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REPROGRAMMING CANCER CELL PHYSIOLOGY THROUGH EPIGENETIC MECHANISMS: INSIGHTS INTO NEURO-ONCOLOGY

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ABSTRACT

The interactive nature of epigenetic control and cancer cell physiology has come to be one of the primary paradigms in tumorigenesis studies, especially in the difficult field of neuro-oncology. Epigenetic modifications, (a DNA methylation, histone acetylation, chromatin remodelling and non-coding RNA-mediated regulation) are reversible and very sensitive to intrinsic and extrinsic signals, unlike genetic mutations which are permanent changes in the DNA sequence. This plasticity permits cancer cells to restructure their transcriptional networks, to respond to the microenvironmental stresses, and to develop the features of malignancy, including persistent proliferation, immune evasion, and resistance to therapy. Epigenetic deregulation will acquire a particular importance in the context of primary and metastatic brain tumors because biochemical restraint of the central nervous system and blood-brain barrier is unique to this organ. The following review compiles the existing information on the epigenetic processes involved in cancer cell reprogramming, with a particular emphasis on glioblastoma multiforme and other malignant central nervous system neoplasms. We also discuss the new epigenetic therapies, such as histone deacetylase inhibitors, DNA methyltransferase inhibitors, and epigenetic-editing platforms, considering their potential to rescue the pathological phenotypes and restore the normal functioning of the cells. Lastly, we touch on the translation issues and the future perspective of incorporating epigenetic approaches to precision neuro-oncology.

Keywords: epigenetics, cancer reprogramming, neuro-oncology, glioblastoma, DNA methylation, histone modification, chromatin remodeling, epigenetic therapy.

1. Introduction

Cancer has always been viewed as a genetic mutational disease-a collection of faults in oncogenes and tumor suppressor genes that confer unchecked growth. However, with the advent of high-throughput sequencing technologies, it has become clear that changes in epigenetics are also widespread throughout malignancies, and are frequently the antecedents or even cause of genetic instability (Jones & Baylin, 2007). As a mechanistic account of how cancer cells attain such outstanding phenotypic plasticity, epigenetics, or heritable alterations in gene expression which do not entail modifications to the underlying DNA sequence will help. Cancer has always been viewed as a genetic mutational disease-a collection of faults in oncogenes and tumor suppressor genes that confer unchecked growth. However, with the advent of high-throughput sequencing technologies, it has become clear that changes in epigenetics are also widespread throughout malignancies, and are frequently the antecedents or even cause of genetic instability (Jones & Baylin, 2007). As a mechanistic account of how cancer cells attain such outstanding phenotypic plasticity, epigenetics, or heritable alterations in gene expression which do not entail modifications to the underlying DNA sequence will help. This plasticity has a special implication in neuro-oncology. Primary brain tumors, including glioblastoma multiforme (GBM) are highly heterogeneous in an intratumoral way, both between individuals and within the individual tumor. Such heterogeneity is a formidable challenge to treatment because it allows subpopulations of cancer cells to survive surgery, radiation and chemotherapy by adapting to reprogramming. The microenvironment of the central nervous system (CNS) makes the situation even more complicated and introduces unique selective pressures and presents different epigenetic vulnerabilities. The objective of this review is to summarize recent insights into the role of epigenetic processes in the re-programming of cancer cell physiology within the CNS and its implications in therapeutics. We start with a description of the primary epigenetic mechanisms involved in neuro-oncology, then proceed to an analysis of how the mechanisms contribute to typical cancer phenotypes. We then consider the epigenetic therapeutic landscape as of today, noting advances made and remaining obstacles, and conclude with future prospects of research and clinical application.

2. Core Epigenetic Mechanisms in Cancer

2.1 DNA Methylation

The most studied epigenetic mark is DNA methylation, which consists of the addition of a methyl group to the 5' base of cytosine residues in CpG dinucleotides. CpG islands in promoter regions of normal cells are usually unmethylated, and they are free to be actively transcribed as shown in Figure 1. Promotion of tumor suppressor genes, including MGMT, CDKN2A, and BRCA1, is also silenced by hypermethylation of the promoters, eliminating essential brakes in the process of proliferation and DNA repair (Esteller, 2008). On the other hand, worldwide hypomethylation helps to lead to genomic instability and oncogenes. The MGMT promoter methylation is also used as a paradigmatic biomarker in neuro-oncology. The MGMT methylation is a predictor of response to temozolomide in patients with GBM because it inhibits repair of the DNA damage caused by alkylating agents (Hegi et al., 2005). This observation highlights the relevance of DNA methylation in functional terms as an agent of malignancy as well as a predictor of therapeutic outcome.

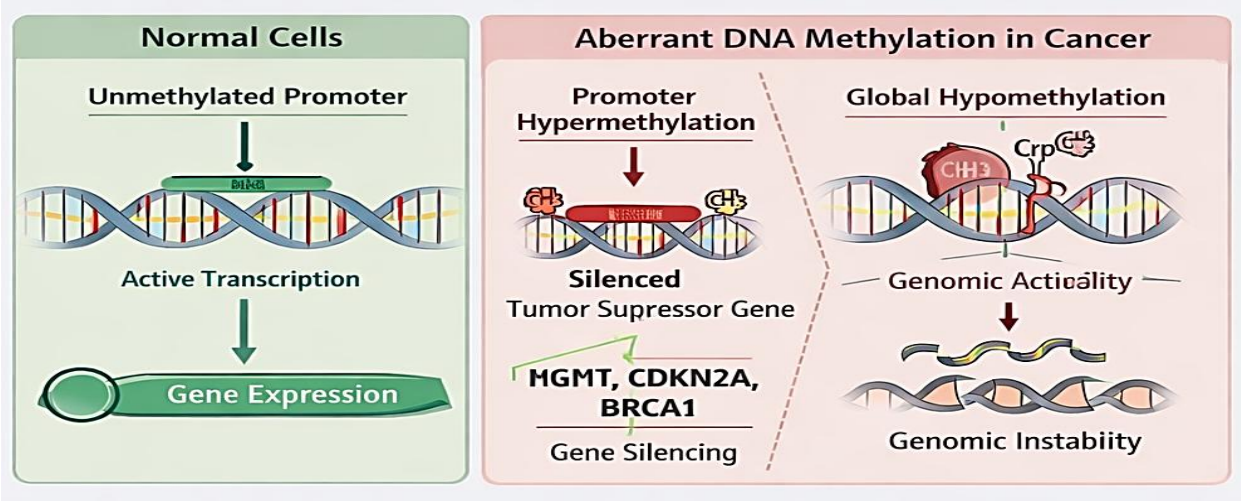


Figure 1. DNA Methylation in Normal and Cancer Cells with Relevance to Neuro-Oncology. The diagram illustrates epigenetic regulation via DNA methylation. In normal cells, unmethylated CpG islands in promoter regions allow active transcription and gene ex

2.2 Histone Modifications

A second epigenetic regulation layer is post-translational modification of histone tails, which includes acetylation, methylation, phosphorylation and ubiquitination. These changes change the availability of the chromatin and bring in effector proteins that regulate the transcription. Histone acetylation is usually associated with open chromatin and transcription. Abnormal HDAC activity has been shown to silence tumor suppressors in cancer, and has been observed to cause mutations in histone-modifying enzymes in many types of tumors. Interestingly, there are frequent mutations of the histone H3 genes (H3F3A and HIST1H3B), which causes the replacement of lysine 27 with methionine (K27M) as shown in Figure 2. This mutation has been identified worldwide as having H3K27 trimethylation which is a repressive mark resulting in widespread transcriptional dysregulation and a distinct epigenetic landscape characteristic of a subclass of diffuse midline gliomas (Wu et al., 2012). These results demonstrates that an epigenetic change in just one cell can reassemble the whole cellular identity.

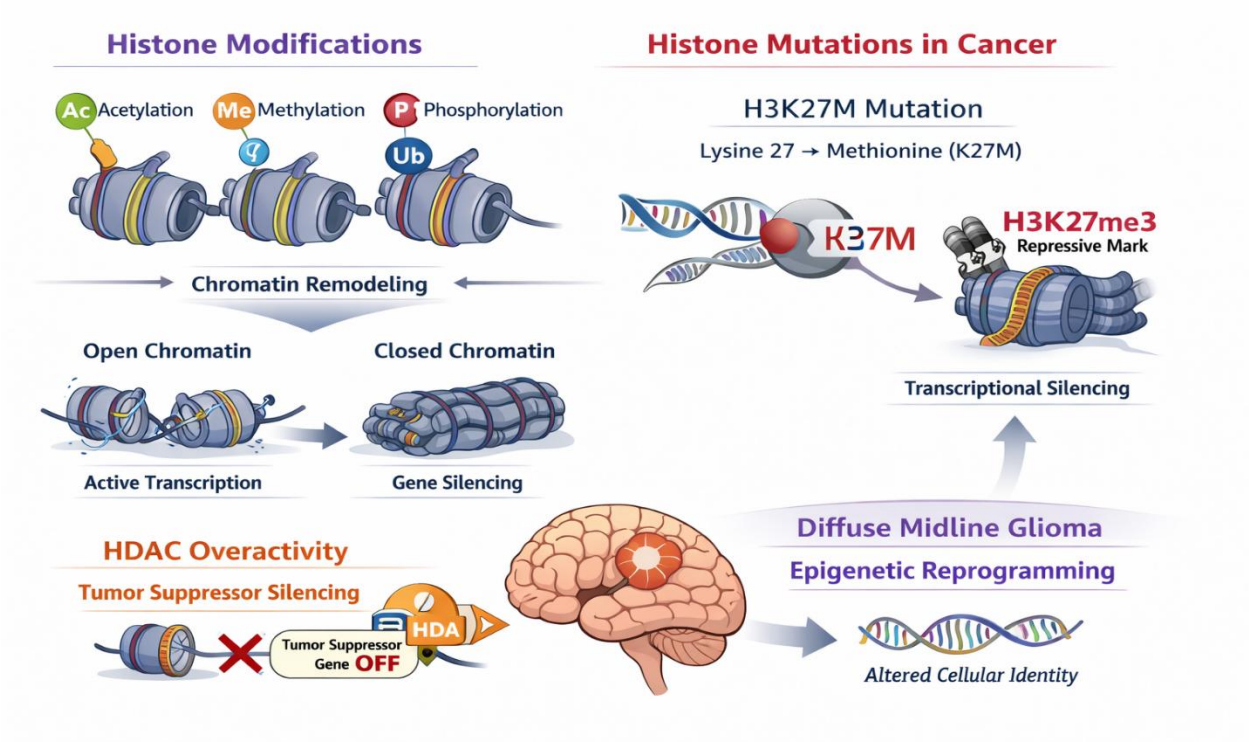


Figure 2 This figure illustrates the role of histone modifications and mutations in shaping the epigenetic landscape of cancer, particularly in diffuse midline gliomas. Normal histone modifications, including acetylation, methylation, and phosphorylation, regulate chromatin structure and gene expression by transitioning between open (active) and closed (repressive) states. In contrast, oncogenic alterations such as the H3K27M mutation disrupt normal histone methylation patterns, leading to loss of repressive marks (H3K27me3) and widespread transcriptional dysregulation. Additionally, increased histone deacetylase (HDAC) activity contributes to tumor suppressor gene silencing, further promoting tumor progression. Together, these epigenetic changes drive chromatin remodeling, transcriptional repression, and ultimately alter cellular identity, highlighting their critical role in glioma pathogenesis.

2.3 Chromatin Remodeling

SWI/SNF, ISWI, and CHD families of chromatin remodeling complexes use ATP to reposition nucleosomes thus regulating access to DNA. Cancer-associated mutation in subunits of these complexes is becoming common. Overexpression of core SWI/SNF subunits through loss of SMARCB1 inactivation in atypical teratoid/rhabdoid tumors (AT/RT) as well as other CNS malignancies contributes to oncogenesis by affecting chromatin structure and allowing aberrant expression of proliferative programs (Versteege et al., 1998).

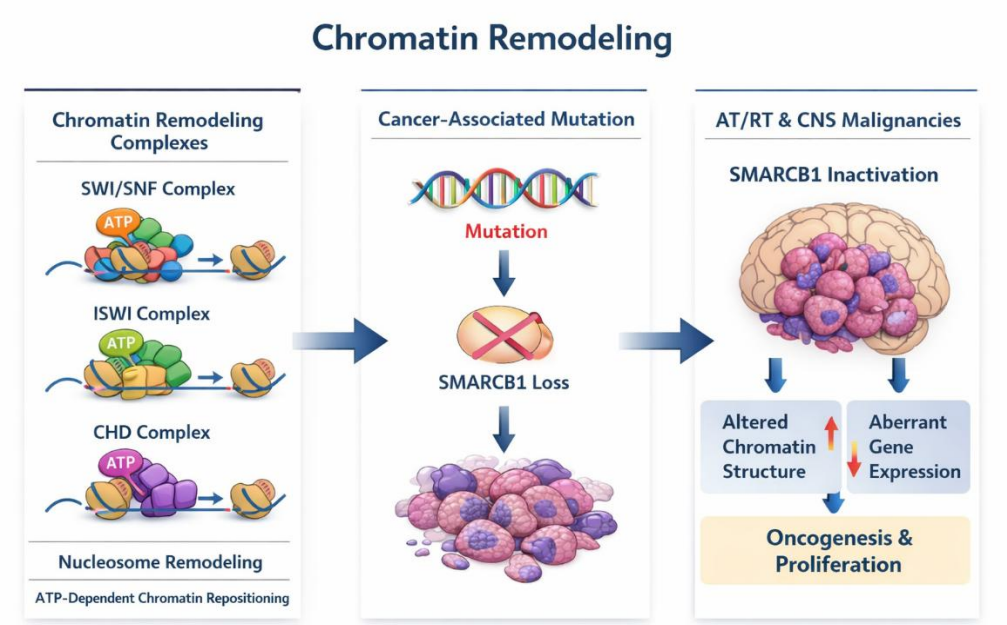
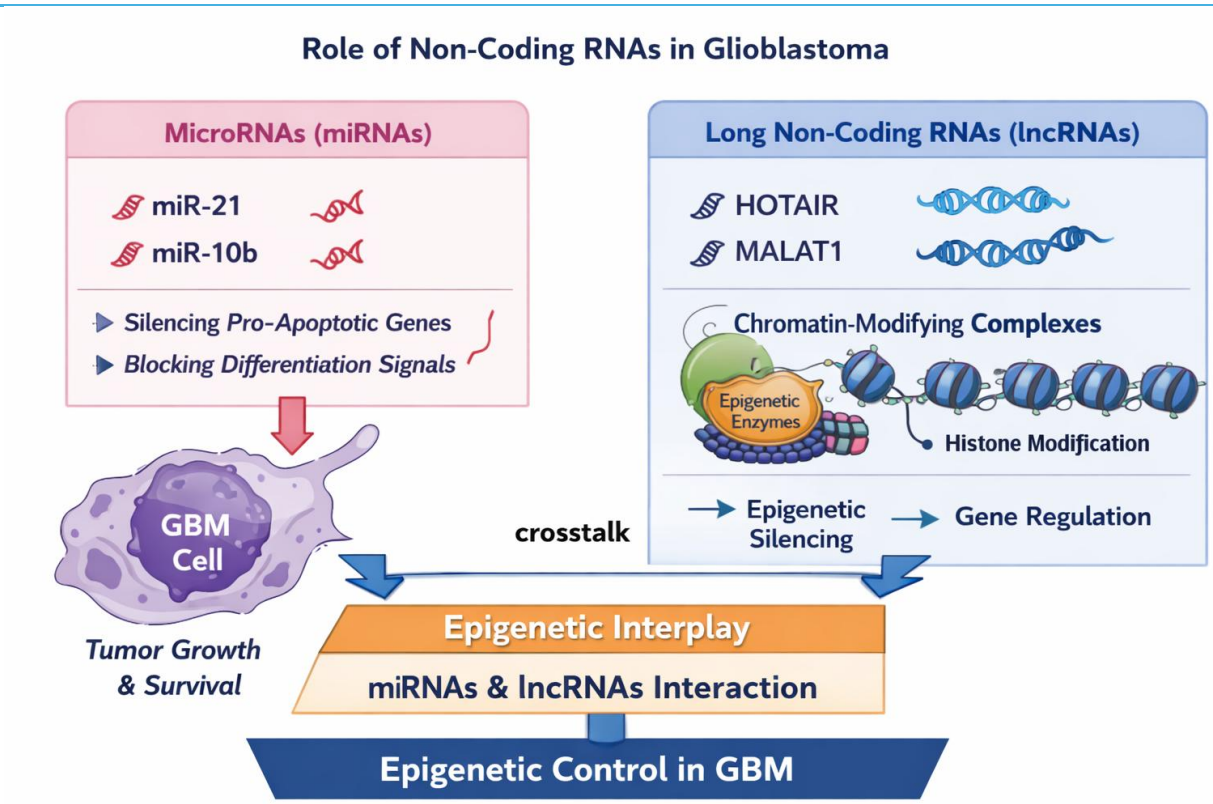


Figure 3 This figure presents a detailed overview of the conceptual and textual framework related to the discussed topic, highlighting key structural elements and organized information within the document. It reflects how complex scientific concepts are systematically arranged to support clarity, coherence, and logical progression in academic writing. The layout emphasizes the importance of structured presentation in effectively communicating research findings and theoretical insights.

2.4 Non-Coding RNAs

Epigenetic regulation has another dimension in non-coding RNAs, especially miRNAs (miR-21 and miR-10b) and long non-coding RNAs (lncRNAs) which are always upregulated in GBM and they silence pro-apoptotic and differentiation-related transcripts. LncRNAs, such as those represented by HOTAIR and MALAT1, are molecular scaffolds, recruiting chromatin-modifying complexes to particular genomic loci which allows the long-range epigenetic silencing of genomic loci. The interaction between these RNA species and conventional epigenetic apparatus is a field of research under development.



3. Epigenetic Reprogramming of Cancer Hallmarks

The overlap of these epigenetic processes makes cancer cells develop and maintain hallmark functions. In the CNS, epigenetic reprogramming occurs on a variety of levels:

Proliferative signal transduction and inhibition of growth. *Epigenetic repression of CDKN2A (p16INK4a) and CDKN2B abolishes essential cell-cycle controls. At the same time, persistent mitogenic signaling is caused by hypomethylation of oncogenic promoters such as PDGFRA and EGFR.*

Resistance to cell death*. Apoptotic responses are suppressed by hypermethylation of pro-apoptotic genes like BIM and PUMA by the promoter. Deacetylation mediated by HDAC also inhibits the activity of death receptors, enabling glioma cells to resist intrinsic and extrinsic cues of death.*

Immune evasion*. Epigenetic processes can play a role in the immunologically cold phenotype of GBM. Promoter methylation and histone deacetylation lead to silencing of components of antigen presentation machinery (e.g., B2M, HLA genes) and upregulation of immune checkpoint ligands (e.g., PD-L1) to allow tumors to avoid cytotoxic T-cell responses.*

Therapeutic Resistance *In addition to MGMT methylation, new data point to the involvement of epigenetic plasticity in the acquired resistance to targeted therapies. As an example, EGFR-inhibitor therapy can select subclones that go through chromatin-mediated transcriptional reprogramming to adopt alternative receptor tyrosine kinase dependencies (Nathanson et al., 2014).*

Tumor microenvironment interactions. *Reciprocal epigenetic crosstalk between cancer cells and stromal components—including microglia, astrocytes, and infiltrating immune cells—shapes the CNS tumor microenvironment. Tumor-derived factors induce epigenetic changes in microglia that convert them from surveillant to tumor-promoting phenotypes, illustrating the systemic nature of epigenetic reprogramming.*

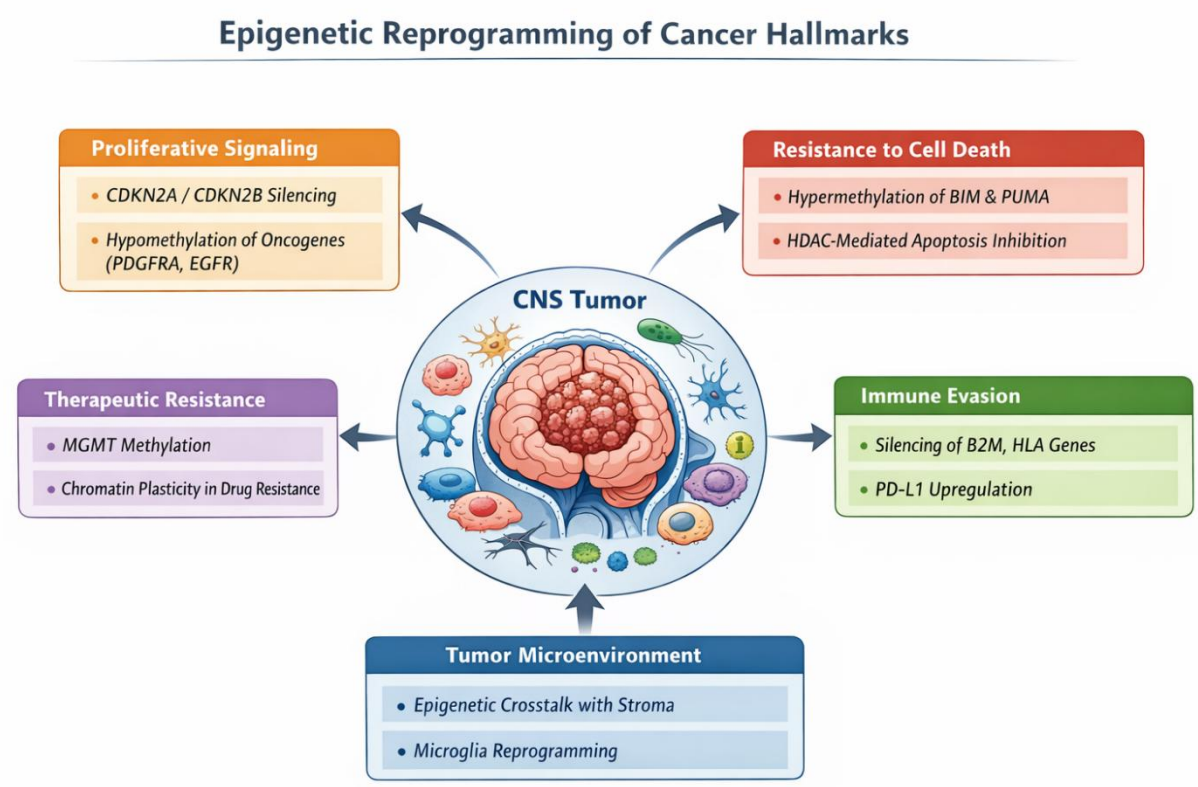


Figure 4: Epigenetic reprogramming plays a central role in shaping key cancer hallmarks within central nervous system (CNS) tumors. Through mechanisms such as DNA methylation, histone modification, and chromatin remodeling, tumor cells acquire sustained proliferative signaling, evade apoptosis, and escape immune surveillance. Silencing of tumor suppressor genes (e.g., CDKN2A/CDKN2B) and activation of oncogenic pathways (e.g., EGFR, PDGFRA) promote uncontrolled growth, while repression of pro-apoptotic factors (e.g., BIM, PUMA) enhances survival. Additionally, epigenetic alterations contribute to immune evasion by downregulating antigen presentation machinery and upregulating immune checkpoint molecules such as PD-L1. These dynamic changes also drive therapeutic resistance and facilitate complex interactions with the tumor microenvironment, including modulation of microglia and other stromal cells. Collectively, these interconnected processes highlight the pivotal role of epigenetic regulation in tumor progression and adaptation.

3. Therapeutic Strategies Targeting Epigenetic Machinery

Epigenetic modifications are also interesting drug targets because they are reversible. A number of epigenetic agent classes have been subjected to clinical neuro-oncology trial with both encouraging and discouraging outcomes.

4.1 DNA Methyltransferase Inhibitors

Nucleoside analogs of azacitidine and decitabine, which enter the DNA and covalently bind DNA methyltransferases (DNMTs), have also shown effects in hematologic malignancies. Preclinical trials in gliomas have indicated that low doses of DNMT inhibitors could re-express silenced tumor suppressors, and increase response to temozolomide. In solid tumors, however, clinical translation has been hampered by toxicity, problems with pharmacokinetics and absence of strong predictive biomarkers.

4.2 Histone Deacetylase Inhibitors

Vorinostat and panobinostat are HDAC inhibitors that have been tested in recurrent GBM. Although preclinical evidence indicates that these agents are capable of causing differentiation, inducing apoptosis and being complementary to radiation, phase II trials

have produced modest single agent activity. It is important to note that panobinostat, a pan-HDAC inhibitor panobinostat has shown preclinical efficacy in H3K27M-mutant diffuse midline gliomas, and is currently undergoing clinical trials in children (Grasso et al., 2015). The heterogeneity of isoform functions of HDAC and the necessity of multiple approaches is still a burning issue.

4.3 Combination Strategies

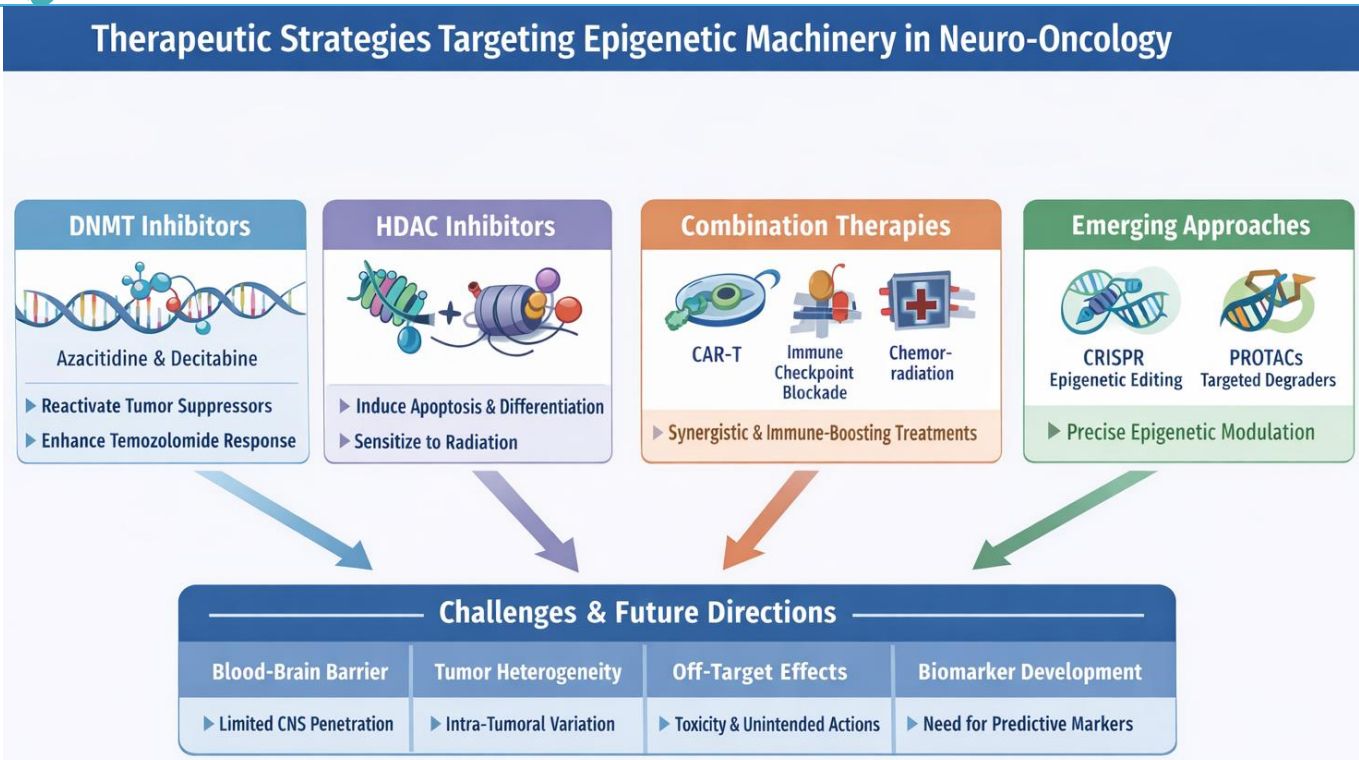
The use of epigenetic agents together with standard treatments is why the rationale is great. It is possible that epigenetic modulators prepare tumors by reinstating silenced drug transporters, increasing antigen presentation or bypassing adaptive resistance. Combinations of DNMT or HDAC inhibitor with immune checkpoint blockade, CAR-T cells and conventional chemoradiation are also being tested. Emerging evidence indicates that epigenetic priming has the potential to enhance tumor immunogenicity, and that optimal schedules of dosing and choice of patient needs optimization.

4.4 Emerging Approaches: Epigenetic Editing and Targeted Degraders

In terms of small-molecule inhibitors, the next-generation approaches should target locus-specific epigenetic regulation. CRISPR-based systems coupled with histone-modifying or DNA-methylating domains CRISPR-dCas9-based systems are capable of performing a precise reprogramming of a single locus and have the potential to reverse aberrant epigenetic states without global toxicity. Also, proteolysis-targeting chimeras (PROTACs) which degrade individual epigenetic writers, erasers or readers are in preclinical development, with potential to be more specific and long-lasting in target inhibition.

4. Challenges and Future Directions

Although the progress is enormous, a number of challenges hinder the translation of epigenetic therapy in neuro-oncology: Penetration of the blood-brain barrier. The penetration of many epigenetic agents in the CNS is limited and thus rational drug development or alternative delivery routes like convection-enhanced delivery or nanoparticle development need to be considered. Tumor heterogeneity. Genetic heterogeneity of subclones in a single tumor is complicated by the fact that organisms can harbor genetically and epigenetically different subclones, and in this case, monotherapy is impossible. It will be necessary to implement comprehensive single-cell epigenomic profiling to map the approach of intra-tumoral epigenetic variation and detect shared vulnerabilities. Off-target effects and poisoning. Global epigenetic modulators are associated with the risks of unwanted gene activation such as the possibility of oncogene up-regulation or immune dys-regulation. The crucial aspect of enhancing the therapeutic windows will be the development of isoform-selective inhibitors and locus-specific editing tools. Biomarker development. Predictive biomarkers to stratify patients are yet to be developed. As shown by MGMT, methylation profiling needs to be extended to encompass more broad epigenetic signatures that reflect tumor sensitivity to particular agents. In the future, this combination of epigenomic profiling with sensors of sophisticated neuroimaging and liquid biopsy techniques will have the potential of making epigenetic statuses monitored in real-time and used to modify therapeutic treatment plans.



5. Conclusion

Epigenetic processes are not just passengers of the malignant transformation process, but active reprogrammers that allow cancer cells to evade the single specifications of CNS microenvironment. Since the epigenome is composed of DNA methylation and histone changes to chromatin restructuring and non-coding RNAs, these modifications determine an expression program that maintains proliferation, resistance, and immune evasion. Given the highly heterogeneous nature of neuro-oncology tumours and the fact that treatment choices are still limited, the reversibility of epigenetic changes is an attractive treatment method. The way forward will involve a concerted effort to generate CNS-penetrant, isoform-specific epigenetic modulators; to synergize these agents with other modalities; and to find strong biomarkers that will allow these agents to be used more precisely. With the expansion of our knowledge of epigenetic plasticity, so does the possibility of re-programming cancer cells into a state of normalcy- an aim that is at the core of future neuro-oncology.

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