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REVIEW

Targeting epigenetic remodeling of the blood-brain barrier: current knowledge for drug therapy

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ABSTRACT

The blood – brain barrier (BBB) is a dynamic regulator of brain homeostasis, and its dysfunction is a hallmark of many neurological and psychiatric disorders. Yet, in most conditions, the causal relationship between BBB injury and disease progression remains unclear, as shared systemic risk factors, such as inflammation, infection, oxidative stress, and genetic predisposition, produce highly variable patterns of barrier disruption. Epigenetic mechanisms, including DNA and RNA methylation, histone modifications, chromatin remodeling, and noncoding RNAs, have emerged as key regulators of BBB integrity. Their dysregulation contributes to pathological BBB remodeling in disorders such as cerebrovascular and neurodegenerative diseases, promoting a decline in barrier function (structural and biochemical) and accelerating disease progression. Owing to their reversible nature, epigenetic modifications represent promising therapeutic targets, and their disease-stage-specific patterns offer potential as biomarkers for BBB injury and recovery. This review summarizes current knowledge on how epigenetic processes drive BBB dysfunction and highlights emerging epigenetic signatures with diagnostic and therapeutic relevance across neurological and psychiatric diseases.

PLAIN LANGUAGE SUMMARY

The blood-brain barrier (BBB) is a dynamic interface that maintains the brain's stable internal environment by precisely controlling the exchange of molecules between the bloodstream and the central nervous system. Its dysfunction is a hallmark of many neurological and psychiatric disorders, often driven by factors like inflammation and oxidative stress that disrupt this delicate balance. Emerging research indicates that these disruptions are governed by epigenetic mechanisms, such as DNA methylation and chromatin remodeling, that regulate gene activity without changing the underlying DNA code. While these epigenetic processes normally maintain the barrier's structural and biochemical integrity, their dysregulation can weaken the interface and accelerate disease progression. Critically, because epigenetic modifications are reversible, they represent a promising frontier for therapy; unlike fixed genetic mutations, these molecular signals can potentially be "reset" to restore barrier function. By identifying these unique epigenetic signatures, scientists can develop new biomarkers to diagnose brain injury earlier and monitor recovery more accurately, paving the way for targeted, stage-specific treatments for a wide range of complex brain diseases.

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1. Introduction

The blood-brain barrier (BBB) is a major gatekeeper of brain homeostasis. Situated at the interface between blood and brain, the BBB can sense events in both compartments and dynamically adapt to protect and maintain brain function. Beyond cerebrovascular disorders, various neurological (e.g., Alzheimer's disease, epilepsy, traumatic brain injury) and psychiatric conditions (e.g., depression and bipolar disorder) have a substantial vascular component in their pathogenesis that can initiate and/or exacerbate disease progression. However, in most of these conditions, there is a blurred line between the cause and effect of the BBB injury. For instance, numerous neurological disorders share systemic risk factors and pathological mechanisms that can disrupt the BBB, such as infection, inflammation, genetic predisposition, and oxidative stress [1,2]. This shared etiology contributes to substantial variability in BBB injury, even when common mechanisms and factors are at play. An additional layer of complexity in BBB remodeling is added by bidirectional, self-reinforcing interactions between BBB dysfunction and, for example, neuroinflammation, which accelerate brain damage. Addressing such complexities is crucial to developing therapies that prevent or mitigate disease progression by targeting the BBB. Despite extensive research, reliable biomarkers for the different stages of BBB injury remain lacking, and the fundamental processes that mediate and regulate BBB remodeling in neurological diseases remain unknown.

Over the past two decades, epigenetic mechanisms have emerged as a molecular basis for a variety of developmental and neurological disorders. Epigenetic processes, including DNA methylation, histone modifications, chromatin remodeling, and noncoding RNAs, are essential for maintaining BBB integrity and function without altering the DNA sequence [3]. In neurological and psychiatric disorders, dysregulation of these mechanisms

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Article highlights

- BBB dysfunction is a common feature of many CNS diseases.
- Systemic risk factors drive variable and disease-specific patterns of BBB disruption.
- Epigenetic mechanisms are key regulators of BBB integrity and remodeling.
- Dysregulated epigenetic signaling promotes barrier breakdown, inflammation, and impaired repair.
- Reversible epigenetic changes offer promising biomarkers and therapeutic targets.

promotes pathological BBB remodeling, leading to increased permeability, neuroinflammation, and disease progression [3–7]. Owing to their reversibility, epigenetic modifications are promising therapeutic targets for restoring BBB function. Furthermore, as specific epigenetic factors/profiles may reflect disease stages, they may also serve as robust biomarkers of BBB injury and recovery throughout disease progression [5,6]. This review will summarize current knowledge of basic epigenetic mechanisms underlying BBB dysfunction in neurological and psychiatric conditions, highlighting recent work on how epigenetic modifications, primarily DNA and RNA methylation, histone modification, as well as ncRNA, drive BBB injury and identifying specific epigenetic profiles that can serve as biomarkers for disease initiation and progression, as well as valid therapeutic targets.

2. Blood–brain barrier: structure and function

The BBB is a highly specialized structural (physical), biochemical (transport and metabolic), and immunological barrier formed by the brain capillary bed that tightly regulates the penetration of molecules into the brain. Its primary functions are to maintain ionic and metabolic homeostasis and to protect neural tissue from toxins and pathogens. Structurally, the BBB consists of brain capillary endothelial cells (EC) with unique barrier properties, supported by perivascular cells, including pericytes and astrocytes, which envelop the abluminal capillary surface and provide stability and regulation [8,9].

Pericytes and astrocytes are essential for BBB integrity and function. Pericytes act as chemical sensors that mediate communication between EC and parenchymal cells and regulate cerebral blood flow, BBB integrity, vasculogenesis, angiogenesis, neurovascular coupling, and neuroinflammation [10,11]. Astrocytes, through their perivascular end-feet, regulate endothelial permeability and repair, pericyte recruitment, cerebral blood flow, angiogenesis, inflammation, metabolism, and water homeostasis [8,11,12]. Together with neurons, microglia/macrophages, and extracellular matrix components, these cells form the neurovascular unit (NVU), which coordinates neurovascular coupling and regional cerebral blood flow [11].

The defining feature of the BBB is the presence of highly specialized brain ECs that form a restrictive physical and metabolic barrier. These cells exhibit exceptionally high electrical resistance (~1500–2000 $\Omega{\cdot}cm^2$), compared with peripheral endothelium (~33 $\Omega{\cdot}cm^2$), reflecting minimal paracellular permeability [13]. This is achieved through complex intercellular junctions – tight junctions (TJs), adherens junctions (AJs), and gap junctions (GJs) – that resemble epithelial barriers more than peripheral vascular ECs [14]. TJs are the primary determinants of BBB impermeability and consist of transmembrane proteins (occludin, claudin −1,3,5,11,12 and junctional adhesion molecules), scaffolding proteins (e.g., ZO-1, ZO-2, ZO-3, Par3/6, afadin), and the actin cytoskeleton [15–18]. Claudin-5 is particularly critical for sealing the paracellular space [14]. The cytoskeletal complex regulates junctional stability, mechanosensing, and mechanotransduction by generating centripetal tension that influences TJ adhesion [14,19,20]. AJs, composed of VE-cadherin and associated catenins, support barriergenesis, regulate TJ formation, and maintain endothelial permeability via outside – in signaling [14,21]. GJs, formed by connexins (Cx37, Cx40, C×43 in ECs; C×43 and C×30 in astrocytes and pericytes), facilitate intercellular communication and contribute to barrier homeostasis, although they are not primary physical barrier components [22–24].

Because paracellular diffusion is highly restricted, molecular exchange across the BBB relies on transcellular pathways, which include energy-dependent processes (i.e., receptor-mediated, adsorptive, and caveolae-associated transcytosis) and energy-independent transcytosis (i.e., passive diffusion for lipophilic molecules, facilitated diffusion) [25,26]. The energy-dependent processes are tightly regulated and occur at much lower rates than in peripheral endothelium, providing an additional layer of selectivity [9].

The BBB also functions as a biochemical barrier through selective carrier-mediated transport systems. Influx transporters deliver essential nutrients such as glucose (GLUT1), amino acids (LAT1, CAT1), monocarboxylates (MCT1), nucleosides, and creatine [27,28]. Efflux transporters remove neurotransmitters, metabolites, and toxins, maintaining neural homeostasis [29]. Notably, ATP-binding cassette (ABC) transporters, including *P*-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and MRPs, play a critical role in both neuroprotection but also drug efflux, a major therapeutic obstacle [29–33]. Such transporters in endothelial and parenchymal cells contribute to multidrug resistance. As a metabolic barrier, brain endothelial cells express a diverse array of enzymes that metabolize neurotransmitters, xenobiotics, and pharmacological agents. Brain ECs also have enzymes contributing to a metabolic barrier. Enzymes like Monoamine Oxidase (MAO) and Catechol-O-methyltransferase (COMT), degrade neurotransmitters, γ-glutamyl transpeptidase regulates amino acid and glutathione metabolism, while various cytochrome P450 detoxify xenobiotics and pharmacological agents [9,34,35] (Figure 1).

3. BBB in neurological disease: what is altered and how

BBB dysfunction is a central contributor to the initiation and progression of many neurological disorders. A hallmark pathological feature is decreased BBB integrity, leading to increased permeability and uncontrolled exchange between blood and brain. This allows the entry of potentially harmful blood-derived molecules and immune cells into the brain parenchyma [1,27]. Notably, the extent of BBB disruption is a dynamic

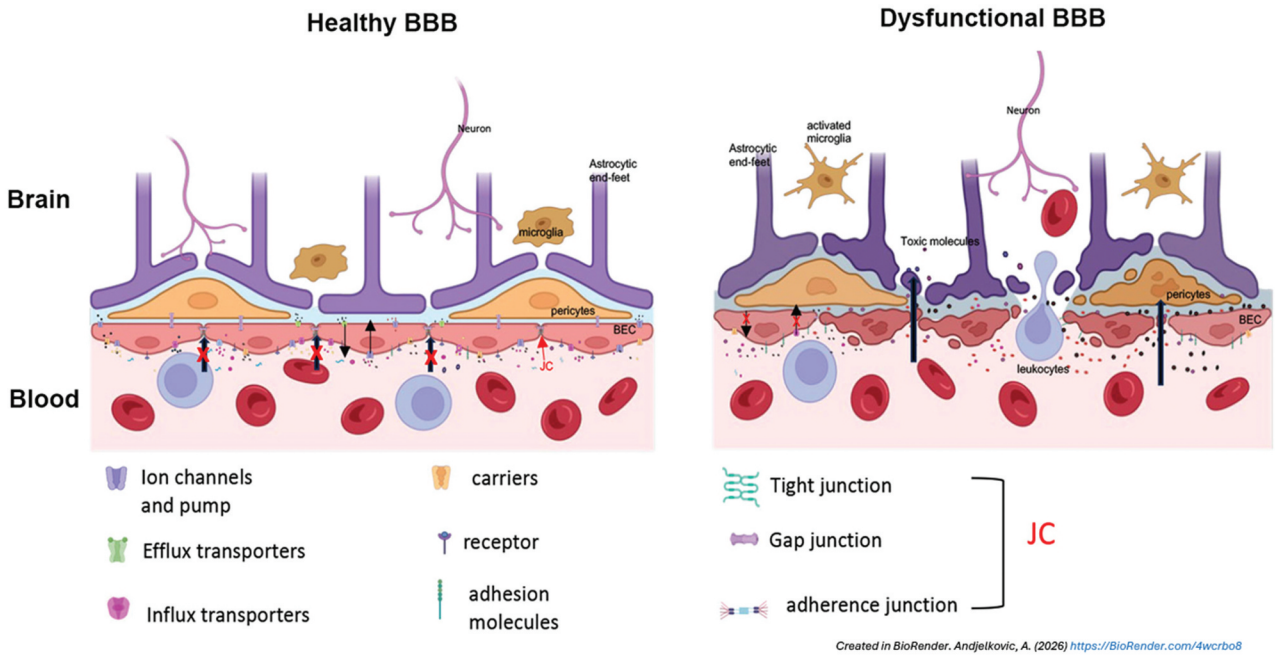

Figure 1. Schematic representation of a healthy versus dysfunctional BBB. In the healthy BBB, intact junctional complexes (JC) restrict paracellular transport, while regulated transcellular exchange is mediated by influx (GLUT-1) and efflux (P-glycoprotein) transporters, receptors, and carrier systems. In contrast, BBB dysfunction is characterized by disrupted junctional complexes, increased paracellular permeability and toxin diffusion, reduced transporter expression, upregulation of endothelial adhesion molecules promoting leukocyte recruitment, loss of interactions with pericytes and astrocytic end-feet, and activation of microglia.

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continuum within individual pathologies rather than being strictly segregated by disease type. For instance, conditions like stroke and traumatic brain injury (TBI) often have an acute, severe BBB breakdown characterized by vasogenic edema and massive cellular infiltration [27,35,36]. That transitions into a phase of chronic, persistent leakage that promotes long-term neurovascular remodeling [37]. However, in neurodegeneration, the barrier may exhibit varying degrees of dysfunction over time, ranging from subtle molecular leakage to more extensive structural failure with disease progression [1,38].

BBB dysfunction arises from impairment of all components of the NVU, including brain ECs, pericytes, and astrocytes. Several shared pathological mechanisms underlie BBB disruption across diseases. These include (i) TJ remodeling, characterized by reduced expression, altered localization, and impaired interactions of junctional proteins, as well as actin cytoskeletal reorganization, leading to paracellular barrier opening; (ii) inflammation, both systemic and local, which promotes TJ disassembly, leukocyte transmigration, and activation and migration of brain-resident immune cells; (iii) oxidative stress, which accelerates degradation of junctional proteins and impairs EC metabolism and viability; and (iv) remodeling of the perivascular environment, including loss or dysfunction of pericytes and astrocytes, compromising structural and functional barrier [27,36,39,40]. Together, these processes form a self-amplifying loop that perpetuates BBB injury and accelerates neuronal damage.

Beyond structural impairment, BBB transport is frequently disrupted. Dysfunction of efflux transporters, may reduce clearance of neurotoxic metabolites and xenobiotics, leading to their accumulation in the brain [27,31]. Concurrently, impairment of influx transporters, including GLUT1, RAGE, and LRP-1, compromises nutrient delivery and metabolic homeostasis, further exacerbating neuronal dysfunction and neuroinflammation [38,39,41] (Figure 1).

Although TJ remodeling, altered vesicular trafficking, transporter dysfunction, and inflammation are common features across neurological diseases, the initiating triggers, temporal dynamics, and molecular drivers differ between conditions, resulting in disease-specific BBB signatures. (Figure 1) Understanding both common and shared and unique mechanisms is essential for developing targeted strategies to protect BBB function or therapeutically modulate its permeability for drug delivery.

4. Epigenetic code and mechanism: a new avenue for understanding BBB dysfunction

The tight modulation of gene expression in physiological and disease conditions also includes a specific epigenetic code. Through key mechanisms such as DNA methylation, histone post-translational modifications (HPTMs), RNA methylation and non-coding RNAs, the epigenetic code effectively acts as a higher-order instruction controlling gene expression [42]. These mechanisms also converge to influence environmental factors (e.g., diet, stress, toxins) on the genome, contributing to the unique pathological profile of diseases [42]. Since epigenetic changes are potentially reversible, they offer a promising avenue for novel therapies.

4.1. Epigenetic mechanisms

4.1.1. DNA methylation

DNA methylation is a fundamental epigenetic modification involving the covalent addition of a methyl group (CH_3) to cytosine residues at CpG dinucleotides, generating

5-methylcytosine (5mC). CpG sites are widely distributed across the genome; approximately 70–80% reside in CpG-poor "open sea" regions and are constitutively methylated to maintain genomic stability. In contrast, CpG-rich regions known as CpG islands (300–3000 bp), located primarily at gene promoters and within gene bodies, are often unmethylated, permitting active transcription [43]. This genomic organization allows DNA methylation to function as a regulatory switch, whereby site-specific methylation patterns govern gene repression or expression [43,44]

Promoter CpG island methylation is typically associated with transcriptional repression through inhibition of transcription factor binding and recruitment of methyl-binding repressor proteins, whereas unmethylated CpG islands promote an open chromatin state and active transcription [43]. In contrast, methylation within gene bodies (exons and introns) is often positively correlated with transcription, particularly in constitutively expressed genes, a phenomenon known as the "DNA methylation paradox" [45]. An additional level of transcriptional modulation is also achieved through DNA methylation of enhancers, which regulate transcription factor binding and enhancer – promoter interactions [46].

DNA methylation is established and maintained by DNA methyltransferases (DNMTs), referred to as "writers" [43]. DNMT1 preserves methylation during DNA replication, while DNMT3A and DNMT3B catalyze de novo methylation at previously unmethylated loci, often in a transcription factor – dependent manner [47,48]. DNMT3L, although catalytically inactive, enhances DNMT3A/3B activity by recognizing unmethylated histone H3 tails [49]. DNMTs repress transcription either directly, by blocking transcription factor binding, or indirectly, by recruiting corepressor complexes [50]. Active DNA demethylation is primarily mediated by ten – eleven translocation (TET) enzymes (TET1–3), which oxidize 5mC to intermediate forms, ultimately restoring cytosine via base excision repair involving thymine DNA glycosylase (TDG) [43,51]. Passive demethylation can also occur during cell division through reduced DNMT1 activity [52].

DNA methylation is interpreted by "reader" proteins that translate epigenetic information into functional outcomes. These include methyl-CpG-binding domain (MBD) proteins such as MeCP2, UHRF proteins that recognize hemimethylated DNA, DNMT1-associated complexes, and zinc-finger proteins such as Kaiso, which act as methylation-dependent transcriptional repressors [44,53,54] (Figure 2(A)).

4.1.2. Histone modifications

Histones are evolutionarily conserved basic proteins that package DNA into chromatin. The core histones (H2A, H2B, H3, and H4) assemble into nucleosomes, while linker histones (H1/H5) stabilize higher-order chromatin structure [55]. The N-terminal tails of histones undergo extensive post-translational modifications (PTMs) that dynamically regulate chromatin organization and gene expression [56].

Histone acetylation is dynamically regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HATs catalyze the transfer of acetyl groups from acetyl-CoA to lysine residues, neutralizing positive charges and weakening histone – DNA interactions, thereby promoting transcriptionally active euchromatin [57,58]. Major HAT families include p300/CREB-binding protein (CBP), GCN5 histone acetyltransferase (GNAT), and MYST lysine acetyltransferases [4,58]. HDACs, on the other side, remove acetyl groups, leading to chromatin compaction and transcriptional repression. HDACs are classified into zinc-dependent classes I, II, and IV, and NAD^+ -dependent class III sirtuins [59,60]. The dynamic balance between acetylation and deacetylation is essential for transcriptional control, cellular metabolism, and aging [57,61,62].

Histone methylation is catalyzed by histone methyltransferases (HMTs) using S-adenosylmethionine as a methyl donor and is reversed by histone demethylases (HDMs). Lysine methyltransferases typically contain SET domains, whereas non-SET enzymes target specific histone residues [63,64]. Demethylation is mediated by LSD/KDM1 and Jumonji C (JMJC) domain-containing enzymes [65,66]. The functional outcome of histone methylation depends on the modified residue and methylation state: H3K4me3 marks active promoters, whereas H3K9me2/3 and H3K27me2/3 are associated with transcriptional repression [66]. Enzymes such as KDM6 and KDM5 remove repressive and activating marks, respectively, to fine-tune gene expression [67,68]. Unlike acetylation, histone methylation does not alter charge but instead creates binding sites for reader proteins such as heterochromatin protein 1 (HP1) and Polycomb complexes [53,62,65,69].

Additional histone PTMs include phosphorylation, ubiquitination, as emerging metabolic-linked modifications [56,70]. Histone phosphorylation, regulated by kinases and phosphatases, is involved in transcription, cell-cycle progression, and DNA damage responses; phosphorylation of H2AX (γH2AX) is a key signal for recruitment of DNA repair machinery [71–73]. Histone ubiquitination, primarily targeting H2A and H2B, is mediated by E1–E3 enzyme cascades and reversed by deubiquitinases, regulating transcription and DNA repair through non-proteolytic mechanisms [53,74,75]. More recently described modifications, such as crotonylation, lactylation, and butyrylation, link cellular metabolic states to chromatin regulation, although their precise functions remain under investigation [55].

Histone PTMs are interpreted by specialized "reader "proteins that recognize specific modifications and recruit transcriptional regulators and chromatin remodelers [62]. These include bromodomain proteins that bind acetylated lysines, chromodomain proteins that recognize methylated residues, and BRCT domain proteins that bind phosphorylated histones [53,76]. For example, bromodomain-containing protein 4 (BRD4), along with readers such as HP1 and MDC1, integrates histone modification signals to coordinate gene activation, repression, DNA repair, and inflammatory responses [77] (Figure 2(B)).

4.1.3. Crosstalk between DNA methylation and histone PTMs

DNA methylation and histone post-translational modifications (PTMs) are tightly interconnected through bidirectional crosstalk that stabilizes transcriptional states. Active histone modification, such as H3K4me3, inhibit recruitment of DNMT3A/3B, thereby protecting promoters from DNA methylation [49,78]. In contrast, repressive modifications, including H3K9me2/3, recruit DNMTs via

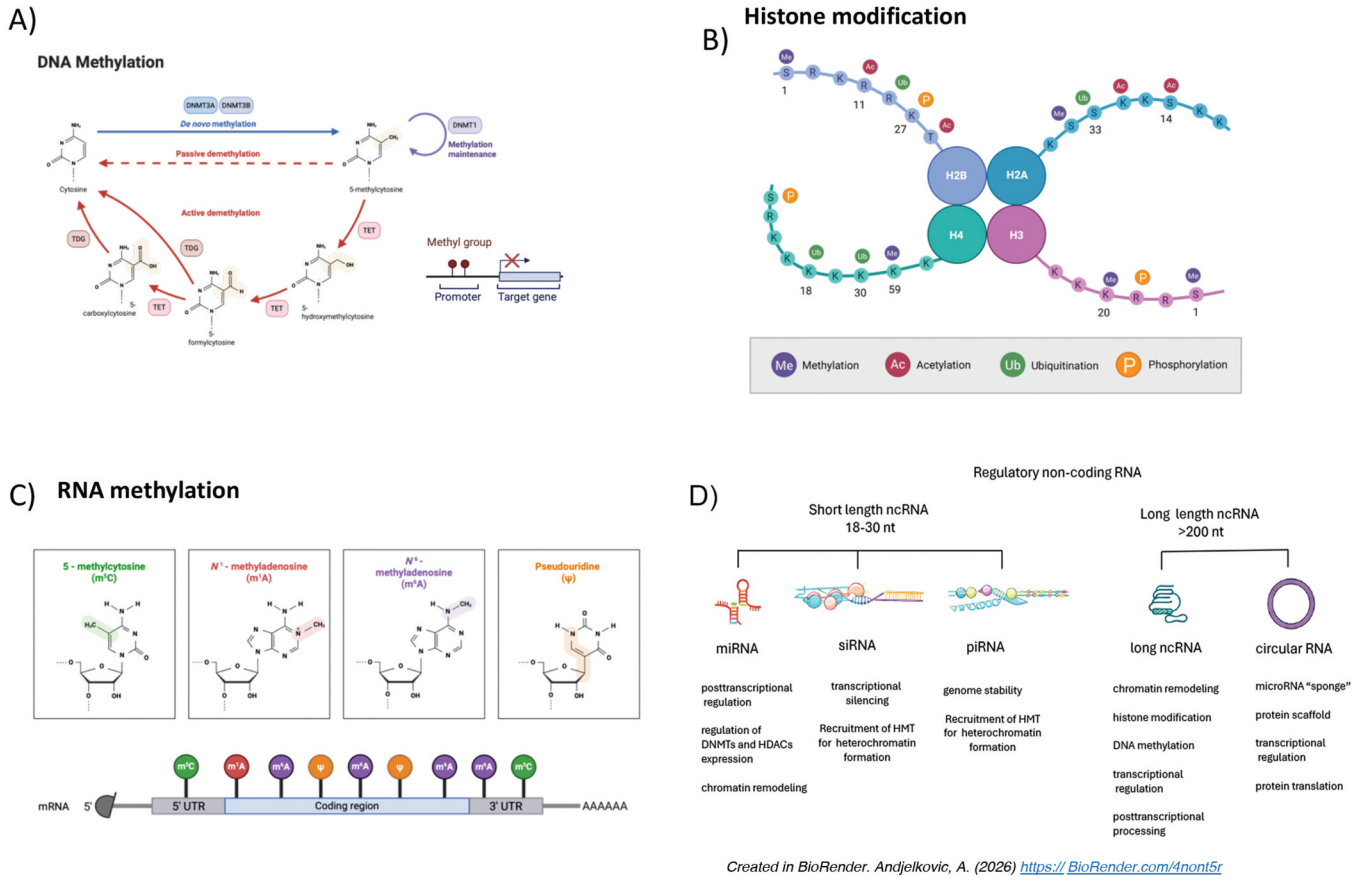

Figure 2. Epigenetic mechanisms. (A) DNA methylation. Cytosine residues are methylated by DNA methyltransferases (DNMTs) to form 5-methylcytosine, primarily at CpG sites, leading to transcriptional repression. Demethylation can occur passively during replication or actively via TET enzymes and base-excision repair pathways. (B) Histone modifications. Post-translational modifications of histone tails – including methylation, acetylation, phosphorylation, and ubiquitination – alter chromatin structure and recruit regulatory proteins, thereby modulating transcriptional activation or repression. (C) RNA methylation. Chemical modifications such as m^6 A, m^5 C, and others are added to RNA by "writer" enzymes, removed by "erasers," and recognized by "reader" proteins, influencing RNA stability, splicing, localization, and translation efficiency. (D) D) non-coding RNA- Schematic overview of non-coding RNAs (ncRNAs). Short ncRNAs include miRNAs, siRNAs, and piRNAs, while long ncRNAs include lncRNAs and circular RNAs. These ncRNAs regulate gene expression through post-transcriptional mechanisms, chromatin and histone modification, and transcriptional control.

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reader proteins such as HP1 and UHRF1, reinforcing gene silencing while gene-body H3K36me3 directs DNMT3A/3B activity to suppress aberrant transcription initiation [62,79]. Conversely, DNA methylation shapes histone landscapes through reader proteins such as MeCP2 and by recruiting histone deacetylases and methyltransferases, promoting chromatin compaction and the formation of stable repressive domains [4,80–82]. This coordinated interplay ensures the long-term maintenance of epigenetic memory and heterochromatin.

4.1.4. RNA methylation

RNA methylation represents an additional epigenetic layer of gene regulation. The most common modifications include N6-methyladenosine (m^6 A), 5-methylcytosine (m^5 C), and N1-methyladenosine (m^1 A) [83]. RNA methylation is dynamically regulated by "writer" complexes, such as the METTL3–METTL14–WTAP methyltransferase complex, "erasers," including fat mass and obesity-associated protein (FTO) and AlkB homolog 5 (ALKBH5), and "reader" proteins that determine RNA fate by modulating transcript stability, splicing, translation, and localization [84,85]. For example, m^6 A readers of the YTH domain family (e.g., YTHDF2) promote RNA degradation, whereas insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) enhance transcript stability [84,86]. RNA methylation also crosstalk with DNA methylation and histone modifications, forming an integrated epigenetic regulatory network [87] (Figure 2(C)).

4.1.5. Non-coding RNA (ncRNAs)

Noncoding RNAs (ncRNAs) constitute a diverse and functional component of the transcriptome that are not translated into proteins but exert broad regulatory control over gene expression, cellular identity, and genomic integrity [88]. ncRNAs are primarily classified into two major groups, housekeeping and regulatory ncRNAs. The former includes ribosomal RNA (rRNA), transfer RNA (tRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNAs). The regulatory ncRNAs – microRNAs, small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), long non-coding RNAs (lncRNAs),

and circular RNAs (circRNAs)- exert critical control over transcriptional, post-transcriptional, and epigenetic processes [89].

LncRNAs (over 200 nucleotides) are the most diverse group of epigenetic regulators [90]. They are generated from various genomic regions (intergenic, intronic, or enhancer loci) by RNA Polymerase II and processed via canonical (i.e., capping, splicing,) or non-canonical processing (i.e., snoRNA-capping, circularization), to ensure stability and specific subcellular localization [90,91]. LncRNAs exert critical control over transcriptional, post-transcriptional, and epigenetic processes by regulating DNA methylation through interactions with DNMTs, chromatin modification via recruiting histone-modifying complexes and chromatin reorganization [90,91]. piRNAs (24–32 nucleotides) primarily function in genome defense by guiding PIWI proteins to transposable elements, inducing DNA methylation and repressive histone modifications to maintain genomic integrity and epigenetic memory [92]. SncRNAs include microRNAs (miRNAs, ~22 nucleotides), generated through a canonical biogenesis pathway (Drosha-DGCR8 complex and Dicer) involved predominantly in post-transcriptional gene silencing in the cytoplasm [93]. miRNAs classically known for post-transcriptional gene silencing, also influence epigenetic regulation by targeting enzymes involved in DNA methylation and histone modification and, in some cases, by directly modulating transcriptional activity within the nucleus [93,94]. circRNAs, generated through back-splicing, are highly stable ncRNAs that contribute to epigenetic regulation by modulating DNA demethylation, histone modification, and RNA methylation, while also acting as miRNA sponges and protein scaffolds that fine-tune gene regulatory networks [95] (Figure 2(D)).

5. Epigenetic profile BBB in neurological disease and conditions

Growing evidence indicates that epigenetic dysfunction is a critical contributor to the onset and progression of numerous neurological and psychiatric disorders [96,97]. These epigenetic alterations affect gene-expression programs essential for neuronal function and survival, thereby linking genetic susceptibility to environmental influences [96,97]. BBB dysfunction is closely implicated in the pathogenesis of these disorders, and emerging studies indicate that epigenetic dysregulation is also mirrored within the BBB and the neurovascular unit (NVU) [4–6]. This section reviews current knowledge of epigenetic changes at the BBB in neurological and psychiatric disorders, highlighting the contribution of vascular factors to these disorders and identifying potential new therapeutic targets and strategies for their treatment. As non-coding RNA also includes microRNA regulation, which is the subject of several extensive reviews, we will focus here only on the effect of long non-coding RNA and circular RNA, an emerging area of BBB research [98–100]. The pathological signs of BBB impairment and epigenetic changes are summarized in Table 1.

5.1. Cerebrovascular disease: stroke and brain vascular malformations

5.1.1. Stroke

In recent decades, the role of the epigenome and related epigenetic modifications in stroke pathogenesis has emerged as a critical field of research. Both DNA methylation and histone modification play dual roles in ischemic and hemorrhagic stroke, exacerbating secondary brain injury (inflammation and cell death), but also being critical for repair [101,102].

Accumulating evidence suggests that epigenetic mechanisms orchestrate distinct molecular signatures across the temporal stages of BBB injury in stroke. The acute phase is primarily defined by the loss of tight junction proteins, (claudin-5 and occludin) and transporter and pump dysregulation (P-gp, Na±K+ ATPase, EAAT2/Glt2, and Glut1) [27,36,103]. These changes, coupled with a neuroinflammatory surge in MMP9 activation, the upregulation of cytokines (TNF-α, IL6, IL1β) and adhesion molecules (ICAM-1, VCAM-1), drive cytotoxic edema and hemorrhagic transformation [36]. The chronic phase transitions toward BBB recovery and tissue remodeling, characterized by angiogenesis with immature junctions, pericyte loss, as indicated by increased soluble PDGFRβ, and extracellular matrix remodeling [37,40]. However, this phase often harbors persistent inflammation, characterized by sustained elevations in VCAM-1 and ICAM-1 [5,104,105].

DNA methylation is directly involved in BBB structural decline after stroke, leading to hyperpermeability. This occurs through the control of junctional gene expression (TJ and AJ proteins), cytoskeletal reorganization, and associated signaling pathways that disassemble junctions [106]. An imbalance between "writers" (DNMTs) and "erasers" (TET dioxygenases) is strongly linked to post-stroke TJ decline. Recent studies using brain ECs and in vivo middle cerebral artery occlusion models demonstrate that oxidative inhibition of TET2 activity at the *ZO-1* promoter, alongside increased DNMT activity, reduces the expression of ZO-1 and VE-cadherin, thereby increasing BBB permeability [106,107]. In mouse thromboembolic stroke models, decreased transcript expression of claudin-5 and occludin, as well as cytoskeletal component ezrin, was associated with hypermethylation of promoters and gene bodies retrospectively [6]. Furthermore, hypermethylation of the tissue inhibitor of metalloproteinase 2 (*TIMP2*) gene promoter disrupts the balance with matrix metalloproteinase-9 (MMP-9), leading to degradation of TJ proteins and the extracellular matrix [108]. Epigenetic control extends to other components of the NVU, such as pericytes, where DNMT/TET imbalances affect PDGFRβ signaling, a critical factor for pericyte-EC crosstalk and vessel stability [101].

DNA methylation after stroke significantly impacts various transporters and ion channels. For instance, decreased DNA methylation in the promoter region of the NKCC1 gene in damaged cortex increases its expression, leading to brain edema [109]. Hypermethylation and subsequent downregulation of the *EAAT2* promoter on astrocytes lead to excitotoxicity [110]. Hypermethylation of the ferroportin promoter on astrocytes modifies iron transport, showcasing cell-type differences in methylation within the NVU [111]. Altered methylation has also been reported in ion channels (K^+ and

Table 1. BBB and epigenetic signature of the injury in various neurological and psychiatric disorders.

Disease	Permeability, Tight Junction (TJ) characteristics	Key transporter alterations	Inflammation /other injury markers	Epigenetic alteration	
Alzheimer's Disease	Leaky barrier, cldn5↓, ocln↓, ZO-1↓	LRP-1↓ P-gp↓, Glut1↓	MMP9↑, MMP2↑, PAR-1↑, ICAM-1↑, VCAM-1↑, PDRGRβ↓, osteopontin ↑ BACE1↑	DNA methylation ↓ (BACE1, PSEN1), ↑ (cldn5, APP, LPR1), H4K16ac↓, H3K9me2↑, H3K27ac↑, HDAC1↑, HDAC3↑ CircDENND1B↑	[38,96,146,151,156–159]
Parkinson's Disease	Leaky barrier, cldn5↓, ocln ↓	SLC7A5↓, P-gp ↑ (early), ↓ (late) BCRP↑	NF-kB/TNF-a↑	DNA methylation ↓ (*SNCA*, *CYP2E1*) circFTO↑, lncRNA AL049437 ↑	[1,5,168]
Ischemic Stroke	Hyperpermeability (acute), leaky chronic cldn5↓, ocln ↓, ZO-1↓, actin cytoskeletal protein ↑, Ve-cadherin↓	P-gp↑, Na±K+ ATPase↓, EAAT2/GLt2↓ Glut1↓, Slc40a1↓	MMP9↑, MMP3↑, TIMP↓, ICAM-1↑, VCAM-1↑, cytokines (IL1β↑, TNF-α↑, IL6) ↑, sPDRGRβ↑, VEGF↑	DNA methylation ↑ (cldn5 ocln, TIMP2, EEAT2,SLC40a1) HDAC1↑, HDAC3↑, HDAC6↑ METTL3↑ circDLGAP4↓	[27,36], [101,106], [113–115], [119,124]
Vascular Dementia	Leaky barrier, cldn5↓, ocln ↓, ZO-1↓,	LRP-1↓ P-gp↓, Glut1↓	MMP9↑, MMP3↑, TIMP2↑, BDNF↓, VCAM-1↑, JAM-A↑	DNMT1↑, DNMT3a↑, HDAC1↑, HDAC3↑, HDAC6↑ H3K27ac↓, circDENND1B↑	[113,120], [161,163–165,167]
Epilepsy	Leaky barrier cldn5↓,	Kir4.1 ↓, GluR2↓, P-gp↑, ABCC1/2↑, MCT1↓, MCT2↓	*BDNF*↑, IL10↓, IL6↓, E-selectin ↓, AQP4↓	DNA methylation ↑(ABCB1) ↓(Cldn5, GLUT1), ↑HDAC1-4, ↓H3K27me3, ↑H3k9ac, ↑H3K4ac, ↑circPTPN4	[175–177]
Traumatic Brain Injury	Leaky barrier to hyperpermeable barrier cldn5↓, pericyte ↓	Increased transcytosis and general breakdown of selective transport mechanisms	MMP9↑, IGF-1B↑	Global DNA methylation, HDAC1↑, HDAC2↑, H3K9ac,↑ H3K14ac↑, circLphn3↓, circPtpn14↑	[86], [170–173]
Brain Vascular Malformations	Hyperpermeability, cldn5↓, ocln ↓	P-gp↓, Glut1↓, ALPL↓,	NF-κB↑, IL-6↑, TNF-α↑, VEGF↑, PDGF, ↑ MTA1 ↑	DNA methylation ↓ (MTA1 and ↑(PTEN), HDAC2↑, H3K27me3↓, METTL3↓, ENST00000423394 ↓	[23,129,134,138], [140]
Schizophrenia Bipolar disorder	Leaky barrier, cldn5↓, ocln ↓	P-gp↑, Glut1↓	MMP9↑, IL1β↑, TNF-α↑, IL6) ↑	DNA methylation ↓ (MMP9), H3K27me3↑, H3K27ac↓, HDAC1↑, HDAC2↑, ↓Circ-FoxO3 and ↑MALAT1	[144], [180–183]

Summary of BBB dysfunction and epigenetic alterations across neurological and psychiatric conditions. The pathological features include alterations in tight junction protein expression, BBB permeability, transporter/receptor expression, an inflammatory endothelial profile, and disease-specific epigenetic mechanisms (DNA and RNA methylation, histone modifications, and non-coding RNA) that contribute to barrier dysfunction.

Abbreviations: Cldn5 - claudin-5; ocln - occludin; ZO-1 - zonula occludens-1; GLUT - 1-glucose transporter 1; LRP - Low-density lipoprotein receptor-related protein 1; P-gp - P-glycoprotein; MMP - matrix metalloproteinase –2 (MMP2), –3 (MMP3), –9 (MMP9); TIMP - Tissue Inhibitor of Metalloproteinases. ICAM-1 - Intercellular Adhesion Molecule-1; VCAM-1 - vascular cell adhesion molecule-1; PDGFβ - platelet-derived growth factors-β; VEGF - Vascular Endothelial Growth Factor; BACE1 - beta-site amyloid precursor protein cleaving enzyme 1; PSEN1 - Presenilin 1; NFκB - Nuclear Factor kappa-B; IL6 - Interleukin6; IL1β - interleukin1β; TNF-α - tumor necrosis factor-α; MCT1 - Monocarboxylate transporter-1; MCT2 - Monocarboxylate transporter-2; MTA1 - metastasis-associated protein 1; BDNF - Brain-derived neurotrophic factor; IGF-1B - Insulin-like Growth Factor 1; AQP4 - Aquaporin-4.

Ca^{2+} channels), receptors (LPR), and the efflux transporter *P*-gp [6]. The inflammatory response at the BBB is also under epigenetic control. While direct promoter methylation of ICAM-1/VCAM-1 after stroke is not firmly established, some endothelial adhesion-related genes show methylation changes with ischemia [67].

It is important to underline that DNA methylation pattern implies an acute→subacute→chronic trajectory, with early methylation change linked to acute ischemic stress and promoter hypermethylation (e.g., thrombospondin-1) with reversion after reoxygenation, and different methylation landscape in subacute and chronic phase associated with epigenomic remodeling during repair and maladaptive remodeling [112].

Similarly, histone modification modulates BBB stability after ischemic injury by integrating inflammatory and metabolic cues that determine TJ expression and endothelial permeability. Class I/II histone deacetylases (HDACs) play a complex regulatory role; while dysfunction of HDAC1 increases MMP activity and junction loss, selective inhibition of preserves barrier integrity and reduces edema [113,114]. Conversely, HDAC4 has been reported to protect the BBB via elevation of TJ proteins and reduction of NADPH oxidase and MMP-9 [115]. A novel finding highlights metabolic-epigenetic crosstalk, where β-hydroxybutyrate increases H3K9ac at the *ZO-1* promoter to upregulate ZO-1 and promote BBB repair [103]. Histone methyltransferases also contribute; Smyd2 promotes BBB breakdown, while inhibition of G9a and DNMT1 reduces infarct size [67,116]. Another example is the histone reader protein (BRD4). BRD4 via Rnf43/β-catenin axis regulates claudin-5 degradation and promotes neurovascular damage. Conversely, inhibiting BRD4 "reseals" the barrier, reduces neuroinflammation, and improves functional recovery after acute brain ischemic injury [117].

RNA methylation, specifically N6-methyladenosine (m^6A), is gaining recognition for its significant role in stroke pathogenesis and BBB integrity [118]. Altered levels of the m^6A methyltransferase METTL3 post-ischemia modulate microglial phenotype, activate the inflammasome, and increase BBB permeability via MMP3 expression [119]. "Reader" proteins also regulate BBB function: IGF2BP1-3 enhances stability and translation of growth factor mRNAs (like VEGF) to potentially aid repair, while YTHDF2 readers accelerate degradation of target m6A-modified mRNAs, impacting their overall stability and function [120,121].

ncRNAs, particularly lncRNAs and circular RNAs, have also emerged as potent regulators of cerebral ischemia/reperfusion (I/R) injury. LincRNA-p21 maintains BBB integrity during cerebral I/R injury by inhibiting autophagy-dependent degradation of occludin via the PI3K/AKT/mTOR signaling pathway, and VE-cadherin degradation by binding with miR-101-3p [122]. Another lncRNA, MALAT1 is involved in oxidative stress, neuroinflammation, cell death signaling, BBB dysfunction, and angiogenesis following ischemic stroke [123]. One of the functions of circular RNAs is to act as molecular sponges for miRNAs, preventing them from binding to target mRNAs. CircDLGAP4 ameliorates ischemic stroke outcomes by functioning as a miR-143 sponge, inhibiting miR-143 activity, endothelial-mesenchymal transition (EndoMT) and BBB damage in stroke models [124]. Furthermore, multiple circRNAs, including circ-FoxO3, circHECTD1, circSRRM4, circOGDH, circCdr1as, and circANAPC7, attenuate BBB damage by inducing autophagy and maintaining EC homeostasis, promoting cerebrovascular repair, and modulating inflammatory responses during I/R injury [125,126]. Beyond acting as miRNA sponges, circRNAs CircUCK2 interact directly with RNA-binding proteins to regulate EndoMT and BBB function in the chronic phase of stroke [127,128].

5.1.2. Brain vascular malformations

The BBB is compromised in various brain vascular malformations (BVMs), including brain arteriovenous malformations (bAVM), cerebral cavernous malformations (CCMs), and hereditary hemorrhagic telangiectasia (HHT). This dysfunction manifests as a structurally deficient, hyperpermeable barrier (decreased claudin-5 and occludin), stemming from BBB destabilization, loss of pericyte coverage, defective angiogenesis (VEGF-PDGF signaling), EndoMT, inflammation (NFκB activation, IL6 upregulation) and perilesional hypoxia [23,129,130].

Etiologically, BVMs divide into inherited and sporadic forms. In both, epigenetic regulation plays a pivotal role, serving as a crucial interface between genetic blueprints and environmental influences. Key epigenetic alterations, including DNA and RNA methylation and histone modifications, have been identified in human lesions (inherited and sporadic) and in experimental bAVM and CCM models, primarily impacting EC gene programs, angiogenesis, and overall BBB integrity [131,132].

bAVMs lesions are characterized by global DNA hypomethylation alongside focal DNA hypermethylation in the promoter regions of key genes involved in angiogenesis, like *ZNF24, FAAH*, and *AGGF1* [131,133]. In addition, hypermethylation of the cell cycle regulator CDKN2A and lipid signaling *PLA2G7* promoters has been associated with bAVM risk in patient cohorts [133]. Furthermore, aberrant DNA methylation of the Sonic Hedgehog (SHH) signaling pathway, such as hypermethylation of promoters of *CDON, GAS1*, and hypomethylation *GLI2* and *GLI3* as well as hypomethylation components of VEGF-PDGF signaling pathway, also promote abnormal angiogenesis [133]. Together, this methylome profile is associated with development of the high-flow nidus structure of bAVMs. Focal inflammation in bAVMs is also linked to altered DNA methylation, characterized by hypomethylation of the MTA1 promoter, resulting in increased expression of this pro-inflammatory protein and downstream regulation of NF-κB activity and cytokines such as IL6 and TNF-α. Treatment with nicotinic acid (niacin) induces hypermethylation of the *MTA1* gene promoter and reduces this inflammatory response [134].

Aberrant DNA methylation is also a notable feature in human CCMs. While its role in the primary inherited forms (CCM1, CCM2, CCM3) remains controversial, hypermethylation of PDCD10 (*CCM3*) has been reported in sporadic cases [135]. Altered DNA methylation in CCMs is significantly associated with disease progression, notably through hypermethylation of the tumor suppressor gene *PTEN*, reduced protein levels, and, subsequently, overactivated pro-angiogenic signaling pathways [136].

Histone modifications, particularly acetylation and methylation, significantly contribute to bAVM pathogenesis by influencing the expression of genes critical for vascular development and EndoMT. Key changes in bAVM ECs include upregulation of

HDAC2 and downregulation of EZH1 that subsequently affect H3K27 trimethylation levels and expression of Jagged-1 and −2 (increased expression), promoting mesenchymal differentiation [137]. In CCMs, loss-of-function mutations in *CCM1*, *CCM2*, or *CCM3* trigger significant downstream changes in the epigenetic landscape. A notable finding is increased activity of the Polycomb Repressive Complex 1 (PRC1) protein CBX7 within ECs of CCM lesions [138]. CBX7 promotes CCM pathogenesis, particularly EndoMT, by silencing protective gene programs (like KLF2-dependent genes) and activating pathological targets such as *TEK*, *ANGPT1*, and *WNT9* [138]. In addition, CBX7 is linked to alterations in chromatin via repressive histone H3K27me3 and H2AK119ub1, and potentially aberrant HDAC activity (HDAC2), which could further promote a pathological gene expression program [138]. Other relevant findings in CCMs include a loss of HBO1 (histone acetyltransferase) mediated H4 acetylation at the promoter sites of CCM1 and CCM2, causing deficient expression, disruption of EC junctions, and increased BBB permeability [132]. Altered transcriptional regulation and chromatin remodeling events mediated by activated VEGF and PI3K/AKT/mTOR signaling also affect the epigenetic landscape of CCM lesions, including PLVAP, a key indicator of vascular compromise [138].

Aberrant RNA methylation is an emerging area of research in both bAVMs and CCMs, with dysregulation of key m^6A-regulating enzymes. In bAVMs, reduced expression of the methyltransferase METTL3 results in a global decrease in RNA methylation, which persistently activates critical signaling pathways like Notch, ultimately contributing to disease progression via targets such as *DSP*, DTX1/DTX3L – Notch axis, and *LGALS8* [139].

In bAVMs, specific lncRNAs (TCONS_00013855 and ENST00000423394) influence vessel integrity and energy metabolism [140]. Regarding CCMs, transcriptomic profiling has identified thousands of differentially expressed lncRNAs that regulate EndoMT and inflammatory pathways, generating the CCM lesions [141]. circRNAs display a similar role. In bAVMs, molecules circRNA-100338 and various VEGFA-related circRNAs act as "sponges" for miR-200a-3p and miR-18a, fueling uncontrolled endothelial proliferation and smooth muscle cell instability that characterize the high-flow nidus [142]. In CCMs, circ-FoxO3 has emerged as a critical protective factor that preserves BBB integrity by promoting autophagy and inhibiting mTORC1 signaling, thereby mitigating the "leaky" vessel phenotype [126].

5.2. Neurodegeneration

5.2.1. Alzheimer disease

One intense area of research is the epigenetics of neurodegenerative diseases. All epigenetic mechanisms are implicated in several neurodegenerative disorders, including AD, Parkinson's disease, vascular dementia (VD), and Huntington's disease. A prominent feature across these conditions is an epigenetic imbalance. For example, this can lead to the silencing of protective genes such as *BDNF*, and the overexpression of genes like *APP* and *SNCA*. This imbalance accelerates the accumulation of toxic proteins (Aβ, tau, α-synuclein) and contributes to neuroinflammation and synaptic dysfunction [96].

BBB dysfunction is well documented in AD and involves TJ loss (claudin-5, occludin, and ZO-1), vascular inflammation (upregulation of VCAM-1, ICAM-1, osteopontin, MMP9, MMP2, thrombin inflammatory factor PAR-1), altered vascular gene expression (decreased PDGFRβ, thrombin inhibitor proteases nexin-1, P-gp, and LRP-1) and increased expression of senescence-associated secretory phenotype (SASP) [1,38,39,143]. However, direct links between specific DNA methylation or histone-modification changes and BBB dysfunction in AD are still sparse. A few recent studies pinpoint links between both DNA hyper- and hypomethylation in fine-tuning gene expression at the BBB in AD [6]. For example, DNA hypermethylation in the *CLDN5* gene locus downregulates this essential TJ proteins, thereby compromising BBB integrity and increasing permeability [97,144]. On the other hand, DNA hypomethylation of the *APP* gene in neuronal and glial cells accelerates Aβ accumulation and plaque formation, which, in turn, indirectly compromises the vascular interface [145]. Other targets of aberrant methylation include *LRP1*, which is primarily expressed in brain ECs and shows increased methylation at the promoter region effectively reducing gene transcription and protein expression [146]. Compromising LRP1 expression hinders Aβ clearance from the brain into the circulation, leading to the accumulation of toxic Aβ plaques in brain parenchyma and accelerating cognitive decline [146]. Another example is hypomethylation of the *BACE1* gene promoter and its associated enhancers in neurons, glia, and brain ECs, leading to elevated BACE1 transcription and enzymatic activity [147,148]. This causes overproduction of Aβ peptides, contributing to cerebral amyloid angiopathy (CAA) and vascular dysfunction. This process initiates a vicious cycle: early Aβ accumulation triggers further *BACE1* hypomethylation, which exacerbates Aβ production, driving neuroinflammation, BBB breakdown, and overall disease progression [148]. Another prominent alteration in DNA methylation linked to AD BBB dysfunction is PSEN1 promoter hypomethylation [149]. The pathological overexpression of PSEN1 increases γ-secretase activity and the subsequent accumulation of neurotoxic Aβ, which in turn affects cell metabolism and barrier integrity, triggering a vicious cycle BBB dysfunction-amyloid accumulation- neuroinflammation that further accelerates AD pathology [150].

Regarding histone modifications in AD, they are predominantly present on histones H3 and H4 within brain ECs and neurons. Specific histone modifications in AD include a global loss of H4K16ac linked to synaptic dysfunction, and to gene-specific hyperacetylation of inflammatory gene promoters, regulated by the NF-κB pathway, which drives chronic neuroinflammation and BBB damage [151]. Furthermore, increased repressive H3K9me2 at the promoter of Neprilysin (NEP), a primary enzyme responsible for degrading Aβ peptides, impairs the brain's ability to clear Aβ, while altered H3K27me3 levels downregulate protective genes like *NEP* as well as critical genes for BBB integrity [152,153]. In addition to DNA methylation, *BACE1* expression at the BBB in AD is also regulated by histone modification. Increased H3K27ac at the *BACE1* promoter creates an "open chromatin" state, enhancing transcriptional activity and increasing BACE1 protein levels [154]. Disruption of the dynamic balance of H4K16 acetylation and H3K9/27 methylation represses neuroprotective genes and activates inflammatory pathways via NFκB [151]. These changes compromise TJ integrity and hamper Aβ clearance mechanisms, exacerbating AD pathology. Genes associated

with altered H3K27ac status in AD include TGF-β/SMAD4-SP1 signaling pathway, *LAMC1*, extracellular matrix proteins *COL4A1*, and transcriptional factor *ERG*. Histone deacetylase-like HDAC1 and HDAC3 dysregulation is linked to promoting neuroinflammation and vascular permeability by controlling claudin-5, and occludin, while HDAC6 is elevated in the AD cortex and involved in BBB disruption by regulating the endothelial cytoskeleton [154,155].

Aberrant m^6A RNA methylation in AD contributes to neuroinflammation by modulating immune cell activation/migration across the BBB and impairing clearance of Aβ plaques. For instance, deletion of the methyltransferase METTL3 in macrophages can enhance Aβ clearance in mouse models [85]. In addition, decreased METTL3 or FTO and ALKBH5 alterations in brain ECs compromise the NVU by influencing gene pathways related to oxidative stress, inflammation, and neuronal survival [156].

One function of lncRNAs is to act as competing endogenous RNAs (ceRNAs) and sequester miRNAs, modulating the expression of target mRNAs. In Aβ-exposed brain microvascular ECs, the lncRNA SNHG7, via interaction with the RNA-binding protein TARBP2, acts as a ceRNA for miR-17-5p, leading to increased NFATC3 expression, reduced TJ proteins expression, and BBB hyperpermeability [157]. The lncRNA LINC00662 has similar effects [158]. The circRNA, CircDENND1B, was recently found to contribute to cognitive impairment in AD by enhancing BBB permeability and inflammatory response [159].

5.2.2. Vascular dementia

Vascular dementia (VD) and vascular cognitive impairment (VCI) share similarities with AD-related BBB pathology. While specific, universally accepted epigenetic landscapes or a single set of causative genes for VD and VCI remain unidentified, data strongly indicate an indirect link between epigenetic modifications and these conditions [160]. Epigenetic changes associated with ischemia, chronic hypoperfusion, and hypertension are implicated as key drivers of VD and VCI pathogenesis [160].

The major BBB injury in VD and VCI is characterized by hyperpermeability (leakage), resulting from junction complex remodeling, impaired metabolic status at the BBB, perivascular inflammation, and impaired neurovascular coupling. Preclinical models of ischemia or hypoxia show that DNA hypermethylation in the promoter region of key genes, including *CLDN5*, *TIMP2*, *BDNF*, and *GLUT1*, is linked to their lower expression and a subsequent barrier function decline [96]. Studies of brain tissue from human VCI patients reveal a predominant pattern of hypermethylation, further implying the repression of genes critical for barrier integrity [161].

The indirect link between epigenetic modification and VD or VCI is further supported by studies on hypertension-induced alterations in DNA methylation. This includes hypermethylation of the *BDNF*, *ERalpha*, and renin-angiotensin genes like *AT2R*, all of which are relevant to BBB function [162]. Finally, chronic hypoperfusion has been linked to "Global Methylation Shifts," initiating a decrease in global DNA methylation followed by an increase in methylation over a longer period. These shifts are associated with altered expression of DNMT1and DNMT3a, which affects TJ proteins expression and levels of *TIMP2*, thereby regulating BBB permeability [163].

Histone modifications are significant drivers of BBB dysfunction in VCI and VD by regulating genes crucial for endothelial integrity and inflammatory responses. HDACs activation in particular plays a critical role. HDAC6 and HDAC3 are indicated in regulating BBB permeability and endothelial cytoskeletal remodeling. General HDAC inhibitors such as valproic acid or sodium butyrate (which inhibit Class I and IIa HDACs) attenuate BBB disruption and brain edema by suppressing NF-κB activation and MMP-9 expression, a key enzyme for the degradation of TJs [164,165].

On the other hand, increased levels of repressive histone methylation, such as H3K9me2 mediated by the G9a/GLP enzyme, lead to the silencing of genes vital for maintaining BBB integrity and neuroprotection [5,152]. These epigenetic changes compromise TJs, exacerbate neuroinflammation, and contribute to the vascular damage and cognitive decline in VCI and VD. Another histone modification and HDAC activity associated with compromised BBB integrity are HDAC1 and H3K27 acetylation. HDAC1 is thought to be recruited to promoters, and its inhibition stabilizes H3K27 acetylation at genes such as claudin-5, thereby regulating BBB hyperpermeability and neuroinflammation [113]. Furthermore, HDAC3 activity has detrimental effects on the expression (degradation) of TJ proteins like ZO-1, occludin, and claudin-5 after cerebral ischemia [114].

Alterations in RNA methylation in VD and VCI are closely linked to chronic cerebral hypoperfusion. An increase in N6-methyladenosine (m^6A) was reported to have severe impacts on BBB integrity by disrupting the regulation of key mRNAs responsible for maintaining BBB structure, leading to reduced claudin-5 expression and increased levels of barrier-degrading enzymes such as MMP3 [120,121]. Furthermore, altered RNA methylation exacerbates neuroinflammation and impairs cerebrovascular repair via angiogenesis [120].

lncRNAs (H19, MALAT1, NKILA, GM12371) are key regulators of VD pathology, having either protective or damaging roles. MALAT1, for example, is implicated in maintaining BBB integrity, promoting angiogenesis, and "sponging" microRNAs like miR-9-3p to upregulate synaptic proteins (SAP97) [166]. Similarly, NFκB interacting LncRNA (NIKLA) is a regulator of overactive NFκB pathways, thereby modulating neuroinflammation and BBB permeability. In contrast, H19 overexpression is associated with increased BBB permeability and neuroinflammation in VD [166]. Both H19 and NIKLA have been identified as potential biomarkers of vascular aging, lacunar stroke, and VCI. Among circRNAs, circ-FoxO3 and circRNA-PTPN4 act as protective agents by maintaining TJ proteins and mitigating barrier injury, while circDENND1B plays a more damaging role, contributing to increased BBB permeability and neuroinflammation, exacerbating hippocampal damage, and accelerating VCI [167].

5.2.3. Other neurodegenerative diseases

BBB dysfunction is documented in Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (ALS), where the respective disease proteins, α-synuclein,

mHTT, and TDP-43/C9ORF72, affect TJ proteins expression and BBB permeability. These changes involve altered transporter expression, remodeling of the extracellular matrix, disrupted interaction between astrocytes and ECs, dysregulated signaling pathways (e.g., Wnt/β-catenin, VEGFA, and MEK1/2 in PD) and inflammation (e.g., NFκB/TNFα) [1,5]. Although extensive transcriptional dysregulation is observed, direct evidence that specific DNA methylation or histone modifications drive BBB dysfunction has not yet been fully characterized.

lncRNAs and circRNAs are recognized as key regulators of BBB stability in PD and ALS. In PD, circFTO and lncRNA AL049437 promote neuroinflammation and oxidative stress by sponging protective microRNAs, thereby increasing BBB permeability and neuronal damage [168]. Conversely, lincRNA-p21 and circ-FoxO3 act as protective agents by upregulating TJ proteins and promoting autophagy to clear toxic protein aggregates. In ALS, BBB and blood-spinal cord barrier dysfunction are driven by C9ORF72-derived circRNAs, which contribute to motor neuron toxicity [169].

5.3. Traumatic brain injury

Following TBI, the intricate relationship between DNA methylation and histone modifications significantly influences BBB integrity, contributing to long-term pathology by altering expression of crucial genes. In terms of histone modifications, TBI affects histone deacetylases (HDACs) and methyltransferases, which modify chromatin structure to make genes more or less accessible for transcription. An example is the observation of global histone hypoacetylation in the injured cerebral cortex and hippocampus after TBI, which generally correlates with gene silencing and is linked to inflammation [170,171]. One activated HDACs is HDAC2, an enzyme implicated in neurodegenerative conditions and potentially associated with TBI [172]. A prominent change is in the IGF-1 gene that produces the neuroprotective IGF-1B splice variant. These modifications include altered DNA methylation patterns across the promoter (P1) and exon 5/ESE regions, and an increase in activating histone PTMs H3K9 and H3K14 acetylation, at the P2 and exon 5/ESE regions [86]. The coordinated epigenetic changes transiently increase IGF-1B, thereby aiding the brain's response to injury and promoting recovery [86].

lncRNAs are also recognized as pivotal epigenetic regulators of BBB injury after TBI, acting as molecular switches that dictate the severity of secondary damage. While specific lncRNAs, like MALAT1 and lincRNA-p21, serve a protective role by preserving TJ proteins and reducing brain edema, others, such as MEG3 and GAS5, are rapidly upregulated and act as miRNA sponges, sequestering protective microRNAs to trigger the NLRP3 inflammasome and activate MMP-9 [173]. Similarly, circRNAs (circLphn3 and circPtpn14) act as persistent "molecular sponges," sequestering specific microRNAs to downregulate TJ proteins expression exacerbate secondary injury by triggering oxidative stress and mitochondrial dysfunction within the NVU [174].

5.4. Epilepsy

In epilepsy, DNA methylation and histone modifications profoundly influence the development of seizures and associated BBB/NVU dysfunction by regulating genes involved in barrier integrity (claudin-5), ion and glutamate metabolism. For instance, in animal models of seizures, DNA hypermethylation of the *Kir4.1* and glutamine synthase promoters is associated with decreased expression in astrocytes, affecting astrocyte function in maintaining BBB integrity [175]. Reduced expression of *Kir4.1* and glutamine synthase is associated with persistent DNA hypermethylation of their promoters in patients [175]. Regarding histone modifications, an early study in seizure models found reduced histone H4 acetylation at the locus of the glutamate receptor 2 (*GluR2/Gria2*) gene. Since *GluR2* makes its receptor complex less permeable to Ca^{2+}, the epigenetic silencing of this gene enhances neuronal excitability, contributing to epileptogenesis and BBB disruption [176]. On the other hand, increased H4 acetylation has been linked to upregulation of the neuroprotective gene *BDNF*, illustrating that complex epigenetic changes can promote both detrimental and adaptive responses in epilepsy [176]. Among circRNAs, circPTPN4 has recently emerged as a key driver of barrier dysfunction by sponging miR-145a-5p, triggering the p38/MAPK pathway to degrade TJ proteins, and facilitating seizure activity [177].

6. Psychiatric disorders

A rapidly increasing area of research examines the influence of inflammation and BBB function on the development of psychiatric disorders such as schizophrenia and depression [178]. BBB integrity has been reported to be compromised through specific DNA methylation and histone modifications by altering the expression of genes associated with structural BBB integrity and barrier maintenance. An example is claudin-5 where postmortem brains of patients with depression and schizophrenia consistently show decreased claudin-5 protein levels, a reduction linked in some cases to DNA hypermethylation of its promoter region, silencing of the gene, decreased protein expression, and consequent increases in BBB permeability [144,178]. Beyond structural genes, DNA hypomethylation of *MMP9*, resulting in increased expression in peripheral blood cells of schizophrenia patients, leads to TJ degradation and remodeling of the extracellular matrix, regulating BBB permeability and neuroinflammation [179].

Regarding histone modifications, an imbalance in acetylation and methylation is reported for H3K27 modification and regulation of claudin-5 expression. In a preclinical model of stress-induced depression, there is a higher deposition of repressive H3K27me3 at the *CLDN5* promoter, coupled with a decreased deposition of the activating H3K27ac [180]. This implies gene silencing, and low protein expression that leads to BBB dysfunction and depression-like behaviors. This shift in H3K27 modification status represents a key epigenetic mechanism linking stress, BBB breakdown, and the pathology of depression.

Other examples include high levels of HDAC2 in neurons, which can reduce overall histone acetylation, leading to the silencing of genes like *BDNF* that support neuronal and vascular health [181]. Furthermore, early life stress, a major risk factor for psychiatric illness, can induce lasting changes in histone modifications in brain, altering microglial expression of inflammatory genes and contributing to the BBB disruption seen in adults [180]. These specific epigenetic changes are linked to environmental factors that can leave a molecular "memory" of disrupting BBB function and heightening vulnerability to psychiatric disorders.

lncRNAs and circRNAs are also regulators of BBB integrity in MDD, schizophrenia, and bipolar disorder [182]. Circ-FoxO3 and MALAT1 serve as protective anchors, maintaining TJ proteins expression and promoting autophagy to "seal" the barrier against neuroinflammatory leakiness associated with chronic stress. Conversely, dysregulated molecules such as XIST and H19 are linked to increased vulnerability in mood disorders by influencing oxidative stress and glial activation [183].

7. Targeting BBB dysfunction in neurological and psychiatric disorders: epigenetic biomarkers and emerging therapeutic strategies

Epigenetic modifications, including DNA methylation and histone modifications, represent a powerful frontier in the development of both biomarkers and therapeutics for diseases involving BBB dysfunction and neurological compromise. In accessible biofluids such as blood and CSF, characteristic epigenetic signatures (e.g., specific DNA methylation patterns of the *CLDN5* gene or levels of modified histones) can serve as sensitive, noninvasive biomarkers for early diagnosis, monitoring disease progression, and personalizing treatment plans [5,6]. Due to their resistance to degradation, circRNAs (circDLGAP4 and circHtra1) are utilized as "liquid biopsy" markers to detect acute BBB leakage and neuroinflammation in stroke and TBI, while circDENND1B is significantly upregulated in AD mice and patients [124,125]. lncRNAs also show biomarker potential. In AD, BACE1-AS and 51A in plasma and downregulation of MALAT1 in CSF are indicators of AD progression. In ischemic stroke, several lncRNAs (H19, XIST, MATA1, p21) are associated with BBB dysfunction and poststroke inflammation [123,169,183].

The reversibility of epigenetic modifications presents attractive therapeutic avenues. Pharmacological agents, such as histone deacetylase inhibitors (HDACi), are being actively investigated to promote a healthier gene expression profile within the NVU, potentially enhancing the expression of TJ proteins and reducing neuroinflammation [114,165,170]. These "epi-drugs" offer a unique approach to restore BBB integrity and neuronal function, opening new pathways for treating complex brain disorders where current therapies are limited.

While the primary treatments for conditions like stroke, AD, VD, and TBI are not fundamentally rooted in epigenetics, several compounds with epigenetic-modifying properties are emerging as promising candidates for novel therapies. The most widely studied agents are HDACi, such as valproic acid, a common anti-seizure medication that has demonstrated neuroprotective potential in preclinical models of stroke and AD [164,172]. Other HDACi, like vorinostat and sodium butyrate, are being explored preclinically to improve cognitive function and reduce inflammation [165,184]. Natural compounds, including resveratrol and curcumin, which act as sirtuin or general HDAC modulators, also show promise in reducing amyloid burden and improving neuronal health in AD [185,186].

Therapeutically targeting DNA methylation is still challenging. Preclinically, a DNMT inhibitor, 5-azacytidine, showed efficacy in stroke, promoting recovery and protecting from ischemic damage. However, it failed in clinical trials due to high-dose toxicity and the potential to accelerate neurodegeneration [101]. Optimal dosing or adjuvant therapy are potential directions. S-adenosylmethionine (SAMe), a methyl group donor, showed efficacy in abolishing DNA hypomethylation, and it is increasingly recommended alone or as adjunctive therapy for MDD [187]. Its potential in treating AD is still at the preclinical phase. Though no FDA-approved drugs specifically target the epigenome for neurological and psychiatric disorders, these agents are being investigated in early-stage research and clinical trials, offering hope for future treatments.

Having dual roles as biomarkers and therapeutic targets, ncRNAs are at the forefront of translational neurovascular research. Therapeutically, engineered delivery of protective RNAs, such as circSCMH1, circ-FoxO3, lincRNA-p21, or MALAT1, has been used to promote neurovascular remodeling, alleviate BBB disruption, and activate autophagy to clear toxic aggregates [122,123,126]. However, such therapies carry several limitations for clinical translation including dual effects (protective and damaging), narrow therapeutic window, delivery, potential off-target effects, optimal timing and treatment duration, and patient stratification based on ncRNA expression profiles. A summary of some epigenetic targets and compounds is provided in Table 2.

8. Conclusion

Epigenetic regulation has emerged as a central driver of BBB dysfunction across neurological, neurodegenerative, psychiatric, vascular, and age-related conditions. Disease-related alterations in DNA and RNA methylation, histone modifications, and chromatin structure disrupt BBB stability, transport functions, and inflammatory signaling, thereby contributing to barrier dysfunction and accelerating disease progression. Although the specific epigenetic signatures vary by disorder, common themes include the silencing of TJ and neuroprotective genes, activation of inflammatory pathways, and impaired repair mechanisms.

Importantly, the reversibility of epigenetic modifications positions them as promising biomarkers and therapeutic targets. Epigenetic drugs, particularly HDAC inhibitors and modulators of DNA/RNA methylation, show potential to restore BBB integrity and attenuate neuroinflammation, though most remain in early translational stages. Overall, integrating epigenetic insights with BBB biology offers a powerful framework for understanding disease mechanisms and developing more

Table 2. Current epigenetic drugs in preclinical studies and clinical trials.

Class of agent	Drugs	Condition(s) studied	Status	
HDAC Inhibitors	Valproic Acid (VPA)	AD, Stroke, Epilepsy	FDA-approved for epilepsy; in trials/preclinical for AD/Stroke	[164,172]
HDAC Inhibitors	Vorinostat (SAHA)	AD, Stroke	FDA-approved for cancer; in early trials/preclinical for AD/Stroke	[165]
HDAC Inhibitors	Sodium Butyrate	AD, Stroke, TBI	Preclinical studies only	[172]
HDAC3 Inhibitor	RGFP966	Stroke, TBI	Preclinical studies only	[114]
DNMT Inhibitors	5-Azacytidine	Stroke	Preclinical studies only (challenges for CNS use)	[101]
Natural Modulators (Sirt1 agonist)	Resveratrol	AD	In clinical trials (Phase II)	[185]
Natural Modulators	curcumin	AD, PD, ALS, HD, epilepsy, stroke, TBI	Preclinical study, early clinical trial	[186]
DNA methylation, Histone modification				
DNA methylation (methyl group donor)	S-adenosyl-methionine	AD, MDD	Clinical trial (MDD), preclinical study (AD)	[187]

Summary of epigenetic-targeting agents evaluated in preclinical models and clinical trials for stroke, Alzheimer's disease (AD), Traumatic Brain Injury (TBI), Parkinson's disease (PD), epilepsy, and Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), and Major depressive disorder (MDD). Listed compounds include inhibitors or modulators of DNA methyltransferases (DNMTs), histone deacetylases (HDACs), and histone modifications. For each agent, the table indicates molecular target, disease context, and stage of development (preclinical or clinical).

precise, targeted strategies to diagnose, monitor, and treat neurological disorders characterized by vascular dysfunction.

9. Future perspectives

Neurovascular epigenetics is approaching a paradigm shift. Having cataloged extensive epigenetic alterations associated with neurological disease and blood – brain barrier (BBB) dysfunction, the field must now confront a more ambitious goal: redefining BBB instability not as a downstream consequence of pathology, but as a programmable and potentially reversible driver of disease. The coming decade will test whether epigenetic circuitry within the neurovascular unit (NVU) can be decoded with sufficient precision to enable causal intervention.

Advances in single-cell multi-omics, spatial epigenomics and high-resolution chromatin profiling will likely expose the dynamic regulatory logic that governs endothelial, pericyte, astrocytic and microglial states during injury. Rather than static markers of dysfunction, these epigenetic programs may reveal coordinated, stage-specific transitions that couple vascular breakdown to neuronal degeneration. Identifying master regulatory nodes within these circuits could transform therapeutic strategy – from broadly dampening inflammation to selectively reprogramming pathological gene networks that sustain BBB failure.

At the diagnostic frontier, epigenetic biomarkers may evolve into early-warning systems for neurovascular vulnerability. Integration of circulating epigenetic signatures with imaging, genetic risk architecture and clinical phenotyping could shift neurological care toward pre-symptomatic detection and dynamic disease monitoring. However, realizing this vision will require rigorous longitudinal validation, standardization of analytical platforms and global data harmonization.

Therapeutically, the next decade may witness the rise of precision epigenome engineering. Isoform-specific inhibitors, locus-targeted editing technologies and programmable non-coding RNA therapeutics, paired with refined neurovascular delivery platforms, could enable restoration of aberrant transcriptional states with unprecedented specificity. If combined with patient stratification based on epigenetic architecture, such approaches may redefine trial design and therapeutic responsiveness.

Collectively, the convergence of epigenetics, systems neuroscience and vascular biology holds the potential to reposition the BBB from a passive barrier to an active regulatory hub in neurological disease. Should these advances succeed, neurovascular dysfunction may become not merely detectable, but interceptable – ushering in a new era of mechanism-driven prevention and repair.

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Author contributions

Maya Akhoury and Anuska V Andjelkovic conceived the review topic and structure.

Maya Akhoury and Nicole Vegara performed the literature search.

Maya Akhoury, Svetlana M Stamatovic, Richard F Keep, and Anuska V Andjelkovic drafted the manuscript.

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