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Chromatin Remodeling in Cancer Stemness, Plasticity, and Therapeutic Resistance: Mechanisms and Targeted Strategies

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Abstract

Cancer stem cells (CSCs) comprise phenotypically plastic tumor-cell states associated with tumor propagation, recurrence, and resistance to therapy. Their self-renewal, differentiation potential, and phenotypic plasticity are shaped by genetic, transcriptional, metabolic, and epigenetic mechanisms, including ATP-dependent chromatin remodeling. This article reviews recent research on how chromatin remodeling regulates CSC characteristics. It first summarizes current research on how chromatin remodeling profoundly affects core stemness-related transcriptional networks and key signaling pathways through mechanisms such as changes in chromatin accessibility, nucleosome positioning, and histone variant exchange. Furthermore, this article explores how chromatin remodeling endows CSCs with plasticity, enabling them to adapt to microenvironmental stress and leading to therapy resistance. Finally, it analyzes emerging therapeutic strategies targeting specific chromatin remodeling complexes or factors to investigate CSC-associated vulnerabilities and potential approaches to treatment resistance, aiming to provide new theoretical foundations and potential intervention targets for developing more effective precision cancer therapies. Although these regulatory dependencies identify potential therapeutic vulnerabilities across several tumor types, most evidence remains preclinical, and their therapeutic relevance likely depends on tumor lineage, remodeling-complex composition, genomic context, and the extent to which CSC-selective dependencies can be separated from chromatin-remodeling requirements in normal tissues.

Keywords: Chromatin remodeling; CSCs; epigenetics; plasticity; stemness regulation; targeted therapy; ATP-dependent chromatin remodelers; SWI/SNF complex.

1. Introduction

Cancer stem cells (CSCs) are functionally defined by self-renewal and the capacity to sustain tumor growth. Lineage-tracing experiments in mouse intestinal adenomas demonstrated that Lgr5-positive cells generated additional stem-like cells and differentiated progeny while supporting continued adenoma growth (1). CSC-associated states have also been implicated in metastatic competence, recurrence, and treatment resistance, although these properties vary across tumors and may change through cell-state transitions (2). Genetic and epigenetic mechanisms jointly influence stemness-associated states. In breast cancer models, a poised chromatin configuration at the ZEB1 promoter facilitated transitions from non-CSC to CSC states, providing direct evidence linking epigenetic regulation to malignant cell plasticity (3). ATP-dependent chromatin remodelers, classified into the SWI/SNF, ISWI, CHD, and INO80 families, contribute to transcriptional regulation by altering nucleosome organization and access to genomic DNA (4).

Chromatin remodeling determines gene transcriptional activity by altering chromatin structure and accessibility, thereby playing a switch-like role in cell fate determination. Chromatin-remodeling dependencies vary across malignant contexts. Glioblastoma studies link chromatin regulation to stem-like behavior and treatment resistance (5), whereas experiments in acute leukemia demonstrated that BRG1 supports leukemia maintenance and an oncogenic transcriptional program involving distal MYC enhancers (6). For example, in head and neck squamous cell carcinoma, zinc finger and SCAN domain-containing 4 (ZSCAN4) promotes hyperacetylation of histone H3, remodeling the chromatin state at the promoters of stemness genes such as octamer-binding transcription factor 3/4 (OCT3/4, encoded by POU5F1) and nanog homeobox (NANOG), thereby maintaining the CSC phenotype (7). Similarly, in glioblastoma, chromatin-remodeling programs link stem-like behavior to therapy resistance, thereby shaping the epigenetic identity of CSCs (5).

Integrated transcription-factor and chromatin analyses in glioblastoma identified POU3F2, SOX2, SALL2, and OLIG2 as a core regulatory network that can reprogram differentiated tumor cells toward a tumor-propagating state (8). Separately, ATAC-seq analysis of patient-derived glioblastoma stem-cell cultures identified functionally distinct chromatin-accessibility subgroups associated with patient survival (9). For instance, in castration-resistant prostate cancer and triple-negative breast cancer (TNBC), the oncoprotein mucin 1 C-terminal subunit (MUC1-C) drives alterations in global chromatin structure, inducing regions of differential accessibility across the genome that correlate with differentially expressed genes (10). In these experimental models, MUC1-C promoted chromatin-accessibility changes and JUN/BAF occupancy at enhancer-like regulatory regions (10). In prostate cancer models, MUC1-C induced PBAF-component expression and cooperated with NRF2 and PBRM1 at SLC7A11, linking chromatin accessibility and antioxidant regulation with CSC-associated properties (11). Understanding how chromatin remodeling shapes the epigenetic identity of CSCs not only helps elucidate the underlying mechanisms of tumorigenesis and progression but also opens avenues for developing novel therapies targeting this resilient cell population (12).

This review examines how chromatin-remodeling systems intersect with CSC-associated transcriptional programs, plasticity, and therapeutic resistance, distinguishes mechanistic evidence from associations, and highlights the barriers that currently limit clinical translation.

2. Classification of Chromatin Remodeling Complexes in Tumor Stem Cells

2.1 Core Families of ATP-Dependent Chromatin Remodeling Complexes

ATP-dependent chromatin remodeling complexes primarily regulate chromatin structure and gene expression. They harness energy from ATP hydrolysis to alter chromatin accessibility by sliding, evicting, assembling, or editing nucleosomes (4). ATP-dependent chromatin remodelers are classified into four core families: SWI/SNF, ISWI, CHD, and INO80 (4). Direct evidence linking remodeling activity to cell identity includes experiments showing that CHD1 maintains open chromatin and pluripotency in mouse embryonic stem cells (13). These families play indispensable roles in maintaining genomic stability and determining cell fate, and their dysfunction is closely associated with various diseases, including cancer (14). Understanding these remodeling complexes is essential for elucidating disease regulatory networks and developing targeted therapies. However, cancer stemness is inconsistently defined, with evidence ranging from stem-cell markers and tumorsphere formation to lineage tracing and functional tumor re-initiation. These endpoints are not interchangeable, and changes in chromatin accessibility or remodeler expression alone do not establish a causal role in CSC maintenance.

2.1.1 SWI/SNF Complex

The SWI/SNF complex is a key ATP-dependent chromatin remodeling complex. Its core function is to use energy from ATP hydrolysis to increase chromatin accessibility by sliding or evicting nucleosomes, thereby promoting gene transcription (15). In cancer biology, mutations in the SWI/SNF complex are closely associated with the occurrence and progression of various tumors (Figure 1).

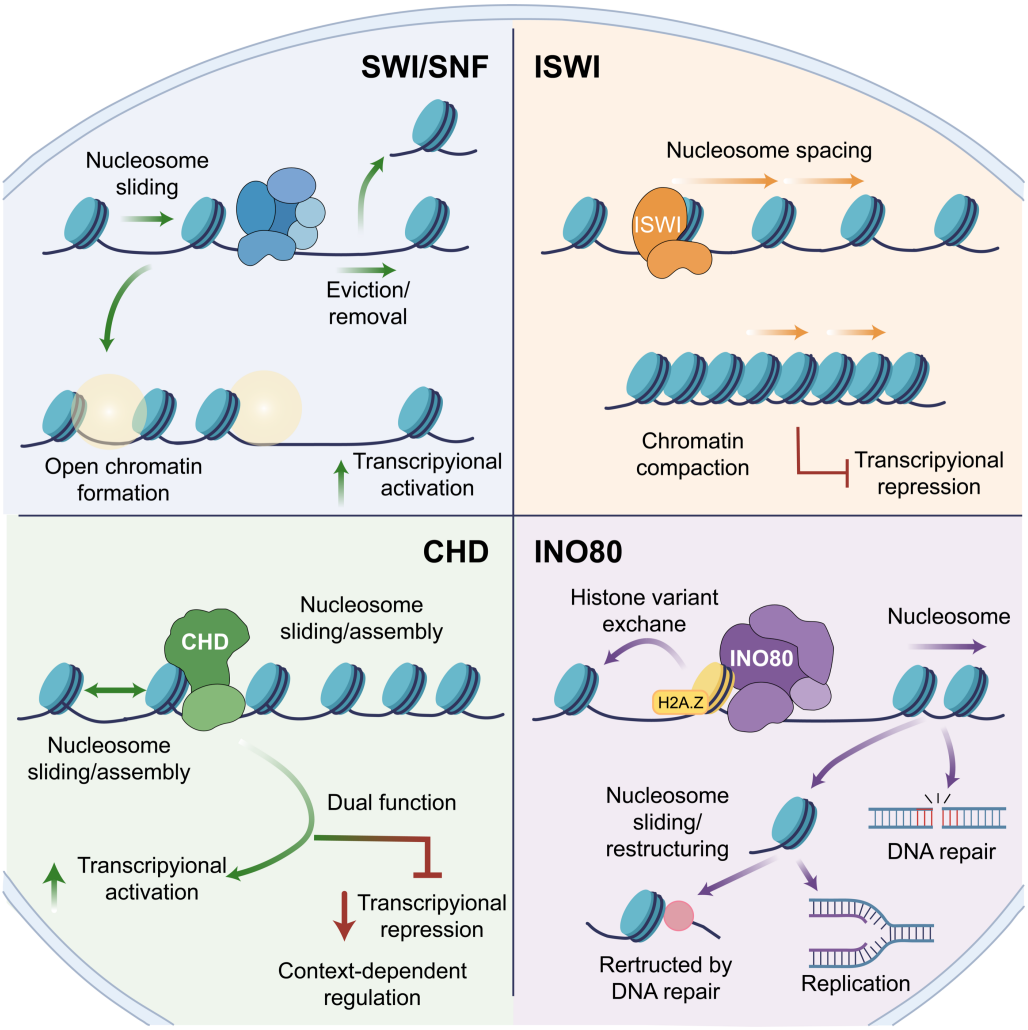


Figure 1. The functions and mechanisms of the chromatin remodeling complexes. *ATP-dependent chromatin remodelers regulate nucleosome positioning, assembly, and composition to control gene transcription, DNA replication, and genome stability. SWI/SNF complexes facilitate chromatin accessibility through nucleosome sliding and eviction, with transcriptional outcomes depending on cellular context. ISWI complexes regulate nucleosome spacing and chromatin organization, with transcriptional effects that depend on complex composition and cellular context. CHD complexes contribute to transcriptional activation or repression through context-dependent nucleosome remodeling. INO80-family complexes regulate nucleosome organization and histone-variant dynamics. H2A.Z deposition is principally associated with SWR1/SRCAP/p400-related complexes, whereas canonical INO80 regulates nucleosome positioning and context-dependent H2A.Z exchange or occupancy. The H2A.Z schematic represents histone-variant regulation across the INO80 family, including SWR1/SRCAP/p400-related complexes, rather than a universal H2A.Z deposition activity of canonical INO80.* ***Abbreviations:*** *SWI/SNF, switch/sucrose non-fermentable; ISWI, imitation switch; CHD, chromodomain helicase DNA-binding; INO80, inositol-requiring 80; H2A.Z, histone variant H2A.Z; ATP, adenosine triphosphate; DNA, deoxyribonucleic acid; SWR1, SWI2/SNF2-related 1; SRCAP, SNF2-related CREBBP activator protein; p400, E1A-binding protein p400. The figure was created using Adobe Illustrator.*

Its functional abnormalities can lead to widespread dysregulation of chromatin structure, affecting cancer cell fate decisions (14). In particular, the SWI/SNF complex plays a key role in regulating CSCs. In MUC1-C-dependent experimental models, MUC1-C engages BAF and PBAF complexes and is associated with genome-wide changes in chromatin accessibility and stemness-related transcriptional programs (11).

Long noncoding RNAs can influence CSC-associated properties through interactions with chromatin-remodeling machinery. In liver CSCs, lncBRM associated with BRM and promoted a BRG1/BRM switch within BAF complexes, activating YAP1 signaling and supporting self-renewal and tumor initiation (16). In embryonic stem cells, specific BAF complexes (esBAF) and their subunits (such as BRG1) are crucial for maintaining an open chromatin state at the promoters of pluripotency genes (such as OCT4 and SOX2). These observations provide a mechanistic framework for understanding related dependencies in CSCs, although evidence from embryonic stem cells should not be interpreted as direct evidence of the same regulatory architecture in malignant stem-like populations (17). The SWI/SNF complex is not limited to transcriptional activation; it also counteracts Polycomb Repressive Complex (PRC)-mediated gene silencing, creating a dynamic balance that supports cell-fate reprogramming and CSC stemness maintenance (11). Therefore, targeting the SWI/SNF complex or its regulatory network offers new therapeutic strategies to disrupt CSC stemness and overcome therapy resistance.

Importantly, SWI/SNF activity cannot be classified uniformly as pro-stemness or tumor-promoting. Loss-of-function alterations in ARID1A, SMARCB1, PBRM1, or SMARCA4 can themselves promote tumorigenesis, whereas other tumor contexts retain or acquire dependence on residual SWI/SNF activity. The therapeutic consequence is therefore genotype- and lineage-dependent: inhibiting a remodeler required by one CSC state could be ineffective, or potentially counterproductive, in tumors in which loss of that activity contributes to malignant progression. Therapeutic strategies should consequently be framed around context-specific dependencies rather than global inhibition of SWI/SNF function.

2.1.2 ISWI Complex

The ISWI complex is another important class of ATP-dependent chromatin remodeling complexes. Its main functions include regular nucleosome spacing and chromatin assembly, playing a core role in maintaining higher-order chromatin structure and mediating gene silencing (4, 18). ISWI complexes regulate nucleosome spacing and chromatin organization, with transcriptional effects that depend on complex composition, genomic location, and cellular context (18). Their developmental functions provide a rationale for investigating roles in cell-state regulation, but do not establish a universal mechanism of CSC quiescence (Figure 1). Quiescent or slowly cycling states occur in subsets of tumor

cells and may contribute to treatment persistence; however, proliferative behavior varies across tumor types and cellular states (19). In glioma models, CD133-positive tumor cells exhibited preferential activation of DNA damage checkpoints and enhanced repair following irradiation, contributing to radioresistance (20). ISWI-family complexes have been implicated in cancer-associated transcriptional and genome-maintenance processes, but their contributions to CSC quiescence and treatment persistence require model-specific functional evidence (21). In glioblastoma, chromatin regulation has been implicated in stem-like behavior and treatment resistance (5), while altered chromatin insulation provides a separate framework for understanding dysregulated gene expression (22). These observations do not directly establish that ISWI complexes maintain glioma stem-cell quiescence or confer resistance to temozolomide and radiation. More direct evidence connects an ISWI-family ATPase to glioblastoma-associated stemness. In experimental glioblastoma models, miR-146a targeted POU3F2 and SMARCA5, reducing stemness-associated properties and increasing sensitivity to temozolomide (23). These findings implicate SMARCA5-associated regulation in treatment response without establishing that its effects are mediated through cellular quiescence. Whether ISWI dependence constitutes a therapeutically exploitable vulnerability remains less well established than for selected SWI/SNF dependencies, and direct functional studies in patient-derived CSC models will be required to distinguish causal roles from associations with quiescent chromatin states.

2.1.3 CHD Complex

The CHD complex family is characterized by members containing chromodomain and helicase/ATPase domains, playing a unique role in the regulation of chromatin dynamics (4, 24). These complexes participate in processes such as nucleosome sliding, histone variant incorporation, and transcriptional regulation (Figure 1). In mouse embryonic stem cells, CHD1 depletion caused heterochromatin accumulation and impaired pluripotency maintenance, directly linking this remodeler to chromatin organization and cellular identity (13). Whether comparable dependencies operate in malignant stem-like populations requires tumor-specific functional evidence. CHD4, a member of the CHD family and a core ATP-dependent chromatin-remodeling subunit of the nucleosome remodeling and deacetylase (NuRD) complex, regulates transcription, DNA-damage responses, and chromatin organization in cancer cells (25). CHD4 also contributes to genome maintenance and has been implicated in treatment resistance through context-dependent effects on DNA repair, cell-cycle regulation, and other stress-response pathways (25).

In TNBC models, MUC1-C/MYC signaling induced expression of the NuRD components MTA1, MBD3, and CHD4 and contributed to repression of luminal differentiation programs, linking MUC1-C to chromatin-associated dedifferentiation (26). In TNBC, low FBXW7 expression correlates with poor prognosis; FBXW7 mediates ubiquitin-proteasomal degradation of CHD4 to restrain CHD4-induced β-catenin nuclear translocation and Wnt/β-catenin pathway activation, thereby suppressing cancer stemness, malignant cellular phenotypes, and in vivo tumorigenicity of TNBC cells (27). Chromatin-remodeling abnormalities can contribute to transcriptional states associated with recurrence and therapy resistance, although their relative importance varies according to tumor lineage, genotype, and treatment context (28). CHD complexes influence CSC fate decisions by regulating the chromatin state of key stemness genes (such as SOX2, OCT4) and differentiation-related genes. Their dysfunction may lead to global changes in chromatin accessibility, enabling CSCs to adapt dynamically to therapeutic pressure and survive (29, 30). Therefore, targeting CHD complexes or the chromatin-remodeling pathways they mediate holds promise for interfering with the stemness-maintenance network of CSCs, offering new strategies to overcome cancer recurrence.

CHD-family proteins also differ substantially in complex membership, genomic localization, and biological function; they should therefore not be treated as a single therapeutic class. In particular, evidence linking individual CHD proteins to CSC maintenance remains uneven across tumor types, and several proposed mechanisms derive from conventional cancer-cell models rather than prospectively defined CSC populations.

2.1.4 INO80 Complex

INO80-family complexes regulate nucleosome organization and histone-variant dynamics. H2A.Z deposition is principally associated with SWR1/SRCAP/p400-related complexes, whereas canonical INO80 regulates nucleosome positioning and context-dependent H2A.Z exchange or occupancy (4, 31). These activities can influence transcriptional regulation during cell-state transitions (Figure 1). During embryonic development and cell differentiation, precise switching of gene expression programs requires large-scale chromatin remodeling. The INO80 complex is an ATP-dependent chromatin remodeler involved in nucleosome organization and histone-variant regulation (4). Its effects on H2A.Z occupancy are context-dependent. In pluripotent stem cells, INO80 promotes H2A.Z occupancy at bivalent promoters and facilitates the transition from naïve to primed pluripotency, demonstrating a role in chromatin regulation during cell-fate transitions (31). These findings provide a mechanistic basis for investigating whether INO80-dependent H2A.Z regulation also contributes to CSC plasticity. Whether the developmental mechanisms described above also regulate malignant stem-like states requires direct investigation in the relevant tumor models. CSCs need to maintain high epigenetic plasticity to switch between self-renewal and differentiation and to adapt to the tumor microenvironment and therapeutic pressure (30, 32).

The dynamic exchange of H2A.Z mediated by the INO80 complex may be a key regulator of this plasticity. For example, enrichment of H2A.Z at gene promoters is closely associated with transcriptional potential, and its abnormal distribution is linked to the occurrence and development of various cancers (31). In hepatocellular carcinoma, the long noncoding RNA HAND2-AS1 recruits the INO80 chromatin-remodeling complex to the promoter of bone morphogenetic protein receptor type 1A (BMPR1A), promoting its transcription and activating BMP signaling to sustain liver cancer stem cell (CSC) self-renewal. Experimental depletion of INO80 impairs liver CSC self-renewal and suppresses tumor growth, providing direct evidence for its contribution to liver cancer stemness (33). In glioblastoma, chromatin-remodeling programs are likewise implicated in glioblastoma stem cell (GSC) maintenance and therapeutic resistance, although the specific contribution of INO80 requires further investigation (5). Furthermore, ATP-dependent chromatin remodelers, including INO80 and SWI/SNF, regulate nucleosome organization and transcriptional accessibility. Their activities may influence stress-response and stemness-associated transcriptional programs, although direct functional cooperation between these complexes in CSCs remains to be established (34).

Therefore, targeting the INO80 complex or the H2A.Z exchange process it catalyzes could interfere with transcriptional programs that support selected CSC states. However, the therapeutic window for INO80 inhibition remains uncertain because INO80-family complexes also participate in DNA replication, DNA repair, and genome maintenance in normal cells.

2.2 Somatic Mutations and Expression Dysregulation of Chromatin Remodeling Complex Genes

Chromatin remodeling complexes, particularly the SWI/SNF (BAF/PBAF) family, play a central role in maintaining genomic stability and regulating gene expression. Large-scale cancer genome sequencing studies have revealed that mutations in genes encoding SWI/SNF subunits occur in over

20% of cancers, making them among the most frequently mutated epigenetic regulators in human cancers (14). These mutations are widespread across solid tumors and hematological malignancies. For instance, in hepatocellular carcinoma, AT-rich interaction domain (ARID) genes such as AT-rich interaction domain 1A/B (ARID1A/B) and AT-rich interaction domain 2 (ARID2) frequently undergo loss-of-function mutations (35).

In melanoma, exome sequencing also commonly identifies loss-of-function mutations in SWI/SNF subunit-encoding genes (36). A study of gastric cancer in the Mizo population of India further confirmed that ARID1A is a significantly mutated gene, with its mutations closely associated with abnormalities in the chromatin remodeling pathway (37). These mutations are not isolated events; they lead to fundamental changes in global chromatin accessibility by disrupting the integrity of the SWI/SNF complex. As ATP-driven molecular motors, SWI/SNF complexes normally reconfigure nucleosome structure and control genomic DNA accessibility. Different SWI/SNF subunit alterations can change complex assembly, recruitment, or residual activity, with consequences that depend on the affected subunit and tumor context. Mutation frequency alone, however, does not establish a CSC-specific mechanism. SWI/SNF alterations can influence proliferation, differentiation, DNA repair, immune signaling, and lineage identity independently of stemness. Studies that infer CSC regulation from bulk-tumor genomic associations should therefore be distinguished from experiments that directly test self-renewal, tumor initiation, or reversible stem-like state transitions.

Chromatin-regulatory abnormalities can alter enhancer activity and differentiation-associated transcription. Distinct mechanisms include loss of tumor-suppressive functions and oncogenic recruitment of otherwise functional remodeling machinery. For example, in fusion-negative rhabdomyosarcoma (FN-RMS), the transcription factor twist family bHLH transcription factor 2 (TWIST2) interacts with chromatin-remodeling factors SMARCA4 and CHD3 to regulate histone modifications at distal enhancers, thereby activating growth-related genes and suppressing myogenic differentiation genes, maintaining the undifferentiated state and tumorigenicity of cells (38). This illustrates oncogenic recruitment of chromatin regulators rather than a demonstrated consequence of SWI/SNF loss-of-function mutations. The SWI/SNF complex also contributes to genome maintenance. Experimental depletion of its ATPase subunit BRG1 increases R-loop accumulation, transcription–replication conflicts, and R-loop-dependent DNA damage, demonstrating a role for SWI/SNF-mediated chromatin remodeling in preserving genomic integrity (39).

Beyond high-frequency somatic mutations, chromatin-remodeling complex subunits often show aberrant expression, and this dysregulation often synergizes with specific oncogenic signals. For example, the well-known oncoprotein MYC can upregulate certain chromatin-remodeling factors, thereby jointly driving transcriptional programs that promote stemness. This dysregulation may also profoundly affect the tumor microenvironment. Studies indicate that in cancers with mutations in SWI/SNF complex subunits (such as PBRM1, SMARCA4, ARID2), the tumor immune microenvironment exhibits distinct activation states. In particular, in gastric cancer with low SMARCA4 expression, T cell effector (such as CD8B), central memory T cell markers, and mature B cell markers (such as CD20, CD38) are upregulated, whereas cancer-related genes like MYC and aurora kinase B (AURKB) are downregulated, and features of tertiary lymphoid structures are observed (40).

This suggests that abnormalities in chromatin-remodeling complexes not only directly alter the epigenetic state and stemness of tumor cells but may also indirectly affect cancer progression and response to therapies (such as immune checkpoint blockade) by reshaping the tumor immune microenvironment. In summary, somatic mutations and expression dysregulation of chromatin-remodeling complex genes regulate CSC characteristics across multiple dimensions and levels—by

altering global chromatin accessibility, disrupting normal gene regulatory networks, inducing genomic instability, and synergizing with oncogenic signals, serving as a key bridge between epigenetic abnormalities and tumorigenesis and development.

2.3 Characteristics of CSCs-Specific Chromatin Accessibility Landscapes

CSC-associated regulatory programs can involve differences in chromatin organization, enhancer activity, and gene expression, although the evidence depends on the experimental system. Comparative epigenomic profiling of glioma stem cells and neural stem/progenitor cells identified distinct DNA-modification patterns and enhancer landscapes associated with differential gene regulation (41). In glioblastoma stem cells, a super-enhancer-associated program promoted polyunsaturated fatty-acid synthesis and supported EGFR signaling, providing direct evidence that enhancer regulation can sustain a tumor-associated metabolic dependency (42). Comparative chromatin-state analysis in glioblastoma CSCs identified activation of developmental transcription-factor programs, including ASCL1-dependent regulation of Wnt signaling. Functional experiments established a requirement for ASCL1 in CSC maintenance and tumorigenicity (43). These findings illustrate distinct regulatory mechanisms rather than a shared pattern of increased accessibility at SOX2, NANOG, and ALDH1A1 loci across cancers.

Histone-defined regulatory landscapes and transcription-factor networks provide complementary evidence of stemness-associated gene regulation. Profiling of primary gliomas identified subtype-associated enhancer states and bivalent chromatin domains enriched for developmental regulators, revealing similarities to glioma stem-cell regulatory programs (44). In a separate study, a SOX2-associated network involving OLIG2 and ZEB1 supported glioma-initiating properties; co-expression of these factors generated glioma-initiating cells from tumor-suppressor-deficient astrocytes in experimental models (45). Together, these findings connect regulatory chromatin states with functional transcriptional programs, without establishing that all CSCs exhibit globally increased accessibility.

A methodological caveat is that differential accessibility is not equivalent to functional enhancer activity or remodeler dependence. ATAC-seq identifies accessible DNA but does not establish which remodeling complex created or maintains that state. Moreover, CSC enrichment based on surface markers can capture heterogeneous populations whose chromatin profiles partly reflect lineage, cell-cycle state, or environmental exposure rather than stemness itself. Integrating accessibility profiling with perturbation experiments, transcription-factor occupancy, and functional CSC assays is therefore necessary to assign causality.

Histone modifications, transcription-factor activity, and chromatin accessibility represent related but distinct layers of gene regulation. In glioma stem-cell models, profiling of DNA modifications and enhancer-associated histone marks revealed regulatory landscapes that differed from those of neural stem/progenitor cells (41). In TNBC models, DOT1L-dependent H3K79 methylation supported stemness-associated transcriptional and metabolic programs (46). Single-cell chromatin-accessibility profiling of primary glioblastomas, combined with analysis of patient-derived glioblastoma stem-cell models, identified distinct regulatory states associated with different transcription-factor dependencies and invasive properties (47). These findings demonstrate heterogeneity within stem-like tumor populations rather than a uniform increase in accessibility at all stemness-associated genes. However, gene expression and marker enrichment alone do not establish increased chromatin accessibility or transcription-factor occupancy at the corresponding regulatory regions. Together, these studies illustrate different mechanisms associated with stemness rather than a single experimentally demonstrated chromatin-accessibility feedback circuit (Figure 2).

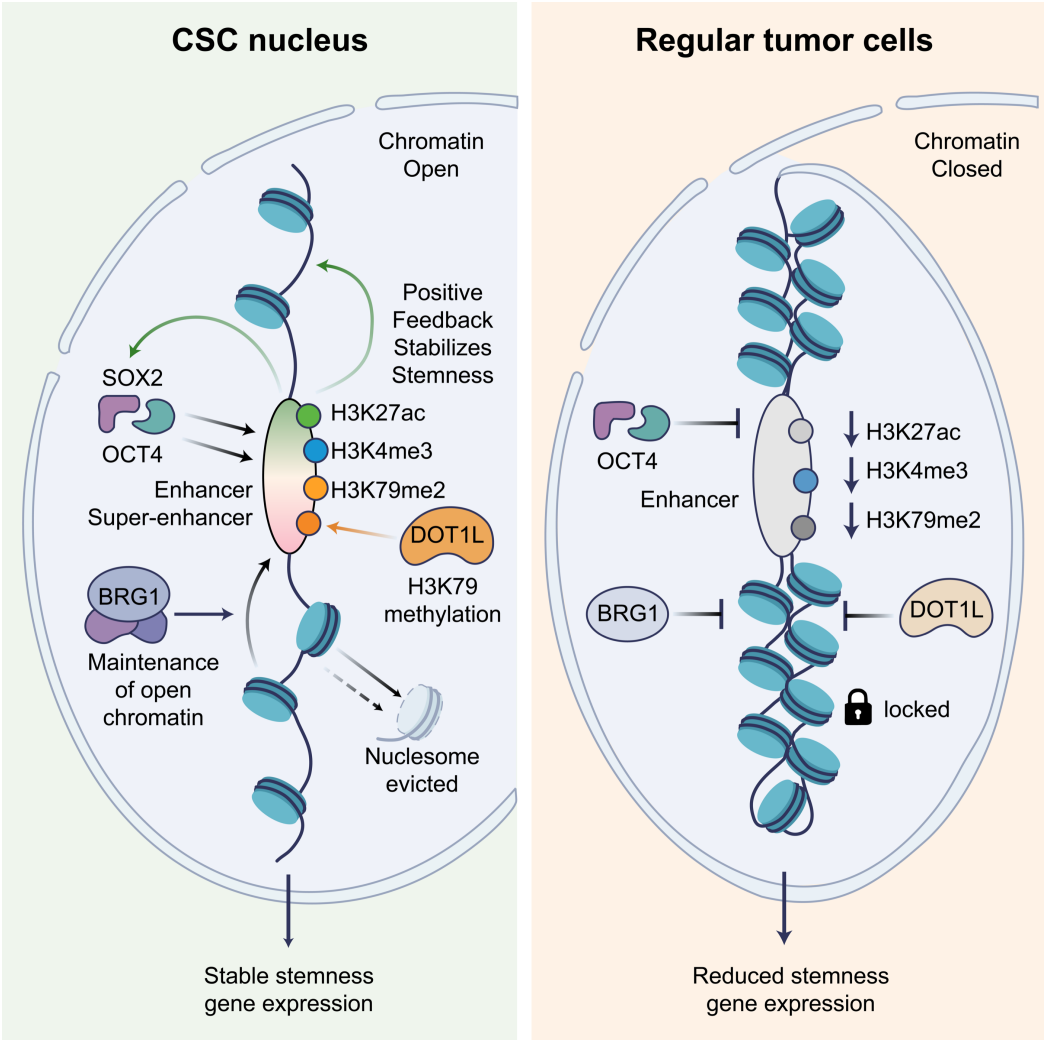


Figure 2. Comparison of chromatin states associated with cancer stemness. *The left panel illustrates how BRG1-mediated chromatin remodeling, DOT1L-mediated H3K79 methylation, and stemness-associated transcription factors can contribute to transcriptionally permissive chromatin in selected experimental contexts. The right panel depicts a comparatively less permissive state at stemness-associated loci in non-stem tumor cells. Reduced BRG1/DOT1L activity and activating histone marks are illustrative features, not defining or universal properties of non-stem tumor cells. Arrows represent proposed or context-dependent relationships rather than a single experimentally established feedback circuit. H3K4me3 is primarily associated with active promoters, whereas H3K27ac marks active promoters and enhancers.* ***Abbreviations:*** *CSC, cancer stem cell; BRG1, Brahma-related gene 1; SMARCA4, SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily A member 4; DOT1L, disruptor of telomeric silencing 1-like; H3K79me2, dimethylation of histone H3 at lysine 79; H3K27ac, acetylation of histone H3 at lysine 27; H3K4me3, trimethylation of histone H3 at lysine 4; OCT4, octamer-binding transcription factor 4; SOX2, SRY-box transcription factor 2. The figure was created using Adobe Illustrator.*

The establishment and maintenance of open chromatin states are not passive; they depend on the precise recruitment of chromatin remodeling complexes to key regions. These complexes dynamically regulate chromatin accessibility by consuming ATP to slide, evict, or reorganize nucleosomes. In CSCs, a series of chromatin-remodeling factors has been shown to be essential for maintaining stemness. For example, the core catalytic subunit BRG1 of the SWI/SNF chromatin remodeling complex plays a key role in colorectal CSCs. Specific knockout of Brg1 in cells expressing Dclk1 (a marker of intestinal tumor stem cells) significantly inhibits tumor growth and reduces stem cell self-renewal capacity through increased apoptosis and downregulation of stemness-related gene expression (48). These results support a functional requirement for Brg1 in the intestinal tumor stem-cell population studied. However, the knockout phenotype alone does not identify the genomic sites where Brg1 acts or demonstrate that

altered accessibility at those sites explains the observed effects. Similarly, the histone methyltransferase DOT1L is highly expressed in TNBC CSCs. It regulates stemness-related gene expression programs, including oxidative phosphorylation, MYC target genes, and the Wnt pathway, by catalyzing H3K79 methylation, thereby maintaining CSC self-renewal capacity (46) (Figure 2). Glioma stem-cell profiling further demonstrated heterogeneous epigenomic and transcriptional responses to differentiation cues, highlighting the context-dependent relationship between chromatin state and cellular identity (41). These observations do not identify which ATP-dependent remodeling complexes causally establish the observed epigenomic states. These chromatin remodeling complexes and modifying enzymes act like architects and switches of the genome that can be recruited by CSC-specific signaling pathways or transcription factors. This consolidates the open chromatin landscape that supports stemness by remodeling local nucleosome structures, ultimately determining the functional state of CSCs and their resistance to therapy.

3. Molecular Mechanisms of Chromatin Remodeling Regulating Tumor Stem Cells

3.1 Synergy Between Remodeling Complexes and Pluripotency Factors OCT4/SOX2/NANOG

Chromatin-remodeling complexes and stemness-associated transcription factors contribute to context-dependent regulatory programs. Mammalian SWI/SNF complexes use ATP hydrolysis to reposition or evict nucleosomes, and their composition and recruitment influence transcription and cell identity (49, 50). Their regulatory effects depend on the genomic regions engaged and the transcriptional machinery available within a particular cellular state. In glioblastoma, POU3F2, SOX2, SALL2, and OLIG2 were identified as a core network that can reprogram differentiated tumor cells toward a tumor-propagating state (8). MUC1-C-associated studies provide a separate framework linking BAF/PBAF activity to stemness-related transcriptional programs (11). These examples illustrate distinct routes through which transcriptional regulators and chromatin-associated processes can support malignant cell identity. Biochemical and structural studies explain how remodelers engage nucleosomes, but do not themselves demonstrate a universal OCT4/SOX2/NANOG–SWI/SNF recruitment circuit in CSCs (34, 51).

Reciprocal interactions between transcription factors and chromatin regulation can help maintain cellular identity. However, the participating factors, remodeling-complex composition, and direction of regulation vary across tumor lineages and cell states (14, 49). A self-reinforcing OCT4/SOX2/NANOG–SWI/SNF circuit should therefore be treated as a context-dependent model rather than a universal feature of CSCs. Establishing such a circuit requires direct evidence of factor binding, remodeler recruitment, chromatin changes, and functional effects at the relevant endogenous loci. Expression correlations or overlapping genomic occupancy alone cannot establish the direction of recruitment or demonstrate that the proposed interaction is necessary for self-renewal. Experimental reprogramming of differentiated glioblastoma cells demonstrates that tumor-propagating potential can be acquired through changes in transcriptional regulatory networks (8). This supports plasticity of malignant cell identity, while leaving the contribution of individual remodeling complexes to be resolved through targeted perturbation. Comparisons between stem-like and differentiated populations, ideally combined with time-resolved measurements, could distinguish mechanisms that initiate state transitions from those that maintain an established state. The relationships summarized in Figure 3 should therefore be interpreted as a conceptual integration of mechanisms from different experimental systems.

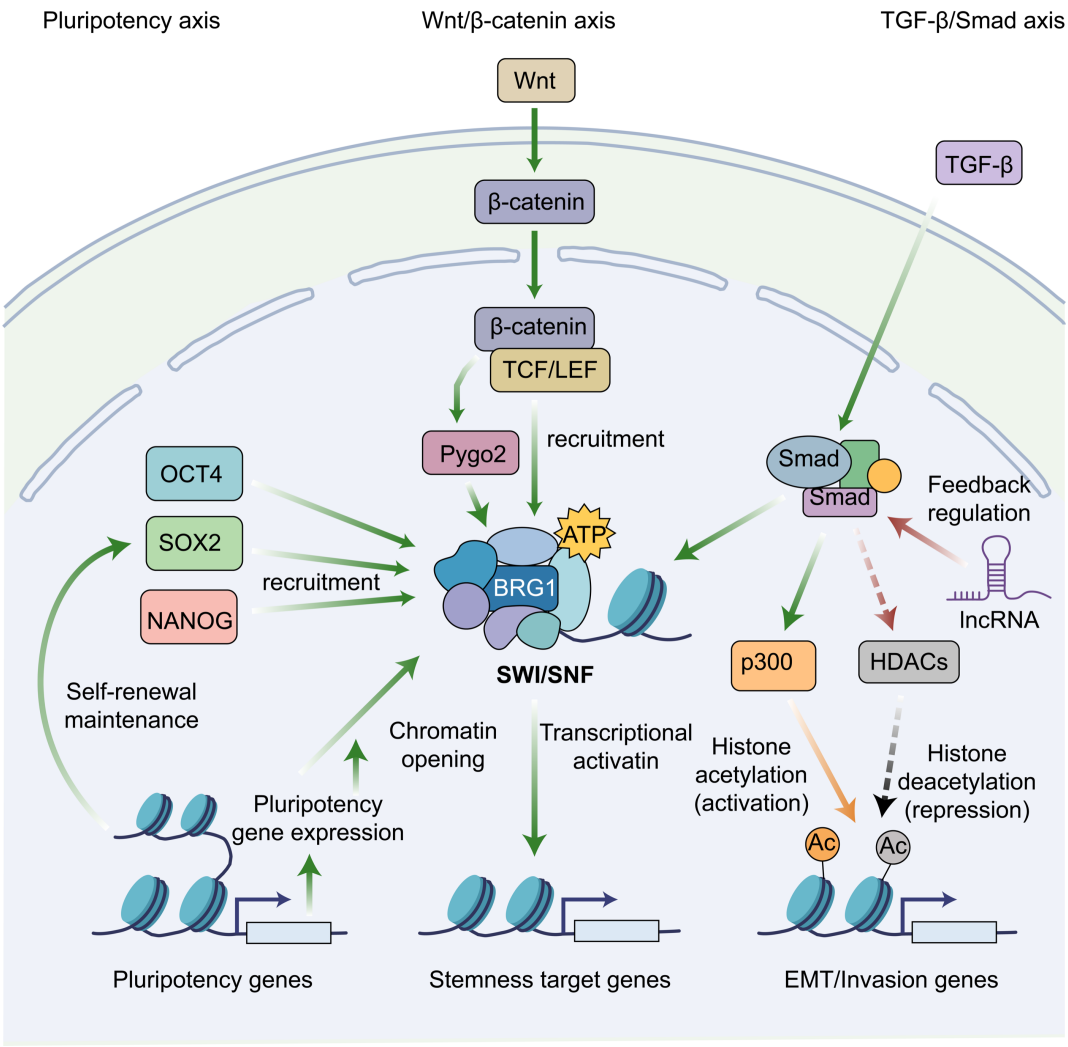


Figure 3. Conceptual integration of chromatin regulation with stemness-associated transcription and signaling. *Conceptual integration of chromatin regulation with stemness-associated transcription and signaling. The schematic combines relationships reported or proposed in different experimental models rather than a single validated BRG1-dependent circuit shared by all CSCs. SWI/SNF-associated regulation can intersect with pluripotency factors and Wnt/β-catenin-responsive transcription. TGF-β-associated transcription involves context-specific cofactors, including histone-modifying enzymes and lncRNA regulators. The depicted recruitment, acetylation and signaling relationships require validation in the relevant tumor model; the diagram does not establish that Pygo2 recruits SWI/SNF or that all three axes converge through one universal BRG1 mechanism.* ***Abbreviations:*** *BRG1, Brahma-related gene 1; SWI/SNF, switch/sucrose non-fermentable; OCT4, octamer-binding transcription factor 4; SOX2, SRY-box transcription factor 2; NANOG, Nanog homeobox; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; Pygo2, Pygopus 2; TGF-β, transforming growth factor beta; Smad, Sma- and Mad-related protein; p300, E1A-binding protein p300; HDAC, histone deacetylase; lncRNA, long noncoding RNA; EMT, epithelial–mesenchymal transition; ATP, adenosine triphosphate; Ac, acetyl group. The figure was created using Adobe Illustrator.*

Developmental and malignant dependencies should be distinguished. Depletion of SMARCB1 or BRD7 altered porcine embryo development and pluripotency-associated expression (52), providing developmental evidence rather than proof of selective CSC targeting. Cancer-associated SWI/SNF alterations can be tumor-suppressive or dependency-forming depending on genotype and lineage (14, 36). In glioma-initiating cells, BRG1 perturbation altered stemness-associated properties and chemosensitivity, supporting a functional role for BRG1 in this experimental context (53). These findings provide a rationale for investigating BRG1-associated dependencies, but should not be generalized to breast cancer or interpreted as direct evidence of nucleosome reoccupation at OCT4,

SOX2, and NANOG promoters. Therapeutic development must account for tumor genotype, remodeling-complex composition, and normal-tissue requirements (54, 55).

3.2 Crosstalk Between Core CSC Signaling Pathways and Chromatin Remodeling

3.2.1 Interaction Between the Wnt/β-catenin Pathway and Chromatin Remodeling

The Wnt/β-catenin signaling pathway is a core regulator of embryonic development and tissue homeostasis. Its aberrant activation plays a key role in the initiation and progression of various cancers, particularly in maintaining CSC stemness (56). β-Catenin stability is regulated by phosphorylation-dependent degradation. Mechanistic experiments demonstrated that casein kinase Iα-mediated priming enables subsequent GSK-3 phosphorylation, linking sequential kinase activity to β-catenin turnover (57). After entering the nucleus, β-catenin not only acts as a classical transcriptional co-activator, binding to TCF/LEF family transcription factors to initiate transcription of downstream target genes (such as c-MYC, CCND1), but also extends its function to epigenetic regulation. Wnt signaling can also influence three-dimensional regulatory architecture. Experimental activation of Wnt signaling induced CTCF binding and loop formation at cis-regulatory elements of target genes, linking pathway activity to changes in chromatin organization (58). For example, in uveal melanoma, the chromatin regulator RUVBL1 enhances CTNNB1 transcription by modulating chromatin remodeling, thereby promoting malignant biological behavior in tumor cells (59). These observations link Wnt-related transcription to chromatin regulation in defined experimental systems but do not establish a universal mechanism of CSC self-renewal.

Structural analysis defined interactions between BCL9–Pygo and LDB–SSBP complexes that contribute to Wnt enhanceosome assembly, providing a molecular basis for the organization of transcriptional cofactors (60). These findings provide a structural basis for cofactor organization, not direct evidence of H3K56 acetylation or SWI/SNF recruitment. The BAF chromatin-remodeling complex, a member of the SWI/SNF family, also cooperates with β-catenin to regulate Wnt-responsive transcription. BRG1, the catalytic subunit of BAF, physically interacts with β-catenin and promotes TCF-dependent target-gene activation. Conversely, ATPase-inactive BRG1 expression inhibits endogenous TCF target-gene expression in colon carcinoma cells, establishing a functional link between chromatin remodeling and Wnt signaling (61).

In colorectal cancer models, BRG1 supports intestinal tumor stem-cell self-renewal and survival (48). These findings suggest that the interaction between chromatin remodeling and Wnt signaling may represent a therapeutic vulnerability, although disrupting the BRG1–β-catenin interaction has not yet been established as a strategy to eradicate colorectal CSCs. In ovarian cancer, alterations in the SWI/SNF subunit ARID1A and the Wnt pathway component CTNNB1 have also been implicated in tumorigenesis, highlighting the context-dependent relationship between chromatin remodeling and Wnt signaling (62).

Crosstalk between Wnt signaling and chromatin-associated regulation provides a rationale for investigating interventions directed at transcriptional cofactors or context-specific remodeling dependencies (63). Their effects on treatment-resistant, tumor-propagating populations require direct evaluation, including functional tumor-initiation assays and comparison with normal-cell dependencies. These approaches remain investigational strategies rather than established methods for selectively eradicating CSCs or preventing recurrence (Figure 3).

3.2.2 Epigenetic Regulation of the TGF-β/Smad Pathway in Stemness Maintenance

The TGF-β/Smad signaling pathway plays a complex and critical role in regulating CSC characteristics, particularly in maintaining stemness. Through its core transcription factors, the Smad proteins, this pathway can directly or indirectly recruit chromatin-remodeling factors and histone-modifying enzymes, thereby reshaping the gene expression profile at the epigenetic level, driving epithelial-mesenchymal transition (EMT), and activating or suppressing stemness-related genes (64). For example, in breast cancer, TGF-β signaling activates p38 MAPK, which phosphorylates the transcription factor ΔNp63 and enhances its DNA-binding ability. Phosphorylated ΔNp63 is recruited to the regulatory regions of TGF-β/Smad target genes, where it promotes recruitment of the histone acetyltransferase p300, increasing H3K27ac while reducing the repressive mark H3K27me3. This creates an open chromatin environment, promoting transcription of genes associated with stem cell characteristics and invasiveness (64). This process shows how TGF-β signaling lays an epigenetic foundation for stemness gene expression by altering local chromatin accessibility. Furthermore, TGF-β signaling can regulate lncRNA expression, which can act as molecular scaffolds or decoys to further influence chromatin state. For instance, LINC00707 can interact with Smad proteins in the cytoplasm, limiting their nuclear translocation and thereby negatively regulating TGF-β signal output. Conversely, TGF-β signaling itself can suppress LINC00707 expression, forming a feedback loop that finely controls epigenetic and transcriptional programs related to cell invasion (65). These studies indicate that the TGF-β/Smad pathway profoundly influences CSCs fate decisions by integrating multiple epigenetic mechanisms (Figure 3).

TGF-β-associated stemness can arise through distinct regulatory mechanisms. In mammary epithelial models, induction of epithelial–mesenchymal transition, including through TGF-β exposure, increased stemness-associated markers and mammosphere formation; transformed cells undergoing EMT also exhibited enhanced tumor-forming capacity (66). In patient-derived glioma-initiating cells, TGF-β promoted self-renewal and inhibited differentiation through Smad-dependent induction of leukemia inhibitory factor (LIF) and subsequent activation of JAK–STAT signaling (67). These findings establish model-specific connections between signaling and stemness-associated behavior, rather than demonstrating a universal mechanism involving recruitment of ATP-dependent chromatin remodelers.

In patient-derived glioblastoma models, TGF-β receptor inhibition reduced a CD44-high/Id1-high population enriched for glioma-initiating activity. This response involved repression of Id1 and Id3 and reduced tumor-initiation capacity, providing preclinical evidence for a TGF-β-dependent vulnerability in a defined cellular population (68). Experimental evidence further links epigenetic regulation of TGF-β/SMAD3 signaling to lung cancer metastasis. The histone methyltransferase SMYD2 promotes SMAD3 expression through epigenetic regulation, whereas SMYD2 depletion suppresses epithelial–mesenchymal transition (EMT)-associated changes, migration, invasion, and metastatic tumor formation in lung cancer models (69). Additionally, in invasive tumors such as glioblastoma, dysregulated TGF-β signaling contributes to tumor progression and therapeutic resistance by promoting EMT-like transitions and stem-like characteristics (70). These processes are accompanied by profound epigenetic reprogramming. For example, TGF-β stimulation can alter the distribution of histone modifications (such as H3K9me3) across the genome. These changes are associated with pro-cancer functions, such as cell migration and adhesion, and may depend on specific transcription factor-binding sites, such as SRY and FOXJ3 (71).

TGF-β-associated transcription and chromatin regulation can influence stemness-related or invasive phenotypes in selected systems, but the contributing cofactors and functional endpoints vary by model (Figure 3).

3.3 Chromatin Remodeling and CSCs Plasticity

CSCs are not a fixed or homogeneous cell population; rather, they exhibit plasticity, allowing transitions between stem-like and differentiated states in response to environmental cues and therapeutic pressures. This capacity to acquire or lose stemness-associated properties contributes to intratumoral heterogeneity, tumor recurrence, and therapy resistance (72). Such plasticity complicates the distinction between a stable CSC hierarchy and a changing distribution of tumor-cell states. Hierarchical organization and reversible transitions need not be mutually exclusive: a tumor may contain populations with different tumor-propagating capacities while retaining the potential for selected cells to change state. Stemness-associated properties should therefore be interpreted in relation to the experimental model, microenvironment, and treatment conditions rather than assumed to define an irreversible cellular identity.

Chromatin remodeling provides an important molecular mechanism underlying these transitions by regulating access to genomic regions involved in cell-fate determination. Glioblastoma reprogramming experiments demonstrate that a defined transcription-factor network can restore tumor-propagating potential in differentiated tumor cells, supporting the plasticity of malignant cell identity (8). These findings illustrate how changes in regulatory programs can alter functional tumor-cell properties, although experimentally induced reprogramming does not establish the frequency or direction of spontaneous transitions in patients. They also highlight the importance of distinguishing the acquisition of a stemness-associated expression profile from the acquisition of experimentally demonstrated tumor-propagating capacity. Whether a particular remodeler initiates a transition, stabilizes the resulting state, or supports cell survival during reprogramming requires direct functional investigation.

Through coordinated alterations in chromatin accessibility and gene expression, chromatin-regulatory mechanisms can facilitate transitions between proliferative, differentiated, and stem-like cellular states. In various cancers, genetic alterations or dysregulated activity of chromatin-remodeling complexes disrupt normal transcriptional programs and differentiation pathways, potentially promoting the acquisition or maintenance of stem-like characteristics and contributing to tumor progression (73). However, chromatin accessibility should not be interpreted as a simple measure of stemness: opening or closing particular regulatory regions can have different consequences depending on their target genes and cellular context. Mechanistic studies must therefore connect changes at defined loci with transcriptional responses and functional phenotypes.

This dynamic regulation suggests that, under specific conditions, non-stem tumor cells may regain self-renewal and tumorigenic capacity through epigenetic reprogramming (Figure 4). Consequently, eliminating an initially identified CSC population may be insufficient if surviving cells retain the capacity to regenerate tumor-propagating states. Therapeutic studies should distinguish selection of pre-existing resistant populations from treatment-induced state changes, because an increased proportion of stemness-marker-positive cells after treatment could reflect either process. Changes in marker expression alone cannot establish conversion. Functional tumor-initiation assays, lineage tracing, and longitudinal profiling are needed to distinguish durable acquisition of tumor-propagating capacity from transient stress responses or reversible drug tolerance. Measurements before treatment, during exposure, and after withdrawal would further clarify whether an altered state persists, reverses, or enables tumor repopulation.

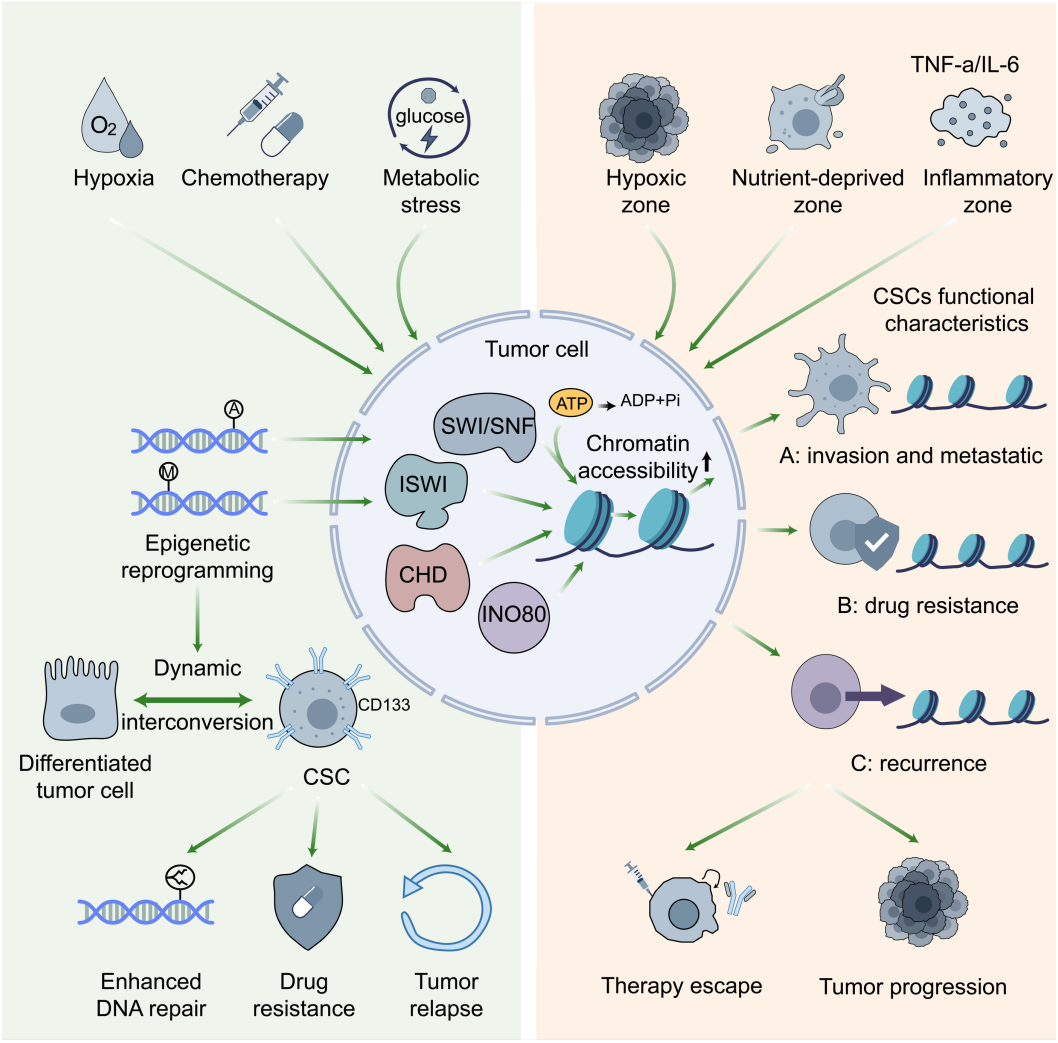


Figure 4. Schematic illustrating chromatin remodeling complexes integrating stress and tumor microenvironment signals to drive the plasticity and heterogeneity of CSCs. *Extrinsic cues, including hypoxia, chemotherapy, metabolic stress, and signals from the hypoxic, nutrient-deprived, and inflammatory tumor microenvironment, converge on ATP-dependent chromatin remodeling complexes (SWI/SNF, ISWI, CHD, and INO80). These complexes can alter chromatin accessibility and transcription in a context-dependent manner. Invasion/metastasis, drug resistance, and recurrence are conceptual functional outcomes rather than three validated, mutually exclusive CSC states. Chromatin-associated regulation may contribute to transitions between stem-like and differentiated states and to treatment persistence in selected models. The depicted relationships require model-specific functional validation. The schematic does not establish that all remodelers increase accessibility or that a single regulatory circuit produces every depicted outcome.* ***Abbreviations:*** *CSC, cancer stem cell; SWI/SNF, switch/sucrose non-fermentable; ISWI, imitation switch; CHD, chromodomain helicase DNA-binding; INO80, inositol-requiring 80; ATP, adenosine triphosphate; ADP, adenosine diphosphate; Pi, inorganic phosphate; DNA, deoxyribonucleic acid; O_2, oxygen; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; CD133, cluster of differentiation 133. The figure was created using Adobe Illustrator.*

External pressures, such as chemotherapy drugs, hypoxia, or metabolic stress, drive chromatin remodeling and cell-state transitions. These stress signals can directly or indirectly affect chromatin-modifying enzyme activity, metabolite levels, and the localization and function of chromatin-remodeling complexes, rapidly and extensively altering chromatin accessibility at numerous genes (74). For example, under hypoxic conditions, cancer cells undergo widespread epigenetic reprogramming to activate gene expression programs adapted to low-oxygen conditions, including pathways that maintain stemness characteristics (74).

In cancer cell-line models, a small subpopulation survived drug exposure by entering a reversible drug-tolerant state associated with altered chromatin regulation and dependence on the histone demethylase KDM5A (75). This finding supports a role for chromatin-associated adaptation in treatment persistence, but does not establish that drug-tolerant persisters are equivalent to functionally defined CSCs. An unresolved issue is whether therapy-induced chromatin changes generate stable CSC populations or transient drug-tolerant states that only partially overlap with conventional definitions of stemness. Distinguishing these possibilities requires longitudinal lineage tracing and paired chromatin/transcriptomic profiling before, during, and after treatment. Without such temporal evidence, post-treatment enrichment of stemness markers cannot establish conversion to a durable CSC state.

Drug-tolerance experiments and glioblastoma reprogramming studies illustrate distinct routes through which tumor cells can acquire treatment-persistent or tumor-propagating properties (75, 8). Neither study alone establishes that chemotherapy, hypoxia, or metabolic stress universally induces self-renewal, drug efflux, and enhanced DNA repair in the same cell population. Determining whether treatment-induced states acquire durable tumor-propagating capacity requires longitudinal and functional validation (Figure 4).

3.4 Chromatin Remodeling and CSCs Heterogeneity

Tumor-cell heterogeneity reflects genetic variation and differences in regulatory state. Breast cancer experiments demonstrate that ZEB1-associated chromatin regulation can facilitate acquisition of CSC properties (3), while broader epigenetic mechanisms contribute to variation in tumor-cell identity (30). SHARE-seq demonstrated simultaneous measurement of chromatin accessibility and gene expression in individual cells and provided a framework for examining relationships between regulatory accessibility and cell-state transitions (76). However, this methodological study was not a direct demonstration of CSC heterogeneity in human tumors. Applying paired profiling to CSC-enriched populations requires careful cell annotation and functional assessment of tumor-propagating capacity.

Invasion/metastasis, treatment persistence, and post-treatment repopulation are used in Figure 4 as conceptual functional outcomes rather than three established, mutually exclusive CSC states. In melanoma models, a slow-cycling JARID1B-positive population supported sustained tumor growth, while JARID1B-negative cells could acquire the positive state, demonstrating dynamic population behavior rather than a fixed, unidirectional CSC hierarchy (77). Direct experiments in mammary epithelial models demonstrated that nonstem cells could spontaneously acquire stem-like properties, with oncogenic transformation enhancing this conversion (78). These findings support plasticity between cellular states, but do not validate the three functional categories depicted in Figure 4 as a universal CSC classification. In glioblastoma, single-cell analyses identified four major malignant cellular states whose distributions were influenced by genetic alterations and the microenvironment, with evidence of state plasticity (79). In breast cancer cell-line models, sorted phenotypic populations re-established characteristic population proportions through stochastic state transitions (80). These studies support plasticity and state interconversion, but do not demonstrate that ISWI inhibition induces differentiation or that SWI/SNF overexpression drives an invasive/metastatic state.

This epigenetic heterogeneity forms through a dynamic process shaped by multiple factors, with spatial heterogeneity in chromatin remodeling complex activity and differences in tumor microenvironment signals playing central roles. Chromatin remodeling complexes, such as the SWI/SNF, ISWI, CHD, and INO80 families, are key regulators of chromatin accessibility. They determine whether specific genomic regions are open or closed by consuming ATP to alter nucleosome positioning and composition (4). Within a tumor, uneven distribution of oxygen and nutrients and differences in cell-

cell interactions across regions can lead to spatial heterogeneity in remodeling complex activity. For example, hypoxic regions of the tumor may affect the expression or recruitment of remodeling complex subunits through specific signaling pathways (such as HIF), leading to changes in the chromatin state of CSCs in that region and activating gene programs related to hypoxia adaptation and invasion. Determining how immune-cell and fibroblast-derived signals alter specific remodeling complexes in CSCs remains an important experimental objective. This reversible epigenetic reprogramming, driven by microenvironmental signals, endows CSCs with high plasticity, enabling them to quickly adapt to therapeutic pressure or pre-metastatic microenvironmental changes (30).

However, this also greatly increases the complexity of targeted therapy because therapies targeting a specific epigenetic state or signaling pathway may not effectively eliminate all heterogeneous CSC subpopulations and may even select for more resistant clones. Therefore, future therapeutic strategies need to comprehensively consider the multidimensional drivers of intratumoral epigenetic heterogeneity and develop combination therapies that can simultaneously target multiple key nodes or induce CSC differentiation (Figure 4).

4. The Role of Chromatin Remodeling in CSCs Therapy Resistance

4.1 Mediating Chemotherapy and Radiotherapy Resistance

Resistance of CSC-associated populations to chemotherapy and radiotherapy can contribute to tumor recurrence and treatment failure, with chromatin regulation influencing several underlying mechanisms. Some CSC populations exhibit relatively quiescent states or increased expression of drug efflux pumps, particularly members of the ATP-binding cassette (ABC) transporter family; however, these properties vary by tumor type and cellular state. Epigenetic mechanisms can regulate multidrug-resistance programs, including expression of ABC transporters such as ABCB1 (MDR1). In human cell models, SMARCB1 loss increased ABCB1 expression and doxorubicin resistance through a SMARCA4-dependent mechanism, demonstrating that SWI/SNF composition can influence drug-efflux-associated resistance (81). This mechanism is drug-dependent and should be distinguished from resistance arising through altered drug targets, enhanced survival signaling, or DNA damage responses.

LncRNAs can influence chemotherapy resistance through transcriptional, chromatin-associated, and post-transcriptional mechanisms. Depending on the experimental context, these activities may alter ABC transporter expression, apoptosis, or other resistance-associated pathways. Studies summarized in the doxorubicin-resistance literature implicate multiple lncRNA-dependent mechanisms, rather than a single universal pathway involving recruitment of chromatin-remodeling complexes to transporter promoters (82). Establishing such a direct mechanism requires evidence connecting lncRNA binding, remodeler recruitment, local chromatin changes, transporter expression, and altered drug sensitivity.

In colorectal cancer, CSC-associated markers such as CD44 and CD133 and signaling pathways including Wnt/β-catenin participate in regulatory networks linked to tumor maintenance and treatment resistance. Epigenetic dysregulation can support these programs, although marker expression alone does not establish a chromatin-remodeling dependency or predict therapeutic response (56). Additionally, high mobility group box 3 (HMGB3), a chromatin-associated protein implicated in DNA damage responses, has been linked to stemness-associated phenotypes and therapy resistance in several malignancies. Reported mechanisms include effects on survival signaling and DNA repair, with their relative contributions depending on the tumor model and treatment examined (83). These observations provide a rationale for investigating chromatin-associated resistance mechanisms, while the

relationships summarized in Figure 5 should be interpreted as context-dependent rather than a single experimentally established pathway.

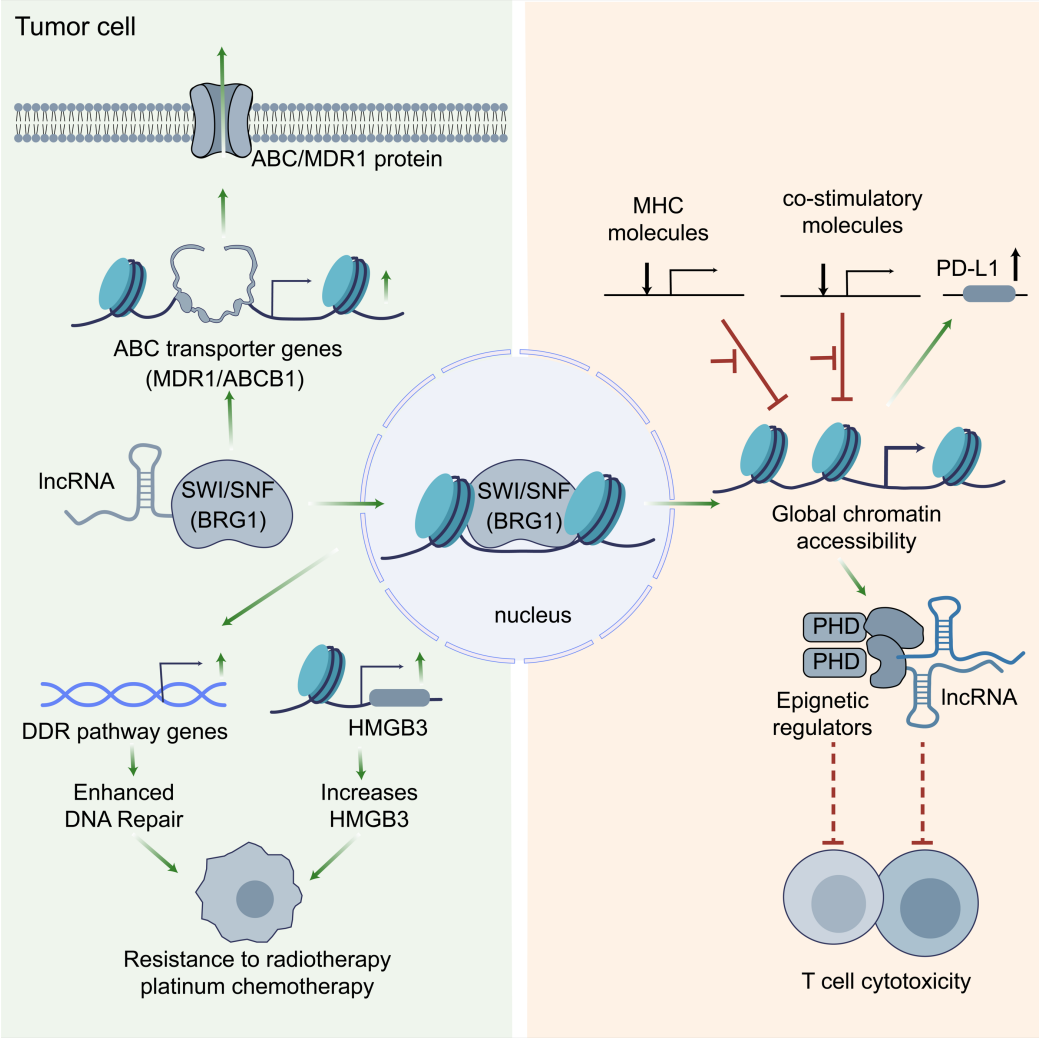


Figure 5. Model linking chromatin regulation to therapy resistance and immune evasion. *The diagram summarizes potential relationships among SWI/SNF-associated chromatin regulation, drug transport, DNA damage responses, and immune-related gene expression. These relationships derive from different experimental settings and should not be interpreted as a single established BRG1-dependent pathway. Effects on antigen presentation, co-stimulatory molecules, and PD-L1 depend on tumor lineage, genotype, remodeling-complex composition, and treatment context; the directions shown are illustrative and may differ across models. Direct BRG1 regulation of ABCB1, HMGB3, or the depicted immune outputs in CSCs requires validation in the relevant experimental system. PHD-domain proteins and lncRNAs represent additional epigenetic regulators rather than necessarily components of one SWI/SNF-mediated mechanism.* ***Abbreviations:*** *CSC, cancer stem cell; SWI/SNF, switch/sucrose non-fermentable; BRG1, Brahma-related gene 1; ABC, ATP-binding cassette; ABCB1, ATP-binding cassette subfamily B member 1; MDR1, multidrug resistance 1, also known as ABCB1 or P-glycoprotein; DDR, DNA damage response; DNA, deoxyribonucleic acid; HMGB3, high mobility group box 3; MHC, major histocompatibility complex; PD-L1, programmed death-ligand 1; PHD, plant homeodomain; lncRNA, long noncoding RNA. The figure was created using Adobe Illustrator.*

Epigenetic regulation can also influence radiation responses through mechanisms that vary across experimental systems (84). In gliomas, altered chromatin insulation can permit abnormal regulatory interactions and oncogene activation, but these findings do not directly establish a mechanism of resistance to temozolomide or radiation (22). In colorectal cancer, Brg1 depletion impaired tumor stem-cell maintenance and survival (48). Separate acute-leukemia experiments demonstrated a BRG1-associated transcriptional dependency involving MYC regulation (6). In colorectal cancer models,

BRG1 suppression activated adaptive JNK signaling, providing a rationale for combined BRG1/JNK pathway inhibition rather than demonstrating that BRG1 inhibition alone reverses radioresistance (85). These findings support investigation of context-specific dependencies, with treatment sensitization requiring direct testing for each therapeutic combination.

Chromatin-associated mechanisms may contribute to treatment resistance by affecting transcription, cellular adaptation, and DNA damage responses. Their relative importance depends on the tumor model and treatment, and therapeutic studies must distinguish general cytotoxicity from selective effects on tumor-propagating populations (Figure 5).

4.2 Maintaining the Immune Evasion Phenotype

Colorectal CSC-associated populations interact with immune and stromal cells through mechanisms that can influence tumor maintenance and immune escape. Reported features include changes in antigen presentation, checkpoint signaling, and the surrounding immune microenvironment, although their direction and functional significance vary across experimental settings (56). These interactions should be evaluated within the relevant tumor context, since stemness-associated markers do not necessarily identify populations with uniform immune properties. Differences between marker-enriched populations may also reflect lineage identity, treatment exposure, or microenvironmental conditions.

Epigenetic regulation provides a framework for investigating these differences, but expression patterns alone do not establish a causal role for a particular ATP-dependent chromatin-remodeling complex (30). Direct perturbation and immune-function assays are therefore needed to connect chromatin regulation with immune evasion. Such experiments should distinguish altered tumor-cell viability from changes in susceptibility to immune-mediated killing and determine whether effects persist after accounting for proliferation and cell-state differences.

Perturbation of specific chromatin-remodeling complexes can alter tumor-cell sensitivity to immune attack. In melanoma models, loss of PBAF components increased sensitivity to T-cell-mediated killing and enhanced interferon-γ-responsive programs, providing direct evidence for a context-dependent connection between chromatin regulation and antitumor immunity (86). These experiments did not establish selective targeting of CSCs or a universal effect of BRG1 inhibition on antigen presentation and PD-L1 expression. Translational evaluation must therefore specify the affected complex, tumor genotype, and immune context rather than treating all SWI/SNF-associated interventions as equivalent. Figure 5 should be interpreted as a conceptual summary of potential relationships rather than a single established immune-evasion pathway.

5. Targeted Chromatin Remodeling Strategies for Anti-CSCs Therapy

5.1 Direct Targeting of Remodeling Complex ATPase Activity

Developing small-molecule inhibitors that directly target the ATPase activity of chromatin-remodeling complexes is an important direction in cancer therapy, including strategies to disrupt CSC-associated dependencies (14). Chromatin-remodeling complexes, such as SWI/SNF, INO80, ISWI, and members of the CHD family, rely on conserved SNF2-like catalytic ATPase subunits to hydrolyze ATP, providing energy for nucleosome sliding, eviction, assembly, or editing and thereby regulating chromatin structure and gene expression (18, 87). Experimental CHD1 studies connect ATP-dependent remodeling with chromatin organization and pluripotency in embryonic stem cells (13), while broader CSC literature describes context-dependent relationships between cell state and tumor propagation (19). In cancer, alterations in genes encoding these complexes can disrupt transcriptional programs and

differentiation, although their consequences depend on tumor lineage, genotype, and complex composition (14). Direct ATPase inhibition may therefore promote differentiation or cell death in tumors that retain a functional dependence on the targeted remodeler. Identifying this dependence is essential because loss of remodeling activity can itself contribute to tumorigenesis in other contexts. Target expression alone is not sufficient evidence of dependence; functional perturbation and confirmation of the relevant molecular response are needed to justify therapeutic targeting.

FHD-286 is an orally bioavailable allosteric dual inhibitor of BRG1/BRM ATPase activity with antitumor activity in preclinical models (88). These findings support the pharmacological tractability of these ATPases, while leaving CSC selectivity and the determinants of treatment response to be established. Evaluation should connect drug exposure and target inhibition with changes in transcription, cellular state, and tumor-propagating function. INO80 represents a separate investigational direction: experiments in HCT116 cells demonstrated reciprocal regulation between INO80-complex components and miR-372, but did not evaluate a selective small-molecule INO80 inhibitor (89). Structural and mechanistic analyses provide additional insight into INO80-family complexes and their substrate interactions without establishing clinical inhibition (90). Revumenib, which inhibits the menin–KMT2A interaction rather than a chromatin-remodeler ATPase, has shown clinical activity in genetically defined acute leukemias (91). Its therapeutic activity illustrates the value of targeting a specific epigenetic dependency, while remaining mechanistically distinct from direct ATPase inhibition.

Selectivity and tolerability remain major challenges because chromatin-remodeling ATPases support essential cellular processes (14, 92). Biochemical selectivity must therefore be distinguished from a therapeutic window between malignant and normal tissues: inhibiting an intended target can still cause toxicity by disrupting its physiological functions. SRCAP depletion impaired replication dynamics in PC3 cells, demonstrating a replication-associated function rather than clinical toxicity in normal tissues (93). A phase I study of FHD-286 in 40 patients with advanced myeloid malignancies reported differentiation and reductions in leukemic burden, but no objective responses; differentiation syndrome was an important safety finding (94). These results emphasize the need to distinguish pharmacodynamic activity from durable clinical benefit and to selectively deplete tumor-propagating populations. Future assessments should also examine response duration and whether treatment-associated differentiation persists after drug withdrawal.

Targeted delivery remains a separate preclinical strategy. CD133-targeted PLGA nanoparticles carrying paclitaxel reduced mammosphere and colony formation in vitro and suppressed tumor regrowth compared with free paclitaxel in a breast cancer xenograft model, providing preclinical evidence for marker-directed drug delivery (95). Nanoparticle delivery of HDAC inhibitors provides additional formulation rationale, although HDAC inhibitors are mechanistically distinct from ATP-dependent remodeler inhibitors (96). Another CSC-associated vulnerability involves CD44 variant-dependent stabilization of xCT, which supports redox defense and tumor growth; this finding does not demonstrate targeted delivery of a remodeler inhibitor (97). Establishing a therapeutic window will require payload-specific delivery studies, confirmation of target engagement, and direct comparison of malignant and normal-cell dependencies. Preferential uptake into marker-positive cells should also be distinguished from selective activity against functionally defined CSCs. Functional and longitudinal assessments will be needed to determine whether treatment eliminates tumor-propagating capacity or produces a temporary change in cell state (Figure 6).

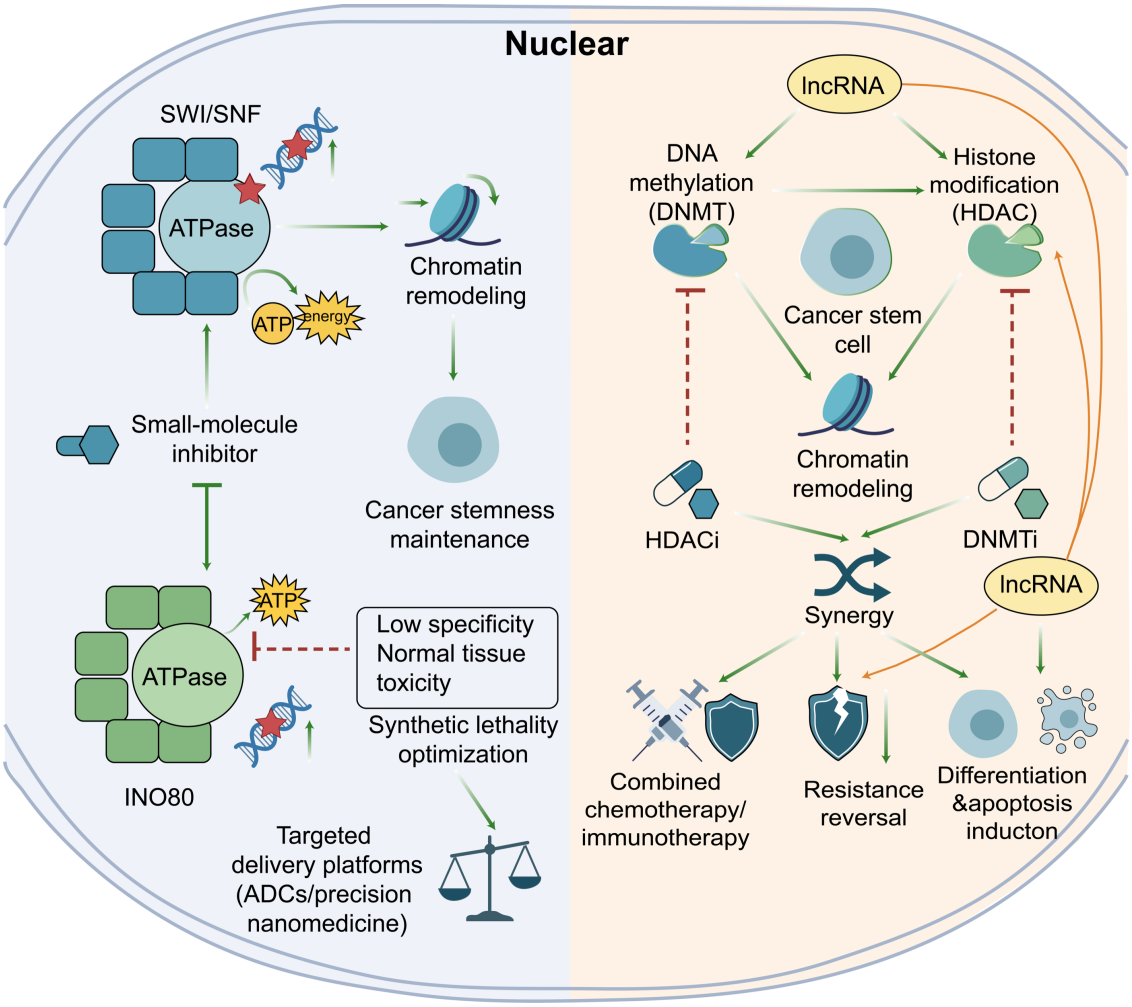


Figure 6. Therapeutic approaches relevant to chromatin regulation and CSC-associated states. *Therapeutic approaches relevant to chromatin regulation and CSC-associated states. The diagram combines strategies at different developmental stages. Direct BRG1/BRM ATPase inhibition has preclinical and early phase I evidence, whereas CSC-selective INO80 inhibition and delivery of ATPase inhibitors through CSC-targeted ADCs or nanoparticles remain exploratory. HDAC inhibitors, DNMT inhibitors, and menin inhibitors act through mechanisms distinct from direct SNF2-family ATPase inhibition. Potential combinations, synthetic-lethal approaches, and targeted delivery require model-specific validation and should not be interpreted as established methods of selective clinical CSC eradication.* ***Abbreviations:*** *CSC, cancer stem cell; SWI/SNF, switch/sucrose non-fermentable; INO80, inositol-requiring 80; BRG1, Brahma-related gene 1; BRM, Brahma; SNF2, sucrose non-fermenting 2; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; DNA, deoxyribonucleic acid; ADC, antibody–drug conjugate; DNMT, DNA methyltransferase; DNMTi, DNA methyltransferase inhibitor; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; lncRNA, long noncoding RNA. The figure was created using Adobe Illustrator.*

5.2 Combination Therapy Strategies

CSC-associated populations can contribute to tumor maintenance, treatment resistance, and recurrence through self-renewal and cell-state plasticity (98). Epigenetic regulation provides a rationale for investigating combinations that alter these properties, although different drug classes act through distinct molecular mechanisms (12). Reviews of colorectal epigenetic therapy describe potential therapeutic approaches (99), while glioblastoma chromatin-insulation biology provides a separate framework for investigating transcriptional vulnerabilities (22). These observations support experimental evaluation of combinations, but do not establish universal synergy, selective CSC elimination, or prevention of recurrence (84) (Figure 6).

Epigenetic therapies differ in their molecular targets and levels of clinical validation. HDAC inhibitors have clinical roles in selected hematologic malignancies (100), while decitabine-based treatment is used in myelodysplastic syndromes and related myeloid disorders (101). Dual BRG1/BRM ATPase inhibition has shown preclinical activity in AML models (102), whereas menin inhibition has demonstrated clinical activity through a separate molecular mechanism (91). Reviews of colorectal epigenetic strategies and DNMT inhibitors provide a rationale for combination studies, but do not establish a universal synergistic or CSC-selective effect of HDACi/DNMTi coadministration (99, 103). Such combinations require direct evaluation of dose, schedule, target engagement, tumor-propagating capacity, and normal-tissue effects.

Epigenetic interventions have been investigated in pediatric nervous-system tumors and CSC-associated experimental systems, but the evidence is heterogeneous and largely preclinical (104). Combining lncRNA-directed approaches with other epigenetic agents is therefore a testable therapeutic hypothesis. Demonstrating benefit will require distinguishing selective effects on tumor-propagating populations from broader cytotoxic or differentiation responses and establishing an acceptable therapeutic window (Figure 6).

A further distinction is needed between clinically validated epigenetic therapy and clinically validated CSC-directed chromatin-remodeling therapy. HDAC and DNMT inhibitors have established clinical roles in selected hematologic malignancies, and other epigenetic agents have entered clinical development, but these observations do not demonstrate that their clinical activity results from CSC depletion. For most ATP-dependent chromatin remodelers discussed here, evidence remains at the mechanistic or preclinical stage. Future trials will therefore need pharmacodynamic biomarkers that demonstrate modulation of the intended remodeling complex, along with longitudinal measures that determine whether stem-like tumor populations are selectively depleted.

Clinical translation is further complicated by the absence of a validated biomarker that uniquely identifies CSCs across tumor types. Markers such as CD44, CD133, and ALDH activity can enrich for tumor-propagating populations in particular settings but are neither universal nor exclusive to CSCs. Consequently, reducing marker-positive cells alone cannot establish CSC eradication. Translational studies should combine phenotypic markers with functional assays, molecular evidence of target engagement, and longitudinal assessment of recurrence or tumor-repopulating capacity.

Discussion

The frequency, proliferative state, and phenotypic definition of functionally identified CSCs vary across tumors and experimental systems, complicating their isolation and comparison. First, isolating CSCs with high purity from complex tumor cell populations is challenging. Traditional surface marker-based sorting methods often fail to capture all CSC subpopulations, and the sorting process may alter the cells' original state (19). Paired single-cell profiling can connect chromatin accessibility with gene expression. SHARE-seq demonstrated this capability and provided a framework for investigating regulatory changes associated with cell-state transitions (76). Its application to CSCs requires appropriate tumor-cell annotation and functional validation. For example, single-cell ATAC-seq can reveal heterogeneity in chromatin accessibility, but when applied to rare cells like CSCs, it still requires sufficient sequencing depth and coverage to capture key regulatory elements (29). Additionally, CSC chromatin states are not static; they undergo rapid reprogramming in response to therapeutic pressure, microenvironmental signals, or different stages of the cell cycle. This requires research methods with high temporal resolution to capture these dynamic changes (5). Therefore, developing platforms capable of non-destructive, high-precision CSC sorting, combined with time-resolved single-cell multi-omics analysis,

is an important direction for overcoming technical bottlenecks and gaining a deeper understanding of the chromatin basis of CSCs in the future.

To target CSCs more precisely, it is essential to analyze mechanisms of action, upstream and downstream regulatory networks, and the association of different chromatin-remodeling complexes with three-dimensional chromatin conformation in specific CSC types. Research indicates that distinct remodeling complexes play unique and intricate roles in maintaining CSC characteristics. In TNBC models, MUC1-C-associated induction of NuRD components illustrates how oncogenic signaling can engage chromatin-regulatory machinery to suppress differentiation-associated transcription (26).

Chromatin-remodeling complexes participate in regulatory networks involving transcription factors and non-coding RNAs. In liver cancer stem-cell models, lncBRM promoted self-renewal through BRM/BRG1-associated remodeling and activation of YAP1 signaling (16). More importantly, chromatin remodeling is closely related to changes in three-dimensional genome structure. Three-dimensional genome organization provides another layer of gene regulation, but changes in accessibility do not automatically demonstrate altered TADs or enhancer–promoter contacts. Establishing the contribution of a specific remodeling complex requires appropriate perturbation and chromosome-conformation measurements (29). Genome-wide RNAi screens identified PHF5A as differentially required for the viability of patient-derived glioblastoma stem cells through its role in splice-site recognition, with additional effects on tumor formation and maintenance (105). This identifies a splicing-associated vulnerability rather than demonstrating that PHF5A regulates CSC growth by remodeling three-dimensional chromatin. Combining perturbation screens with accessibility and chromosome-conformation measurements could help distinguish these mechanisms.

Defining a therapeutic window requires comparison of malignant and nonmalignant dependencies. Inhibition of an essential normal-cell function can produce on-target toxicity even when an agent is biochemically selective; this should be distinguished from inhibition of unintended molecular targets. PHF5A experiments illustrate the value of comparing glioblastoma stem cells with untransformed cells, without establishing systemic clinical safety (105). For direct BRG1/BRM inhibition, the FHD-286 phase I study demonstrates the importance of evaluating tolerability and differentiation syndrome alongside pharmacodynamic activity and clinical response (94). Low abundance and limited sequence conservation can also complicate the development of lncRNA-directed interventions (32).

Synthetic lethality provides a framework for identifying dependencies created by defined genetic alterations (106). The relevant residual remodeling complex, subunit or paralog must be specified, and any therapeutic window requires comparison with normal populations. Tumor-specific dependency and localized delivery are complementary research strategies, but neither should be assumed to spare normal stem cells or selectively eliminate CSCs without direct evidence. Upstream oncogenic regulators may provide additional routes for investigating chromatin-associated dependencies. In TNBC models, MUC1-C promoted NuRD-component expression and dedifferentiation-associated transcriptional regulation (26). These findings provide a mechanistic rationale for further investigation, but do not establish selective clinical depletion of CSCs. Tumor-localized delivery is a potential strategy for modifying drug exposure, but its benefits must be demonstrated for the specific payload and formulation. A CD133-targeted paclitaxel nanoparticle study provides a preclinical delivery example, although its findings do not establish delivery or reduced toxicity of a chromatin-remodeler inhibitor (95). Similarly, HDAC-inhibitor nanomedicine offers formulation examples for a distinct drug class (96). Delivery of direct remodeler inhibitors will require payload-specific studies of distribution, target engagement, efficacy, and safety, including assessment of brain exposure where relevant.

Clinical development will require molecular stratification rather than treating chromatin remodeling as a tumor-agnostic vulnerability. CSC maintenance is closely linked to functional abnormalities in chromatin remodeling complexes. Mutations or expression-profile differences in these complexes are an important basis for tumor heterogeneity. In IDH-mutant gliomas, DNA hypermethylation can disrupt chromatin insulation and alter oncogenic regulatory interactions (22). These observations support mechanism-specific investigation of molecular stratification rather than establishing IDH status as a predictor of response to every CSC-directed chromatin therapy. Distinct mechanisms require distinct therapeutic interpretations. PBAF perturbation increased sensitivity to T-cell-mediated killing in melanoma models (86), whereas PHF5A dependence in glioblastoma stem cells reflected a vulnerability in RNA splicing (105). Menin inhibition represents a separate strategy supported by clinical evidence in KMT2A-rearranged or NPM1-mutant leukemia (91). These findings should not be presented as interchangeable examples of PHD-reader or ATP-dependent chromatin-remodeler inhibition.

Circulating epigenetic signals and lncRNA profiles remain candidate biomarkers rather than established universal measures of CSC burden. Literature linking lncRNAs with epithelial–mesenchymal plasticity and stemness provides a rationale for investigation, but clinical biomarker performance requires separate validation (32). Detecting a circulating methylation pattern or lncRNA does not by itself establish the abundance or tumor-propagating capacity of CSCs. Proposed assays should be evaluated against matched tissue states, functional tumor-propagating capacity, and clinical outcomes before being used to direct treatment (98).

Single-cell and spatial approaches offer opportunities to investigate tumor-state regulation and microenvironmental interactions, as illustrated by studies of Ras-driven tumors and colorectal cancer metastasis (107, 108). In glioblastoma, ATAC-seq of isolated stem-cell populations identified regulatory signatures associated with migration and established a functional role for TEAD1; this was not a single-cell ATAC-seq study or the source of patient-survival subgrouping (109). Targeted protein degradation provides a separate preclinical strategy: the PROTAC ACBI1 degraded the BAF-associated proteins SMARCA2, SMARCA4, and PBRM1 and exposed context-dependent cancer vulnerabilities, without demonstrating CSC-selective clinical efficacy (110). In bladder cancer models, the HDAC inhibitor entinostat promoted antitumor immune responses through immune editing of tumor neoantigens and supported investigation of combinations with immune checkpoint blockade (111). Related prostate cancer work examined ketogenic-diet-associated epigenetic and immune changes in combination-treatment settings (112). These findings support further investigation of distinct therapeutic approaches, but do not establish selective clinical CSC depletion by ATP-dependent chromatin-remodeler inhibitors.

The evidence reviewed here spans biochemical studies, established cell lines, tumorsphere models, genetically engineered systems, patient-derived cultures, xenografts, and early clinical studies. These levels of evidence should not be interpreted equivalently. Direct perturbation followed by functional assessment of tumor initiation provides stronger support for a CSC dependency than expression correlations or marker enrichment, whereas clinical activity of an epigenetic drug does not establish CSC-specific targeting without appropriate pharmacodynamic evidence. Maintaining this distinction will be important as chromatin-remodeling biology moves from mechanistic studies toward therapeutic development.

Conclusion

Chromatin remodeling contributes to transcriptional programs associated with cancer stemness, plasticity, and treatment resistance. These effects depend on tumor lineage, genotype and remodeling-

complex composition. Genetic alterations and epigenetic regulation interact in shaping malignant cell states; functional perturbation is needed to distinguish a therapeutically relevant dependency from expression or accessibility associations. Targeting context-specific chromatin dependencies may offer opportunities to influence tumor-propagating states and treatment resistance. However, preclinical activity and early clinical pharmacodynamic effects should be distinguished from durable clinical benefit or selective CSC depletion. Therapeutic development must account for differences in tumor genotype, remodeling-complex composition, normal-tissue requirements, drug delivery, and adaptive cell-state transitions.

Future studies should integrate longitudinal molecular profiling with functional assessment of tumor-propagating capacity in appropriate experimental models and clinical samples. Direct ATPase inhibitors, targeted protein degraders, and combinations with other epigenetic or immune therapies represent distinct strategies requiring mechanism-specific validation. Their clinical value will depend on demonstrating meaningful benefit within an acceptable therapeutic window.

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Declarations

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