022; 14: 840.
[148] Qin G, Li Y, Xu X, Wang X, Zhang K, Tang Y, Qiu H, Shi D, Zhang C, Long Q, Lee K, Zhai Q, Wang S, Chen M and Deng W. Panobinostat (LBH589) inhibits Wnt/β-catenin signaling pathway via upregulating APCL expression in breast cancer. Cell Signal 2019; 59: 62-75.
[149] Hu Z, Wei F, Su Y, Wang Y, Shen Y, Fang Y, Ding J and Chen Y. Histone deacetylase inhibitors promote breast cancer metastasis by elevating NEDD9 expression. Signal Transduct Target Ther 2023; 8: 11.
[150] Liu YY, Ding CZ, Chen JL, Wang ZS, Yang B and Wu XM. A novel small molecular inhibitor of DNMT1 enhances the antitumor effect of radiofrequency ablation in lung squamous cell carcinoma cells. Front Pharmacol 2022; 13: 863339.
[151] Hsieh CH, Kuan WH, Chang WL, Kuo IY, Liu H, Shieh DB, Liu H, Tan B and Wang YC. Dysregulation of SOX17/NRF2 axis confers chemoradiotherapy resistance and emerges as a novel therapeutic target in esophageal squamous cell carcinoma. J Biomed Sci 2022; 29: 90.
[152] Liu Y, Sun Y, Yang J, Wu D, Yu S, Liu J, Hu T, Luo J and Zhou H. DNMT1-targeting remodeling global DNA hypomethylation for enhanced tumor suppression and circumvented toxicity in oral squamous cell carcinoma. Mol Cancer 2024; 23: 104.
[153] Kuo IY, Huang YL, Lin CY, Lin CH, Chang WL, Lai WW and Wang YC. SOX17 overexpression sensitizes chemoradiation response in esophageal cancer by transcriptional down-regulation of DNA repair and damage response genes. J Biomed Sci 2019; 26: 20.
[154] Sun QY, Ding LW, Johnson K, Zhou S, Tyner JW, Yang H, Doan NB, Said JW, Xiao JF, Loh XY, Ran XB, Venkatachalam N, Lao Z, Chen Y, Xu L, Fan LF, Chien W, Lin DC and Koeffler HP. SOX7 regulates MAPK/ERK-BIM mediated apoptosis in cancer cells. Oncogene 2019; 38: 6196-6210.
[155] Liao YM, Song Y, Li YK, Du JH and Zhou Y. SOX17, β-catenin and CyclinD1 expression in the endometrioid adenocarcinoma and influence of 5-AZA on expression. Cancer Gene Ther 2020; 27: 256-263.
[156] Wang P, Xiao R, Chen J, Guan P, Heng HL, Liu L, Wang Y, Zeng X, Zhong G, Hao J, Gao J, Chan JY, Dima S, Ong CK, Teh BT, Li M, Hong JH and Tan J. PARP inhibitor augments anti-tumor efficacy of DNMT inhibitor by inducing senescence in cholangiocarcinoma. Int J Biol Sci 2025; 21: 3649-3665.
[157] Kurz L, Miklyaeva A, Skowron MA, Overbeck N, Poschmann G, Becker T, Eul K, Kurz T, Schönberger S, Calaminus G, Stühler K, Dykhuizen E, Albers P and Nettersheim D. ARID1A regulates transcription and the epigenetic landscape via POLE and DMAP1 while ARID1A deficiency or pharmacological inhibition sensitizes germ cell tumor cells to ATR inhibition. Cancers (Basel) 2020; 12: 905.

[158] Sun T, Liu Z and Yang Q. The role of ubiquitination and deubiquitination in cancer metabolism. Mol Cancer 2020; 19: 146.
[159] Ding X, Li Y, Lü J, Zhao Q, Guo Y, Lu Z, Ma W, Liu P, Pestell RG, Liang C and Yu Z. piRNA-823 is involved in cancer stem cell regulation through altering DNA methylation in association with luminal breast cancer. Front Cell Dev Biol 2021; 9: 641052.
[160] Cao XC, Peng J, Qiu YB, Zhu W, Cao JG, Zou H, Yu ZZ, Wu D, Lu SS, Huang W, Yi H and Xiao ZQ. FVTF inhibits hepatocellular carcinoma stem properties via targeting DNMT1/miR-34a-5p/FoxM1 axis. Chin Med 2025; 20: 32.
[161] Chen J, Li H, Zhang B, Xiong Z, Jin Z, Chen J, Zheng Y, Zhu X and Zhang S. ABI2-mediated MEOX2/KLF4-NANOG axis promotes liver cancer stem cell and drives tumour recurrence. Liver Int 2022; 42: 2562-2576.
[162] Xin L, Liu L, Liu C, Zhou LQ, Zhou Q, Yuan YW, Li SH and Zhang HT. DNA-methylation-mediated silencing of miR-7-5p promotes gastric cancer stem cell invasion via increasing Smo and Hes1. J Cell Physiol 2020; 235: 2643-2654.
[163] Wu Q, Yan Y, Shi S, Qi Q and Han J. DNMT3b-mediated SPAG6 promoter hypermethylation affects lung squamous cell carcinoma development through the JAK/STAT pathway. Am J Transl Res 2022; 14: 6964-6977.
[164] Lyu C, Wang L, Stadlbauer B, Noessner E, Buchner A and Pohla H. Identification of EZH2 as cancer stem cell marker in clear cell renal cell carcinoma and the anti-tumor effect of epigallocatechin-3-gallate (EGCG). Cancers (Basel) 2022; 14: 4200.
[165] Wen Y, Hou Y, Yi X, Sun S, Guo J, He X, Li T, Cai J and Wang Z. EZH2 activates CHK1 signaling to promote ovarian cancer chemoresistance by maintaining the properties of cancer stem cells. Theranostics 2021; 11: 1795-1813.
[166] Wu J, Sun L, Liu T and Dong G. Ultrasound-targeted microbubble destruction-mediated downregulation of EZH2 inhibits stemness and epithelial-mesenchymal transition of liver cancer stem cells. Onco Targets Ther 2021; 14: 221-237.
[167] Chen ZY, Huang HH, Li QC, Zhan FB, Wang LB, He T, Yang CH, Wang Y, Zhang Y and Quan ZX. Capsaicin reduces cancer stemness and inhibits its metastasis by downregulating SOX2 and EZH2 in osteosarcoma. Am J Chin Med 2023; 51: 1041-1066.
[168] Cao Y, Chai W, Wang Y, Tang D, Shao D, Song H and Long J. lncRNA TUG1 inhibits the cancer stem cell-like properties of temozolomide-resistant glioma cells by interacting with EZH2. Mol Med Rep 2021; 24: 533.
[169] Sanches JGP, Song B, Zhang Q, Cui X, Yabasin IB, Ntim M, Li X, He J, Zhang Y, Mao J, Lu Y and Li L. The role of KDM2B and EZH2 in regulating the stemness in colorectal cancer through the PI3K/AKT pathway. Front Oncol 2021; 11: 637298.
[170] Balinth S, Fisher ML, Hwangbo Y, Wu C, Ballon C, Sun X and Mills AA. EZH2 regulates a SETDB1/ΔNp63α axis via RUNX3 to drive a cancer stem cell phenotype in squamous cell carcinoma. Oncogene 2022; 41: 4130-4144.
[171] Wang S, Cai L, Zhang F, Shang X, Xiao R and Zhou H. Inhibition of EZH2 attenuates sorafenib resistance by targeting NOTCH1 activation-dependent liver cancer stem cells via NOTCH1-related MicroRNAs in hepatocellular carcinoma. Transl Oncol 2020; 13: 100741.
[172] Deng S, Wang J, Zhang L, Li J and Jin Y. LncRNA HOTAIR promotes cancer stem-like cells properties by sponging miR-34a to activate the JAK2/STAT3 pathway in pancreatic ductal adenocarcinoma. Onco Targets Ther 2021; 14: 1883-1893.
[173] Kouhestani SD, Khalili S, Razi A, Aghili M and Moghadam MF. Ectopic expression of miR-34a/-328 sensitizes breast cancer stem cells to gamma rays/doxorubicin by BCL2/ABCG2 targeting. Mol Biol Rep 2025; 52: 490.
[174] Cao X, Liu L, Cao X, Cui Y, Zou C, Chen A, Qiu Y, Quan M, Ren K, Chen X and Cao J. The DNMT1/miR-34a/FOXM1 axis contributes to stemness of liver cancer cells. J Oncol 2020; 2020: 8978930.
[175] Zhao H, Jiang R, Zhang C, Feng Z and Wang X. LncRNA H19-rich extracellular vesicles derived from gastric cancer stem cells facilitate tumorigenicity and metastasis via mediating intratumor communication network. J Transl Med 2023; 21: 238.
[176] Wang F, Rong L, Zhang Z, Li M, Ma L, Ma Y, Xie X, Tian X and Yang Y. LncRNA H19-derived miR-675-3p promotes epithelial-mesenchymal transition and stemness in human pancreatic cancer cells by targeting the STAT3 pathway. J Cancer 2020; 11: 4771-4782.
[177] Mandal S, Arfuso F, Sethi G, Dharmarajan A and Warrier S. Encapsulated human mesenchymal stem cells (eMSCs) as a novel anti-cancer agent targeting breast cancer stem cells: development of 3D primed therapeutic MSCs. Int J Biochem Cell Biol 2019; 110: 59-69.
[178] Wang Z, Chen H, Wang P, Zhou M, Li G, Hu Z, Hu Q, Zhao J, Liu X, Wu L and Liang D. Site-specific integration of TRAIL in iPSC-derived mesenchymal stem cells for targeted cancer therapy. Stem Cells Transl Med 2022; 11: 297-309.
[179] Li M, Sun S, Dangelmajer S, Zhang Q, Wang J, Hu F, Dong F, Kahlert UD, Zhu M and Lei T. Exploiting tumor-intrinsic signals to induce mesenchymal stem cell-mediated suicide gene

therapy to fight malignant glioma. Stem Cell Res Ther 2019; 10: 88.
[180] Qiu W, Guo Q, Guo X, Wang C, Li B, Qi Y, Wang S, Zhao R, Han X, Du H, Zhao S, Pan Z, Fan Y, Wang Q, Gao Z, Li G and Xue H. Mesenchymal stem cells, as glioma exosomal immunosuppressive signal multipliers, enhance MDSCs immunosuppressive activity through the miR-21/SP1/DNMT1 positive feedback loop. J Nanobiotechnology 2023; 21: 233.
[181] Zhao Q, Hai B, Kelly J, Wu S and Liu F. Extracellular vesicle mimics made from iPS cell-derived mesenchymal stem cells improve the treatment of metastatic prostate cancer. Stem Cell Res Ther 2021; 12: 29.
[182] Mercer-Smith AR, Jiang W, Bago JR, Valdivia A, Thang M, Woodell AS, Montgomery SA, Sheets KT, Anders CK and Hingtgen SD. Cytotoxic engineered induced neural stem cells as an intravenous therapy for primary non-small cell lung cancer and triple-negative breast cancer. Mol Cancer Ther 2021; 20: 2291-2301.
[183] Wang LT, Jiang SS, Ting CH, Hsu PJ, Chang CC, Sytwu HK, Liu KJ and Yen BL. Differentiation of mesenchymal stem cells from human induced pluripotent stem cells results in downregulation of c-Myc and DNA replication pathways with immunomodulation toward CD4 and CD8 cells. Stem Cells 2018; 36: 903-914.
[184] Duan S, Yuan G, Liu X, Ren R, Li J, Zhang W, Wu J, Xu X, Fu L, Li Y, Yang J, Zhang W, Bai R, Yi F, Suzuki K, Gao H, Esteban CR, Zhang C, Izpisua Belmonte JC, Chen Z, Wang X, Jiang T, Qu J, Tang F and Liu GH. PTEN deficiency reprogrammes human neural stem cells towards a glioblastoma stem cell-like phenotype. Nat Commun 2015; 6: 10068.
[185] Liu T, Li T, Zheng Y, Xu X, Sun R, Zhan S, Guo X, Zhao Z, Zhu W, Feng B, Wei F, Jiang N, Wang J, Chen X, Fang F, Guo H and Yang R. Evaluating adipose-derived stem cell exosomes as miRNA drug delivery systems for the treatment of bladder cancer. Cancer Med 2022; 11: 3687-3699.
[186] Farouk AH, Aref A, Fathy BA and Abdallah AN. Stem cells derived exosomes as biological nano carriers for VCR sulfate for treating breast cancer stem cells. Sci Rep 2024; 14: 10964.
[187] Paul S, Bhagat S, Dash L, Mohapatra HD, Jena S, Verma SK and Dutta A. ExoDS: a versatile exosome-based drug delivery platform to target cancer cells and cancer stem cells. Front Bioeng Biotechnol 2024; 12: 1362681.
[188] Zhang Y, Zhao M, Gao H, Yu G, Zhao Y, Yao F and Yang W. MAPK signalling-induced phosphorylation and subcellular translocation of PDHE1α promotes tumour immune evasion. Nat Metab 2022; 4: 374-388.
[189] Wang L, Wu C, Xu J, Gong Z, Cao X, Huang J, Dong H, Zhu W, Huang F, Zhou C and Wang M. GC-MSC-derived circ_0024107 promotes gastric cancer cell lymphatic metastasis via fatty acid oxidation metabolic reprogramming mediated by the miR-5572/6855-5p/CPT1A axis. Oncol Rep 2023; 50: 138.
[190] Alizadeh D, Wong RA, Yang X, Wang D, Pecoraro JR, Kuo CF, Aguilar B, Qi Y, Ann DK, Starr R, Urak R, Wang X, Forman SJ and Brown CE. IL15 enhances CAR-T cell antitumor activity by reducing mTORC1 activity and preserving their stem cell memory phenotype. Cancer Immunol Res 2019; 7: 759-772.
[191] Yu Q, Xiu Z, Jian Y, Zhou J, Chen X, Chen X, Chen C, Chen H, Yang S, Yin L and Zeng W. microRNA-497 prevents pancreatic cancer stem cell gemcitabine resistance, migration, and invasion by directly targeting nuclear factor kappa B 1. Aging (Albany NY) 2022; 14: 5908-5924.
[192] Stiff T, Bayraktar S, Dama P, Stebbing J and Castellano L. CRISPR screens in 3D tumourspheres identified miR-4787-3p as a transcriptional start site miRNA essential for breast tumour-initiating cell growth. Commun Biol 2024; 7: 859.
[193] Guilhamon P, Chesnelong C, Kushida MM, Nikolic A, Singhal D, MacLeod G, Madani Tonekaboni SA, Cavalli FM, Arlidge C, Rajakulendran N, Rastegar N, Hao X, Hassam R, Smith LJ, Whetstone H, Coutinho FJ, Nadorp B, Ellestad KI, Luchman HA, Chan JA, Shoichet MS, Taylor MD, Haibe-Kains B, Weiss S, Angers S, Gallo M, Dirks PB and Lupien M. Single-cell chromatin accessibility profiling of glioblastoma identifies an invasive cancer stem cell population associated with lower survival. Elife 2021; 10: e64090.
[194] Hunt KV, Burnard SM, Roper EA, Bond DR, Dun MD, Verrills NM, Enjeti AK and Lee HJ. scTEM-seq: single-cell analysis of transposable element methylation to link global epigenetic heterogeneity with transcriptional programs. Sci Rep 2022; 12: 5776.
[195] Xiao Y, Jin W, Ju L, Fu J, Wang G, Yu M, Chen F, Qian K, Wang X and Zhang Y. Tracking single-cell evolution using clock-like chromatin accessibility loci. Nat Biotechnol 2025; 43: 784-798.
[196] Pine AR, Cirigliano SM, Singhania R, Nicholson J, da Silva B, Leslie CS and Fine HA. Microenvironment-driven dynamic chromatin changes in glioblastoma recapitulate early neural development at single-cell resolution. Cancer Res 2023; 83: 1581-1595.
[197] Al-Ali R, Bauer K, Park JW, Al Abdulla R, Fermi V, von Deimling A, Herold-Mende C, Mallm JP, Herrmann C, Wick W and Turcan Ş. Single-nu-

cleus chromatin accessibility reveals intratumoral epigenetic heterogeneity in IDH1 mutant gliomas. Acta Neuropathol Commun 2019; 7: 201.
[198] Johnson KC, Anderson KJ, Courtois ET, Gujar AD, Barthel FP, Varn FS, Luo D, Seignon M, Yi E, Kim H, Estecio MRH, Zhao D, Tang M, Navin NE, Maurya R, Ngan CY, Verburg N, de Witt Hamer PC, Bulsara K, Samuels ML, Das S, Robson P and Verhaak RGW. Single-cell multimodal glioma analyses identify epigenetic regulators of cellular plasticity and environmental stress response. Nat Genet 2021; 53: 1456-1468.
[199] Zhou D, Alver BM, Li S, Hlady RA, Thompson JJ, Schroeder MA, Lee JH, Qiu J, Schwartz PH, Sarkaria JN and Robertson KD. Distinctive epigenomes characterize glioma stem cells and their response to differentiation cues. Genome Biol 2018; 19: 43.
[200] Benfatto S, Sill M, Jones DTW, Pfister SM, Sahm F, von Deimling A, Capper D and Hovestadt V. Explainable artificial intelligence of DNA methylation-based brain tumor diagnostics. Nat Commun 2025; 16: 1787.
[201] Yuan D, Jugas R, Pokorna P, Sterba J, Slaby O, Schmid S, Siewert C, Osberg B, Capper D, Halldorsson S, Vik-Mo EO, Zeiner PS, Weber KJ, Harter PN, Thomas C, Albers A, Rechsteiner M, Reimann R, Appelt A, Schüller U, Jabareen N, Mackowiak S, Ishaque N, Eils R, Lukassen S and Euskirchen P. crossNN is an explainable framework for cross-platform DNA methylation-based classification of tumors. Nat Cancer 2025; 6: 1283-1294.
[202] Zhou J, Luo C, Liu H, Heffel MG, Straub RE, Kleinman JE, Hyde TM, Ecker JR, Weinberger DR and Han S. Deep learning imputes DNA methylation states in single cells and enhances the detection of epigenetic alterations in schizophrenia. Cell Genom 2025; 5: 100774.
[203] Li ZP, Du Z, Huang DS and Teschendorff AE. Interpretable deep learning of single-cell and epigenetic data reveals novel molecular insights in aging. Sci Rep 2025; 15: 5048.
[204] Lian H, Han YP, Zhang YC, Zhao Y, Yan S, Li QF, Wang BC, Wang JJ, Meng W, Yang J, Wang QH, Mao WW and Ma J. Integrative analysis of gene expression and DNA methylation through one-class logistic regression machine learning identifies stemness features in medulloblastoma. Mol Oncol 2019; 13: 2227-2245.
[205] Wang Y, Ma L, He J, Gu H and Zhu H. Identification of cancer stem cell-related genes through single cells and machine learning for predicting prostate cancer prognosis and immunotherapy. Front Immunol 2024; 15: 1464698.
[206] Ferrer-Diaz AI, Sinha G, Petryna A, Gonzalez-Bermejo R, Kenfack Y, Adetayo O, Patel SA, Hooda-Nehra A and Rameshwar P. Revealing role of epigenetic modifiers and DNA oxidation in cell-autonomous regulation of Cancer stem cells. Cell Commun Signal 2024; 22: 119.
[207] Zhang G, Zhang X, Pan W, Chen X, Wan L, Liu C, Yong Y, Zhao Y, Sang S, Zhang L, Yao S, Guo Y, Wang M, Wang X, Peng G, Yan X, Wang Y and Zhang M. Dissecting the spatial and single-cell transcriptomic architecture of cancer stem cell niche driving tumor progression in gastric cancer. Adv Sci (Weinh) 2025; 12: e2413019.
[208] Lee J, Hyeon DY and Hwang D. Single-cell multiomics: technologies and data analysis methods. Exp Mol Med 2020; 52: 1428-1442.
[209] Liu Y, Rosikiewicz W, Pan Z, Jillette N, Wang P, Taghbalout A, Foox J, Mason C, Carroll M, Cheng A and Li S. DNA methylation-calling tools for Oxford Nanopore sequencing: a survey and human epigenome-wide evaluation. Genome Biol 2021; 22: 295.
[210] Lee I, Razaghi R, Gilpatrick T, Molnar M, Gershman A, Sadowski N, Sedlazeck FJ, Hansen KD, Simpson JT and Timp W. Simultaneous profiling of chromatin accessibility and methylation on human cell lines with nanopore sequencing. Nat Methods 2020; 17: 1191-1199.
[211] Zhu Q, Zhao X, Zhang Y, Li Y, Liu S, Han J, Sun Z, Wang C, Deng D, Wang S, Tang Y, Huang Y, Jiang S, Tian C, Chen X, Yuan Y, Li Z, Yang T, Lai T, Liu Y, Yang W, Zou X, Zhang M, Cui H, Liu C, Jin X, Hu Y, Chen A, Xu X, Li G, Hou Y, Liu L, Liu S, Fang L, Chen W and Wu L. Single cell multi-omics reveal intra-cell-line heterogeneity across human cancer cell lines. Nat Commun 2023; 14: 8170.
[212] Nadalin F, Marzi MJ, Pirra Piscazzi M, Fuentes-Bravo P, Procaccia S, Climent M, Bonetti P, Rubolino C, Giuliani B, Papatheodorou I, Marioni JC and Nicassio F. Multi-omic lineage tracing predicts the transcriptional, epigenetic and genetic determinants of cancer evolution. Nat Commun 2024; 15: 7609.
[213] Du L, Gao P, Liu Z, Yin N and Wang X. TMODI-NET: a trustworthy multi-omics dynamic learning integration network for cancer diagnostic. Comput Biol Chem 2024: 113: 108202.
[214] Zhang Y, Li X, Chen H, Li J, Guo X, Fang Y, Chen L, Li K, Zhang Y, Kong F, Chen A, Lyu J, Zhang W and Wang Z. Cancer cell-derived exosomal miR-500a-3p modulates hepatic stellate cell activation and the immunosuppressive microenvironment. Adv Sci (Weinh) 2025; 12: 2404089.
[215] Li S, Hu X, Yu S, Yi P, Chen R, Huang Z, Huang Y, Huang Y, Zhou R and Fan X. Hepatic stellate cell-released CXCL1 aggravates HCC malignant behaviors through the MIR4435-2HG/miR-506-3p/TGFB1 axis. Cancer Sci 2023; 114: 504-520.

[216] Liu S, Sun Y, Hou Y, Yang L, Wan X, Qin Y, Liu Y, Wang R, Zhu P, Teng Y and Liu M. A novel lncRNA ROPM-mediated lipid metabolism governs breast cancer stem cell properties. J Hematol Oncol 2021; 14: 178.
[217] Chen ZQ, Yuan T, Jiang H, Yang YY, Wang L, Fu RM, Luo SQ, Zhang T, Wu ZY and Wen KM. MicroRNA-8063 targets heterogeneous nuclear ribonucleoprotein AB to inhibit the self-renewal of colorectal cancer stem cells via the Wnt/β-catenin pathway. Oncol Rep 2021; 46: 219.
[218] Liao TT, Cheng WC, Yang CY, Chen YQ, Su SH, Yeh TY, Lan HY, Lee CC, Lin HH, Lin CC, Lu RH, Chiou AE, Jiang JK and Hwang WL. The microRNA-210-Stathmin1 axis decreases cell stiffness to facilitate the invasiveness of colorectal cancer stem cells. Cancers (Basel) 2021; 13: 1833.
[219] Liu J, Niraj M, Wang H, Zhang W, Wang R, Kadier A, Li W and Yao X. Down-regulation of lncRNA MBNL1-AS1 promotes tumor stem cell-like characteristics and prostate cancer progression through miR-221-3p/CDKN1B/C-myc axis. Cancers (Basel) 2022; 14: 5783.
[220] Li WJ, Wang Y, Liu X, Wu S, Wang M, Turowski SG, Spernyak JA, Tracz A, Abdelaal AM, Sudarshan K, Puzanov I, Chatta G, Kasinski AL and Tang DG. Developing folate-conjugated miR-34a therapeutic for prostate cancer: challenges and promises. Int J Mol Sci 2024; 25: 2123.
[221] Ma YS, Yang XL, Liu YS, Ding H, Wu JJ, Shi Y, Jia CY, Lu GX, Zhang DD, Wang HM, Wang PY, Yu F, Lv ZW, Wang GR, Liu JB and Fu D. Long noncoding RNA NORAD promotes pancreatic cancer stem cell proliferation and self-renewal by blocking microRNA-202-5p-mediated ANP32E inhibition. J Transl Med 2021; 19: 400.
[222] Zou J, Yang S, He C, Deng L, Xu B and Chen S. miR-630 as a therapeutic target in pancreatic cancer stem cells: modulation of the PRKCI-Hedgehog signaling axis. Biol Direct 2024; 19: 109.
[223] Liu L, Liu Z, Liu Q, Wu W, Lin P, Liu X, Zhang Y, Wang D, Prager BC, Gimple RC, Yu J, Zhao W, Wu Q, Zhang W, Wu E, Chen X, Luo J, Rich JN, Xie Q, Jiang T and Chen R. LncRNA INHEG promotes glioma stem cell maintenance and tumorigenicity through regulating rRNA 2'-O-methylation. Nat Commun 2023; 14: 7526.
[224] Tang J, Yu B, Li Y, Zhang W, Alvarez AA, Hu B, Cheng SY and Feng H. TGF-β-activated lncRNA LINC00115 is a critical regulator of glioma stem-like cell tumorigenicity. EMBO Rep 2019; 20: e48170.
[225] Zhang L, Liang H, Zhang J, Yang Y, Ling X and Jiang H. Long non-coding RNA SNHG16 facilitates esophageal cancer cell proliferation and self-renewal through the microRNA-802/PTCH1 axis. Curr Med Chem 2022; 29: 6084-6099.
[226] Wu D, He X, Wang W, Hu X, Wang K and Wang M. Long noncoding RNA SNHG12 induces proliferation, migration, epithelial-mesenchymal transition, and stemness of esophageal squamous cell carcinoma cells via post-transcriptional regulation of BMI1 and CTNNB1. Mol Oncol 2020; 14: 2332-2351.
[227] Xu J, Yang R, Li J, Wang L, Cohen M, Simeone DM, Costa M and Wu XR. DNMT3A/miR-129-2-5p/Rac1 is an effector pathway for SNHG1 to drive stem-cell-like and invasive behaviors of advanced bladder cancer cells. Cancers (Basel) 2022; 14: 4159.
[228] Zhan Y, Zhou Z, Zhu Z, Zhang L, Yu S, Liu Y and Zhang X. Exosome-transmitted LUCAT1 promotes stemness transformation and chemoresistance in bladder cancer by binding to IGF2BP2. J Exp Clin Cancer Res 2025; 44: 80.
[229] Wu Q, He Y, Liu X, Luo F, Jiang Y, Xiang M and Zhao R. Cancer stem cell-like cells-derived exosomal lncRNA CDKN2B-AS1 promotes biological characteristics in thyroid cancer via miR-122-5p/P4HA1 axis. Regen Ther 2023; 22: 19-29.
[230] Dai W, Jin X, Han L, Huang H, Ji Z, Xu X, Tang M, Jiang B and Chen W. Exosomal lncRNA DOCK9-AS2 derived from cancer stem cell-like cells activated Wnt/β-catenin pathway to aggravate stemness, proliferation, migration, and invasion in papillary thyroid carcinoma. Cell Death Dis 2020; 11: 743.
[231] Gao Y, Qian H, Tang X, Du X, Wang G, Zhang H, Ye F and Liu T. Superparamagnetic iron oxide nanoparticle-mediated expression of miR-326 inhibits human endometrial carcinoma stem cell growth. Int J Nanomedicine 2019: 14: 2719-2731.
[232] Chen HS, Hsu CY, Chang YC, Chuang HY, Long CY, Hsieh TH and Tsai EM. Benzyl butyl phthalate decreases myogenic differentiation of endometrial mesenchymal stem/stromal cells through miR-137-mediated regulation of PITX2. Sci Rep 2017; 7: 186.
[233] Xu Q, Wang C, Zhou JX, Xu ZM, Gao J, Sui P, Walsh CP, Ji H and Xu GL. Loss of TET reprograms Wnt signaling through impaired demethylation to promote lung cancer development. Proc Natl Acad Sci U S A 2022; 119: e2107599119.
[234] Kamdar S, Isserlin R, Van der Kwast T, Zlotta AR, Bader GD, Fleshner NE and Bapat B. Exploring targets of TET2-mediated methylation reprogramming as potential discriminators of prostate cancer progression. Clin Epigenetics 2019; 11: 54.
[235] Yang J, Ren B, Ren J, Yang G, Fang Y, Wang X, Zhou F, You L and Zhao Y. Epigenetic repro-

gramming-induced guanidinoacetic acid synthesis promotes pancreatic cancer metastasis and transcription-activating histone modifications. J Exp Clin Cancer Res 2023; 42: 155.
[236] Chen J, Xu Z, Huang H, Tang Y, Shan H and Xiao F. SETD1A drives stemness by reprogramming the epigenetic landscape in hepatocellular carcinoma stem cells. JCI insight 2023; 8: e168375.
[237] Wu DC, Wang SSW, Liu CJ, Wuputra K, Kato K, Lee YL, Lin YC, Tsai MH, Ku CC, Lin WH, Wang SW, Kishikawa S, Noguchi M, Wu CC, Chen YT, Chai CY, Lin CS, Kuo KK, Yang YH, Miyoshi H, Nakamura Y, Saito S, Nagata K, Lin CS and Yokoyama KK. Reprogramming antagonizes the oncogenicity of HOXA13-long noncoding RNA HOTTIP axis in gastric cancer cells. Stem Cells 2017; 35: 2115-2128.
[238] Huang T, You Q, Liu J, Shen X, Huang D, Tao X, He Z, Wu C, Xi X, Yu S, Liu F, Wu Z, Mao W and Zhu S. WTAP mediated m6A modification stabilizes PDIA3P1 and promotes tumor progression driven by histone lactylation in esophageal squamous cell carcinoma. Adv Sci (Weinh) 2025; e06529.
[239] Hiew MSY, Cheng HP, Huang CJ, Chong KY, Cheong SK, Choo KB and Kamarul T. Incomplete cellular reprogramming of colorectal cancer cells elicits an epithelial/mesenchymal hybrid phenotype. J Biomed Sci 2018; 25: 57.
[240] Ji Y, Fioravanti J, Zhu W, Wang H, Wu T, Hu J, Lacey NE, Gautam S, Le Gall JB, Yang X, Hocker JD, Escobar TM, He S, Dell'Orso S, Hawk NV, Kapoor V, Telford WG, Di Croce L, Muljo SA, Zhang Y, Sartorelli V and Gattinoni L. miR-155 harnesses Phf19 to potentiate cancer immunotherapy through epigenetic reprogramming of CD8+ T cell fate. Nat commun 2019; 10: 2157.
[241] Liu NQ, Paassen I, Custers L, Zeller P, Teunissen H, Ayyildiz D, He J, Buhl JL, Hoving EW, van Oudenaarden A, de Wit E and Drost J. SMARCB1 loss activates patient-specific distal oncogenic enhancers in malignant rhabdoid tumors. Nat Commun 2023; 14: 7762.
[242] Wu Q, Madany P, Dobson JR, Schnabl JM, Sharma S, Smith TC, van Wijnen AJ, Stein JL, Lian JB, Stein GS, Muthuswami R, Imbalzano AN and Nickerson JA. The BRG1 chromatin remodeling enzyme links cancer cell metabolism and proliferation. Oncotarget 2016; 7: 38270-38281.
[243] Wu Z, Zhou J, Zhang X, Zhang Z, Xie Y, Liu JB, Ho ZV, Panda A, Qiu X, Cejas P, Cañadas I, Akarca FG, McFarland JM, Nagaraja AK, Goss LB, Kesten N, Si L, Lim K, Liu Y, Zhang Y, Baek JY, Liu Y, Patil DT, Katz JP, Hai J, Bao C, Stachler M, Qi J, Ishizuka JJ, Nakagawa H, Rustgi AK, Wong KK, Meyerson M, Barbie DA, Brown M, Long H and Bass AJ. Reprogramming of the esophageal squamous carcinoma epigenome by SOX2 promotes ADAR1 dependence. Nat Genet 2021; 53: 881-894.
[244] Ku SY, Rosario S, Wang Y, Mu P, Seshadri M, Goodrich ZW, Goodrich MM, Labbé DP, Gomez EC, Wang J, Long HW, Xu B, Brown M, Loda M, Sawyers CL, Ellis L and Goodrich DW. Rb1 and Trp53 cooperate to suppress prostate cancer lineage plasticity, metastasis, and antiandrogen resistance. Science 2017; 355: 78-83.
[245] Singovski G, Bernal C, Kuciak M, Siegl-Cachedenier I, Conod A and Ruiz i Altaba A. In vivo epigenetic reprogramming of primary human colon cancer cells enhances metastases. J Mol Cell Biol 2016; 8: 157-173.
[246] Jeter CR, Liu B, Lu Y, Chao HP, Zhang D, Liu X, Chen X, Li Q, Rycaj K, Calhoun-Davis T, Yan L, Hu Q, Wang J, Shen J, Liu S and Tang DG. NANOG reprograms prostate cancer cells to castration resistance via dynamically repressing and engaging the AR/FOXA1 signaling axis. Cell Discov 2016; 2: 16041.
[247] Kar S and Patra SK. Overexpression of OCT4 induced by modulation of histone marks plays crucial role in breast cancer progression. Gene 2018; 643: 35-45.
[248] Xun J, Wang D, Shen L, Gong J, Gao R, Du L, Chang A, Song X, Xiang R and Tan X. JMJD3 suppresses stem cell-like characteristics in breast cancer cells by downregulation of Oct4 independently of its demethylase activity. Oncotarget 2017; 8: 21918-21929.
[249] Mohapatra P, Madhulika S, Behera S, Singh P, Sa P, Prasad P, Swain RK and Sahoo SK. Nimbolide-based nanomedicine inhibits breast cancer stem-like cells by epigenetic reprogramming of DNMTs-SFRP1-Wnt/β-catenin signaling axis. Mol Ther Nucleic Acids 2023; 34: 102031.
[250] Vinchure OS, Sharma V, Tabasum S, Ghosh S, Singh RP, Sarkar C and Kulshreshtha R. Polycomb complex mediated epigenetic reprogramming alters TGF-β signaling via a novel EZH2/miR-490/TGIF2 axis thereby inducing migration and EMT potential in glioblastomas. Int J Cancer 2019; 145: 1254-1269.
[251] Béguelin W, Teater M, Meydan C, Hoehn KB, Phillip JM, Soshnev AA, Venturutti L, Rivas MA, Calvo-Fernández MT, Gutierrez J, Camarillo JM, Takata K, Tarte K, Kelleher NL, Steidl C, Mason CE, Elemento O, Allis CD, Kleinstein SH and Melnick AM. Mutant EZH2 induces a pre-malignant lymphoma niche by reprogramming the immune response. Cancer Cell 2020; 37: 655-673, e11.

[252] Sun J, Zhou H, Bao X, Wu Y, Jia H, Zhao H and Liu G. lncRNA TUG1 facilitates colorectal cancer stem cell characteristics and chemoresistance by enhancing GATA6 protein stability. Stem Cells Int 2021; 2021: 1075481.
[253] Huang Y, Wang L and Liu D. HOTAIR regulates colorectal cancer stem cell properties and promotes tumorigenicity by sponging miR-211-5p and modulating FLT-1. Cell Cycle 2021; 20: 1999-2009.
[254] Ma Y, Zhu Y, Shang L, Qiu Y, Shen N, Wang J, Adam T, Wei W, Song Q, Li J, Wicha MS and Luo M. LncRNA XIST regulates breast cancer stem cells by activating proinflammatory IL-6/STAT3 signaling. Oncogene 2023; 42: 1419-1437.
[255] Bai W, Peng H, Zhang J, Zhao Y, Li Z, Feng X, Zhang J, Liang F, Wang L, Zhang N, Li Y, Zhu H and Ji Q. LINC00589-dominated ceRNA networks regulate multiple chemoresistance and cancer stem cell-like properties in HER2+ breast cancer. NPJ Breast Cancer 2022; 8: 115.
[256] Cui S, Chen Y, Guo Y, Wang X and Chen D. Hsa-miR-22-3p inhibits liver cancer cell EMT and cell migration/invasion by indirectly regulating SPRY2. PLoS One 2023; 18: e0281536.
[257] Hou YR, Diao LT, Hu YX, Zhang QQ, Lv G, Tao S, Xu WY, Xie SJ, Zhang Q and Xiao ZD. The conserved LncRNA DIO3OS restricts hepatocellular carcinoma stemness by interfering with NONO-mediated nuclear export of ZEB1 mRNA. Adv Sci (Weinh) 2023; 10: 2301983.
[258] Wang X, Cai J, Zhao L, Zhang D, Xu G, Hu J, Zhang T and Jin M. NUMB suppression by miR-9-5P enhances CD44+ prostate cancer stem cell growth and metastasis. Sci Rep 2021; 11: 11210.
[259] Li Z, Ma Z, Wang S, Yan Q, Zhuang H, Zhou Z, Liu C, Chen Y, Han M, Wu Z, Huang S, Zhou Q, Hou B and Zhang C. LINC00909 up-regulates pluripotency factors and promotes cancer stemness and metastasis in pancreatic ductal adenocarcinoma by targeting SMAD4. Biol Direct 2024; 19: 24.
[260] Xie B, Wu P, Liu H, Yang X and Huang L. Long non-coding RNA MIR4435-2HG modulates pancreatic cancer stem cells and chemosensitivity to gemcitabine by targeting the miR-1252-5p/STAT1. J Transl Med 2025; 23: 165.
[261] Shi L, Li B, Tan J, Zhu L, Zhang S, Zhang Y, Xiang M, Li J, Chen Y, Han X, Xie J, Tang Y, Rosie Xing H, Li J and Wang J. Exosomal lncRNA Mir100hg from lung cancer stem cells activates H3K14 lactylation to enhance metastatic activity in non-stem lung cancer cells. J Nanobiotechnology 2025; 23: 156.
[262] Yang P, Gu H, Wu X, Chen G, Liu H and Chen Z. Tumour protein p53-activated lncRNA PGM5-AS1 suppresses lung cancer growth and stemness by targeting R-spondin1 via microRNA-1247-5p. Arch Physiol Biochem 2025; 131: 513-525.
[263] Li X, Liu D, Chen H, Zeng B, Zhao Q, Zhang Y, Chen Y, Wang J and Xing HR. Melanoma stem cells promote metastasis via exosomal miR-1268a inactivation of autophagy. Biol Res 2022; 55: 29.
[264] Li F, Xu Y, Xu X, Ge S, Zhang F, Zhang H and Fan X. lncRNA HotairM1 depletion promotes self-renewal of cancer stem cells through HOXA1-nanog regulation loop. Mol Ther Nucleic Acids 2020; 22: 456-470.
[265] Shahzad U, Nikolopoulos M, Li C, Johnston M, Wang JJ, Sabha N, Varn FS, Riemenschneider A, Krumholtz S, Krishnamurthy PM, Smith CA, Karamchandani J, Watts JK, Verhaak RGW, Gallo M, Rutka JT and Das S. CASCADES, a novel SOX2 super-enhancer-associated long noncoding RNA, regulates cancer stem cell specification and differentiation in glioblastoma. Mol Oncol 2025; 19: 764-784.
[266] Lulli V, Buccarelli M, Ilari R, Castellani G, De Dominicis C, Di Giamberardino A, D Alessandris QG, Giannetti S, Martini M, Stumpo V, Boe A, De Luca G, Biffoni M, Marziali G, Pallini R and Ricci-Vitiani L. Mir-370-3p impairs glioblastoma stem-like cell malignancy regulating a complex interplay between HMGA2/HIF1A and the oncogenic long non-coding RNA (lncRNA) NEAT1. Int J Mol Sci 2020; 21: 3610.
[267] Liu X, Chen Y, Li Y, Bai J, Zeng Z, Wang M, Dong Y and Zhou Y. STAU1-mediated CNBP mRNA degradation by LINC00665 alters stem cell characteristics in ovarian cancer. Biol Direct 2024; 19: 59.