

Involvement of noncoding RNA in blood-brain barrier integrity in central nervous system disease

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ABSTRACT

Given the important role of the blood-brain barrier (BBB) in the central nervous system (CNS), increasing studies have been carried out to determine how the structural and functional integrity of the BBB impacts the pathogenesis of CNS diseases such as stroke, traumatic brain injuries (TBIs), and gliomas. Emerging studies have revealed that noncoding RNAs (ncRNAs) help to maintain the integrity and permeability of the BBB, thereby mediating CNS homeostasis. This review summarizes recent studies that focus on the effects of ncRNAs on the BBB in CNS diseases, including regulating the biological processes of inflammation, necrosis, and apoptosis of cells, affecting the translational dysfunction of proteins and regulating tight junctions (TJs). A comprehensive and detailed understanding of the interaction between ncRNAs and the BBB will lay a solid foundation for the development of early diagnostic methods and effective treatments for CNS diseases.

1. Introduction

The BBB is a diffusion barrier with two specific characteristics: integrity and permeability. The BBB is mainly composed of TJs and cells, which include endothelial cells (ECs), astrocytes, podocytes and pericytes. TJs exist between brain ECs to limit diffusion and selectively protect the brain from the invasion of most bloodborne substances [1]. ECs form the basic structure of the BBB by connecting with each other with both sides covered with basement membranes [2]. Astrocytes tightly surround the vascular wall and have a crucial impact on the formation and stability of TJs, but they are not considered to have a barrier function in the mammalian brain [3]. Dysfunction of the BBB, such as damage to TJs, can complicate many neurological diseases, including stroke and neuroinflammatory diseases [4].

NcRNAs are genetic, epigenetic, and translational regulatory factors that are mainly divided into short-chain ncRNAs, long ncRNAs (lncRNAs) and circular RNAs (circRNAs). Short-chain ncRNAs mainly include microRNAs (miRNAs), piRNAs and siRNAs. Each type of RNA plays an important physiological and pathological role by controlling transcription and translation. NcRNAs are expressed in large quantities in the human brain. Many studies have shown that the expression of

ncRNAs in CNS diseases undergoes significant changes (especially miRNAs and lncRNAs), suggesting that they play a key role during the occurrence and development of diseases. These effects include excitotoxicity, oxidative stress, neuroinflammation and apoptosis and are closely related to the BBB [5].

Many studies have shown that BBB mutations are important under pathophysiological conditions. Destruction of the BBB has been taken an insight into during the pathology of lots of CNS diseases, ranging from stroke to infection [6]. Although it is generally believed that BBB leakage is a subsequent process of ischemic stroke and TBI, whether BBB divulgation also occurs in other CNS diseases, such as Alzheimer's disease, remains unclear. Both ischemic and hemorrhagic strokes can cause rupture of the BBB, which may be due to the increase in matrix metalloproteinase activity and free reactive oxygen species [7]. The abnormal structure and function of endothelial cell-cell connections, mainly TJs, is the most important feature in the process of stroke-induced BBB opening. Additionally, it has been reported that vascular permeability is increased in brain tumors and that TJ-related proteins are lost [8]. Other diseases related to inflammation in the CNS, such as TBI and HIV infection, may also cause inflammation in the periphery and CNS, all of which contribute to changes in the integrity of the BBB [9].

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2. Blood-brain barrier

2.1. Structure

2.1.1. Cells of the BBB

The BBB consists of endothelial cells, mural cells, glial cells, immune cells, and neural cells.

ECs, which are mainly dependent on the BBB, are mesodermally derived modified simple squamous epithelial cells [2] (Fig. 1). Compared with ECs in other tissues, ECs in the BBB not only have limitations on the paracellular flux of solutes but also exert restrictions on the vesicle-mediated transcellular movement of solutes [10,11]. Additionally, ECs express a high level of mitochondria that generate ATP for transport functions, and a low level of leukocyte adhesion molecules results in a low number of immune cells in the CNS [12,13]. There are three kinds of specific transportation system in ECs, including outgoing active transport system, pump carrier adjust transport system and receptor regulation system. According to the research carried out by Yin et al. lncRNA rhabdomyosarcoma 2-associated transcript (RMST) was found to regulate the viability, migration and promoting apoptosis of human brain microvascular endothelial cells (HBMEC), which made influence on the integrity of BBB [14]. Wang et al. revealed that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) lncRNA reduced the level of miR-200c-3p, which played a significant role in inhibiting the autophagy and survival in BMECs [15].

Mural cells include vascular smooth muscle cells and pericytes (PCs), whose current accepted molecular identifiers are PDGFR- β and NG2 [16]. PCs in the BBB have distinct features compared with PCs in other tissues. First, CNS PCs are originated from the neural crest instead of the mesoderm [17]. Second, PCs exert significant effects on regulating angiogenesis, extracellular matrix deposition and other aspects [17]. Moreover, PCs maintain BBB function [18]. Complete loss of PCs in platelet-derived growth factor PDGF- β or PDGF- β knockout mice has been shown to lead to CNS microbleeding, TJ dysfunction, increased vascular permeability, and embryonic mortality [19]. Recently, another study emphasized that PCs are involved in the disease phenotype. For example, the progressive loss of PCs accelerated the pathological

features of AD, including neurovascular dysfunction, abnormal elevation of amyloid β -peptide ($A\beta$), tau pathology and neuronal loss in AD mouse models [20].

The basal lamina in the CNS can be divided into the inner endothelial basement membrane secreted by ECs and pericytes and the outer parenchymal basement membrane secreted by astrocytes, indicating that molecules have to cross both the ECs and two layers of basement membrane in the CNS [21,22]. While the endothelial basement membrane expresses higher levels of alpha4 and alpha5, the parenchymal basement membrane is rich in alpha1 and alpha2 [23]. The basement membrane not only acts as a physical barrier on the surface of the outer cavity of endothelial cells and fixes the cells at the BBB, but also is involved in the regulation of the BBB [24]. The research carried out by Yamazaki demonstrated that the basement membrane thickening was a common pathological manifestation of brain capillaries in AD patients, affecting the localization of occluding in ECs and regulating the stability of the barrier [25].

Astrocytes are composed of proteins including dystroglycan, dystrophin, and aquaporin 4, which is important in regulating water homeostasis in the CNS [3]. The Dystroglycan-Dystrophin complex connects the foot processes to the extracellular matrix secreted by vascular endothelial cells, pericytes and astrocytes, forming a neurovascular coupling unique to the central nervous system. After neuronal activation, the astrocytes transmit signals regulating blood flow by regulating the contraction/dilation of vascular smooth muscle cells around arterioles and pericytes around capillaries. Aquaporin 4 is responsible for maintaining water balance in the brain. In addition, the linkage between neuronal circuitry and blood vessels accomplished by astrocytes enables them to regulate blood flow [26]. Recent studies have shown that the production and release of retinoic acid from astrocyte precursors can act on the developing brain ECs through retinoic acid receptor- β , thereby inducing the characteristics of the BBB [27].

Immune cells in the BBB are mainly perivascular macrophages and microglial cells. Macrophages are monocytes derived from hematopoietic stem cells and are usually located in the perivascular space of the central nervous system. Chimeric experiments confirmed that these cells could pass BBB and 80% of the cells could be renewed within 3 months.

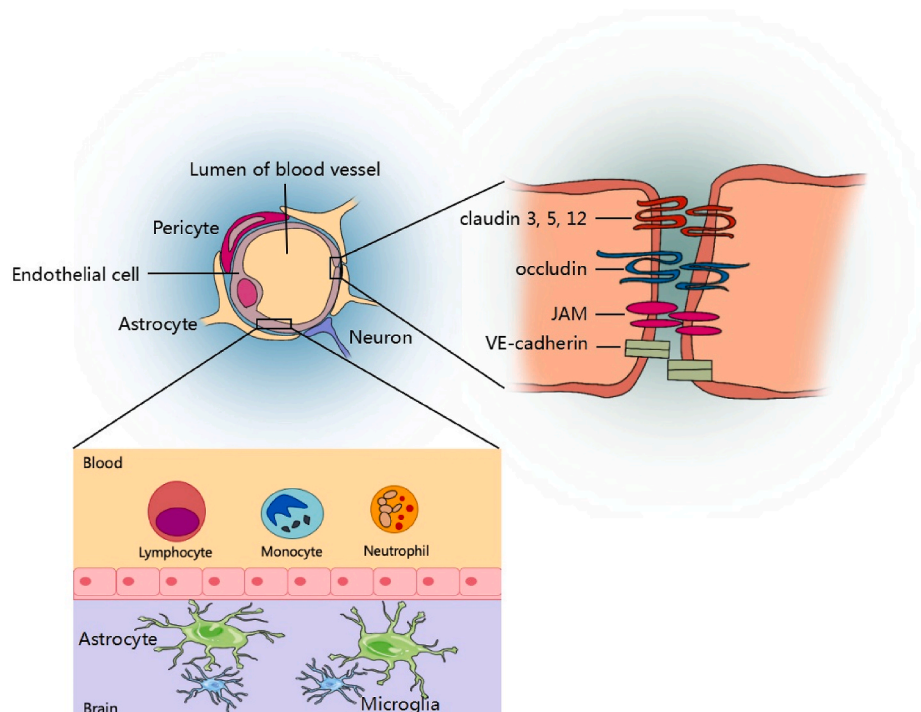


Fig. 1. The composition and structure of BBB.

These cells form the first “line of defense” by phagocytic fragments. Microglia, as the innate immune cells of the central nervous system, originates from the yolk sac and enter the brain during embryonic development. Early studies have shown that activation of other blood-borne immune cells, such as neutrophils, T cells, and macrophages, can also establish a contiguous line with the Mesozoic myozoic blood vessels and have been shown to increase vascular permeability through the release of active oxygen. Then adjust the BBB characteristics [28].

2.1.2. Adherens junction and tight junctions of the BBB

Adherens junctions (AJs) and TJs are different multiprotein complexes located between adjacent brain ECs, which are connected to each other at the structural and functional levels in order to close the paracellular space [29].

As the main protein family of AJs, cadherins including VE-cadherin form affinity interactions between adjacent endothelial cells [30]. AJs are believed to play a crucial role in the initiation of cell-cell contact, the promotion of juvenile cells survival, and the establishment of cell polarity [31].

TJs are mainly composed of three kinds of membrane proteins, namely, claudin, occludin, and junction adhesion molecules, with the help of various cytoplasmic accessory proteins. Cytoplasmic proteins connect membrane proteins to actin, which is the key cytoskeletal molecule for the maintenance of the integrity of the endothelium [1]. Claudins, which are 22-kDa phosphoproteins, are localized at TJ strands. These proteins are the major components of TJs. Currently, 24 members of the claudin family have been figured out [32]. Under pathological conditions such as tumors, strokes, and inflammation, the level of claudin-1 expressed by cerebral blood vessels is decreased and the level of claudin-5 is lower [33]. In allergic encephalomyelitis and glioma multiforme, claudin-3 tight junctions are selectively missing instead of claudin-5 or occludin, which is related to the loss of blood-brain barrier integrity and some other function barriers [34]. Occludin is a 65-kDa phosphoprotein. Occludin can alter paracellular permeability [35]. The loss of occludin in the BBB has been illustrated in CNS diseases such as tumors [36]. Junctional adhesion molecules belong to the immunoglobulin superfamily and include JAM-1, JAM-2, and JAM-3. These molecules are related to cell-to-cell adhesion and monocyte transmigration through the BBB [37]. However, on account of the lack of research, the function and mechanism of JAMs remain to be determined. Cytoplasmic proteins involved in TJs include zonula occludens proteins (ZO-1, ZO-2, and ZO-3), cingulin, 7H6, and several others [1].

TJs and AJs regulation exerts an important influence in the pathological process of CNS diseases. It has been reported that there is a lack of AJ proteins such as VE-cadherin in the brain microsystems of patients with multiple sclerosis [38]. In chronic neurological diseases such as amyotrophic lateral sclerosis and AD, the rupture of TJ is related to increased permeability of the BBB and neuronal dysfunction [39]. A detailed analysis of BBB events after ischemic stroke and traumatic brain injury showed that the TJ complex underwent highly dynamic changes within minutes, hours, and days [29].

2.2. Function

The BBB plays an indispensable role in the CNS. First, it creates a stable fluid microenvironment. In addition, it protects the CNS from chemical insult and damage [40].

2.2.1. Ion regulation

The BBB enables the ion composition to maintain the optimal synaptic signaling function by taking advantage of the combination of specific ion channels and transporters. For example, the concentration of potassium in mammalian CSF fluctuates between 2.5 mM and 2.9 mM, which is nearly half of that in the plasma, approximately 4.5 mM. The concentrations of Ca^{2+} , K^+ , Mg^{2+} and so on in CSF and brain interstitial

fluid are maintained steadily despite changes resulting from pathology [41,42].

2.2.2. Neurotransmitters

The BBB maintains the balance between excitatory neurotransmitters and inhibitory neurotransmitters. For example, the representative excitatory neurotransmitter glutamate is released into brain interstitial fluid in an uncontrolled manner during stroke, cancer and other CNS diseases [43].

2.2.3. Macromolecules

The BBB functions as a barrier to prevent multiple macromolecules from entering the brain. The concentration of total protein in CSF is only 0.443 mg/mL. Due to the lack of proteins such as albumin (0.192 mg/mL), IgG (0.012 mg/mL) and plasminogen (0.000025 mg/mL) in CSF, the BBB prevents seizures and other diseases [44]. In contrast, cystatin-C, known as a serine protease inhibitor, is distinctively rich in CSF to protect BBB permeability [45].

2.2.4. Neurotoxins

The BBB provides a barrier that helps the CNS avoid damage from neurotoxic substances, which may be nutrients or metabolic waste derived from the body or bacteria, viruses or energy substances from the outside obtained by breathing, eating or touching, etc. Neurotoxins in the brain can accelerate the death of neurons, which are nonrenewable [46].

2.2.5. Brain nutrition

The BBB expresses a rich and specific transport system to maintain low passive permeability to different kinds of substances required by the CNS to maintain the normal functioning of the nervous system [40].

3. Noncoding RNA

3.1. Short-chain ncRNAs

In recent years, short-chain ncRNAs have become an indispensable regulators of gene expression in various kinds of mechanisms in cells, among which miRNAs, piRNAs and siRNAs are attached enormous importance to Ref. [47].

3.1.1. MiRNAs

MiRNAs are small molecules with a length of 21–25 nucleotides that are highly abundant and evolutionarily conserved endogenous ncRNAs. Due to base pairing, the inhibition of translation and degradation of mRNAs is mediated by 30 bp untranslated regions (UTRs) of target mRNAs [48].

Generally, miRNAs in mammals are encoded by the genome and transcribed as primary miRNA transcripts by RNA polymerase II. These miRNAs are microprocessed by the RNase III enzyme Droscha and the pri-miRNA binding protein DGCR8/Droscha complexes. Then, exportin5 helps convey the pre-miRNA to the cytoplasm and then the RNase III enzyme Dicer modifies it. Afterwards, either arm of the dsRNA is integrated into the RNA-induced silencing complex (RISC). In this complex, the miRNA connects to members of the Argonaute (AGO) [49,50] protein family and functions as a guide for the complementary region mainly located in the target mRNA 3'UTR. The subsequent binding of TNRC6 protein plays a key impact in all events that lead to the translational inhibition and degradation of target mRNA in animals [49,50]. It is estimated that more than 60% of mRNAs contains miRNA targets in its 3'UTR, indicating that these molecules are involved in strict regulation in normal cell homeostasis and disease states.

In recent years, an increasing number of studies have revealed that miRNAs are associated with the development of many diseases, including cancer, heart disease (such as hypertrophy and ischemia), and mental disorders (such as anxiety or depression) [51]. MiRNAs including

miR-155, miR-150, miR-210, miR-143, miR-130a and miR-15a/16-1 are found to directly or indirectly target TJs including ZO-1, claudin-5, occludin, cadherin, and β -catenin to enhance ischemia-induced BBB leakage [52–57]. Moreover, miR-21–3p and miR-21–5p have also been found to be involved in the damage of the BBB after brain trauma. MiR-21–5p reduces injury-induced BBB leakage by inhibiting inflammation and apoptosis [58]. On the contrary, miR-21–3p aggravates TBI-induced BBB damage, and regulates OGD-induced apoptosis and BBB inflammation [59].

3.1.2. piRNAs

PiRNAs with a length of 21–35 nucleotides belong to the PIWI subfamily of AGO proteins and direct PIWI proteins to cut target RNA, improve heterochromatin assembly and methylate DNA [60]. Due to their 2'-O-methyl-modified 3' termini, piRNAs are able to instruct PIWI-clade AGO instead of AGO-clade proteins, which are involved in the miRNA and siRNA pathways 1–19 [60]. The RNase III enzyme Dicer does not process piRNAs but silences transposon elements, regulates gene expression and fights viral infections. The structure of the piRNA pathway enables them to not only provide adaptive, sequence-based immunity to rapidly developing viruses and transposons but also to regulate conserved host genes [61]. Although the expression of piRNAs in most mammalian cells and tissues is much lower than that of miRNAs, they have a crucial determinant effect on the germline. To maintain the stability of the genome, piRNAs target and inhibit transposable factors and repetitive factors [62].

3.1.3. siRNAs

In addition to miRNAs and piRNAs, dsRNA is used to produce mature small RNAs in the light of the cleavage of the RNase III enzyme Dicer. In endogenous siRNAs, it is the base pairing of sense and antisense transcripts or the extended hairpin structure that contributes to the dsRNA structure [63]. In contrast, exogenous siRNAs (exo-siRNAs) are derived from dsRNAs absorbed in the cellular environment. The mechanism has been confirmed in *Caenorhabditis elegans* and has effects on the antiviral defense mechanism of plants and fruit flies. During infection, viral dsRNA is processed to target the siRNA of the viral mRNA from which it originates [64,65].

3.2. lncRNAs

lncRNAs have a minimum size limited to 200 nt and lack of protein coding potential [66]. They are completely different in terms of characteristics, positioning, and mode of action. These molecules have cell and tissue specificity and can be subdivided according to their function and genomic position relative to gene coding regions or coding genes that overlap in the sense or antisense direction. lncRNAs act as guides for chromatin modification complexes or transcription factors in the nucleus and regulate mRNA translation in the cytoplasm by controlling the stability of mRNAs or as competitive endogenous RNAs [67,68]. More and more studies have revealed the role and mechanism of lncRNAs in the pathogenesis and recovery of ischemic stroke, including oxidative stress, neuroinflammation, autophagy, blood-brain barrier rupture, neuronal apoptosis and neurogenesis and blood vessels generation [69–71], indicating that lncRNA may become a new biomarker and therapeutic target for ischemic stroke.

3.3. circRNAs

CircRNAs have become a novel hot spot in the field of ncRNAs with a covalent closed-loop structure [72]. They are formed by shearing back many simple RNA transcripts from which mRNAs are synthesized [73]. The lack of 5'-3' polarity or a polyadenylated tail ensures that they are stable and resistant to RNase R. By means of working as ceRNA, encoding proteins and so on, circRNAs can manipulate gene expression [74]. Accumulating studies have shown that there is a strong correlation

between circRNAs expression and glioma progression. They not only promote the angiogenesis and proliferation of glioma cells, but also have been shown to play a potential role in regulating tumor cell viability, migration and invasion effect [75]. Barbagallo et al. found that highly expressed circSMARCA5 could regulate VEGF-A mRNA in order to promote angiogenesis and glioma progression, by sponging serine and arginine-rich splicing factor 1 mRNA [76].

4. Impacts

4.1. Stroke

Stroke refers to an acute cerebrovascular disease caused by the sudden rupture or blockage of blood vessels that prevents blood from flowing into the brain, including ischemic stroke and hemorrhagic stroke [77].

Many studies have demonstrated that miRNAs affect BBB function in the process of stroke largely by strengthening or weakening TJs [77] (Fig. 2 and Table 1). MiR-155 reduced the expression of ZO-1 by directly targeting claudin-1 [78], miR-34a impaired mitochondrial function of ECs by targeting CYCS [79], miR-210 suppressed the level of junction proteins by directly targeting occludin and β -catenin [56], miR-150 reduced claudin-5 expression by binding to the angiotensin receptor Tie-2 [57], and miR-130a decreased the expression of occludin by targeting homeobox A5 [80]. MiR-132, which is one of the most popular miRs examined by a number of studies, was shown to be a potent regulator of TJs [81]. Zuo et al. indicated that miR-132 inhibited the expression of MMP-9, which reduced the degeneration of the tight junction proteins VE-cadherin and β -catenin in ischemic stroke [54]. Moreover, the decrease in ZO-1 and claudin-5 expression caused by miR-132 damaged TJs, resulting in the mitigation of BBB permeability [82]. In addition, miR-126 has gained increased attention due to its regulation of vascular inflammation [77]. A study carried out by Xie et al. demonstrated that miR-126–3p preserved BBB integrity and function, with the suppression of neural inflammation by binding to the PI3K/Akt pathway [83]. Another research group investigated the relationship between miR-126 and BBB integrity and found that overexpression of miR-126–3p/-5p protected the BBB from ischemic stroke, which was attributed to decreased levels of the proinflammatory cytokines IL-1 β and TNF- α and the adhesion molecules VCAM-1 and E-selectin [84].

Additionally, other ncRNAs are important for the BBB. Shindo et al. found that administration of PTX3 siRNA on the 3rd day after white matter stroke resulted in aggravated BBB damage, but administration of PTX3 siRNA on the 7th day after white matter stroke promoted cerebral ischemia compensation, which suggested that PTX3 played a dual role in BBB function, providing a basis for the treatment of white matter-related diseases [85]. Bai et al. found that the upregulation of circDLGAP4 expression resulted in the inhibition of endothelial-mesenchymal transition, which contributed to decreased infarct areas and BBB damage in stroke [52]. The upregulation of lncRNA Malat1 expression induced by ischaemia/reperfusion or oxygen–glucose deprivation/reoxygenation treatment impeded the autophagy and survival of ECs by sponging miR-26b and increasing unc-51-like kinase 2 (ULK2), exerting a protective effect on ECs against stroke damage and preventing BBB disruption [86]. Similarly, Snhg8, a member of lncRNA, sponge miR-425–5p, giving impetus to brain microvascular endothelial cell injury by targeting sirtuin1 (SIRT1)-mediated nuclear factor- κ B (NF- κ B) pathway, which indicated that Snhg8 made significant influences in the brain–blood barrier damage in stroke [87].

4.2. Glioma

Gliomas are the most common primary tumors in the central nervous system. While it refers to all tumors of neuroepithelial origin in the broad sense, it refers to tumors of glial cell origin in the narrow sense,

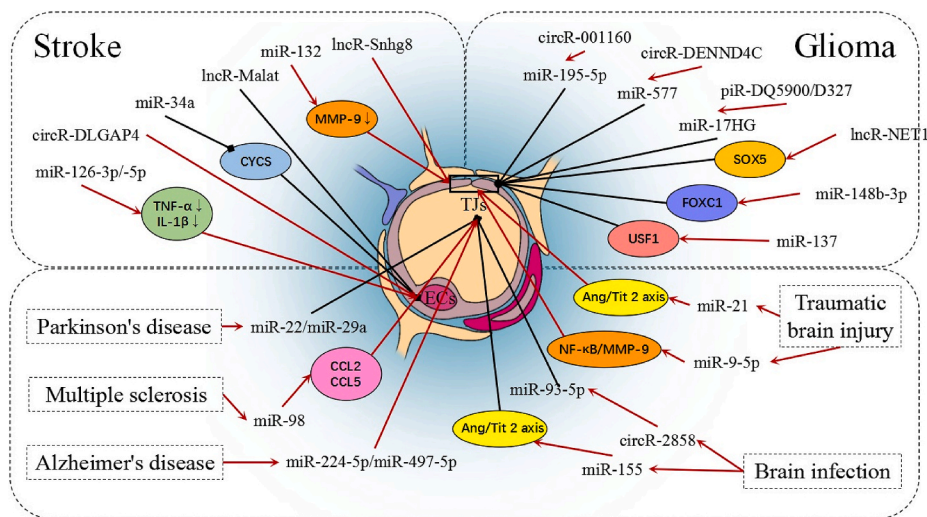


Fig. 2. Representative ncRNAs and their effects on BBB.

including astrocytoma, oligobranhoma, ependymoma and so on. Recently, a large number of studies have discovered the carcinogenic and tumor-suppressive impacts of miRNAs on malignant glioma [88].

Brain metastasis poses a severe threat to breast cancer patients. The results from Lu et al. suggested that exosomes derived from brain metastatic breast cancer cells transferred lncRNA GS1-600G8.5, which downregulated the expression of tight junction proteins, leading to damage to the BBB and the passage of cancer cells [89]. A study found that the degradation of PDPK1 triggered by miR-181c led to the downregulation of phosphorylated cofilin expression, thereby activating cofilin-induced actin dynamic regulation. Therefore, the resulting breakdown of the BBB provides an opportunity for the passage of cancer cells [90]. Further research investigated whether inhibiting miR-509 increased BBB permeability by promoting the secretion of TNF- α , which had a significant impact on the brain metastasis of breast cancer [91].

Similarly, the blood–tumor barrier (BTB) is made up of ECs, which are interconnected and restricted by TJs [92]. Growing evidence has proven that various categories of miRNAs are also associated with the manipulation of the BTB [81]. A study showed that an increase in miR-181a levels resulted in an improvement in the permeability of the BTB and a reduction in ZO-1, occludin, and claudin-5 levels by targeting KLF6, thereby laying a foundation for the treatment of brain gliomas [92]. Similarly, many miRNAs have been proven to significantly increase the permeability of the BTB by decreasing the expression of ZO-1, occludin, and claudin-5. MiR-18a binds to MEF2D [93], miR-144 binds to HSF2 [94], miR-140 binds to NFYA [95], miR-181d-5d binds to SOX5 [96], miR-137 binds to USF1 [97], and miR-148b-3p binds to ZO-2 and FOXC1 [98]. Moreover, lncRNA has been found to play a crucial role in improving the limitation of the delivery of chemotherapeutic agent to brain tumor tissues caused by BTB. Guo et al. demonstrated that lncRNA NET1 not only promoted the permeability of BTB by combining with miR-181d-5p, but also decreased the level of the tight proteins such as ZO-1, occludin and claudin-5 by targeting SOX5, contributing to destroying the integrity of BTB [96]. The research carried out by Zhang et al. revealed that the interaction between lnc00462717 and polypyrimidine tract binding protein (PTBP1) promoted the upregulation of the tight junction-related protein Occludin, providing a promising strategy for the treatment of glioma [99]. The down-regulation of some lncRNAs such as TUG1 and XIST increased BTB permeability, and reduced the level of the tight junction proteins such as ZO-1, occludin, and claudin-5 of BTB [97,100]. What's more, different types of ncRNAs collaborate with each other to regulate BBB TJs. For example, piR-DQ5900/D327/miR-17HG binds to miR-153, which binds to FOXR2

[101], circRNA_001160 binds to miR-195-5p [102], and circular RNA DENND4C binds to miR-577 [103].

4.3. Traumatic brain injury (TBI)

TBI, with a high fatality rate and high disability rate, is defined as craniocerebral injury caused by traffic accidents, high-altitude falls, extreme sports or others, which manifests as memory loss, dysfunction, unconsciousness, or even death [104]. In terms of the pathological process, TBI consists of two stages. The primary injury is attributed to external force, and the secondary injury results in a number of pathophysiological changes in the CNS, including excessive inflammation and BBB rupture [105].

Recent studies revealed that overexpression of miR-21 may alleviate the leakage of the BBB after brain trauma to reduce brain edema and brain damage, resulting in the improvement of nerve function [106]. Ge et al. found that miR-21-5p regulated the levels of apoptotic factors, Akt signaling, inflammatory cytokines and NF- κ B signaling, resulting in leakage of the brain vascular endothelial barrier after TBI [58]. Further research revealed that miR-21 inhibited brain edema after TBI through antiapoptotic effects and improved the expression of the angiogenesis-related molecule VEGF and the Ang-1/Tie-2 axis, which helped repair the leakage of the BBB to promote integrity and maintain the maturation of blood vessels and the stability of the BBB [107]. Another study demonstrated that the inhibition of miR-21 in the Ang-1/Tie-2 axis due to lower levels of miR-21 after TBI reduced the expression of tight junction proteins such as claudin-5 and occludin, which strongly affect the stability and permeability of the BBB [108]. In conclusion, miR-21 can have beneficial effects on the protection of the BBB from damage caused by TBI [109].

Moreover, a previous study found that miRNA-9-5p not only stimulated the Hedgehog pathway but also inhibited the NF- κ B/MMP-9 pathway, contributing to the downregulation of Ptch-1 expression in ECs, which inhibited cellular apoptosis and inflammation and protected TJs. Therefore, the stability of the BBB was maintained to promote the recovery of neurological function after TBI [110]. Burek et al. revealed that tight junction-associated protein 1, the junction protein claudin-1, and junctional adhesion molecule 3 were promising miR-212/132 targets for the maintenance of BBB integrity [111].

4.4. Alzheimer's disease (AD)

For Alzheimer's disease, the disruption of the BBB linked to cerebrovascular deposition of the amyloid-beta ($A\beta$) protein has received

Table 1
Impacts of ncRNAs on the BBB in CNS diseases.

Types of CNS diseases	ncRNAs	Impacts on BBB	Target gene/Mechanism	References	
Stroke	miR-155	Impairing TJs	By targeting claudin-1	[78]	
	miR-34a	Damaging ECS	By targeting CYCS	[79]	
	miR-210	Impairing TJs	By targeting occludin and β -catenin	[56]	
	miR-150	Impairing TJs	By binding to the angiotensin receptor Tie-2	[57]	
	miR-130a	Impairing TJs	By targeting homeobox A5	[80]	
	miR-132	Impairing TJs	By inhibiting the expression of MMP-9 and degenerating the tight junction proteins VE-cadherin and β -catenin	[54]	
	miR-132	Impairing TJs	By decreasing ZO-1 and claudin-5 expression	[82]	
	miR-126-3p	Protecting ECs	By binding to PIK3/Akt pathway components	[83]	
	miR-126-3p/-5p	Protecting ECs	By decreasing the level of the proinflammatory cytokines IL-1 β and TNF- α and the adhesion molecules VCAM-1 and E-selectin	[84]	
	circDLGAP4	Improving ECs	By inhibiting endothelial-mesenchymal transition	[52]	
	lncRNA Malat1	Damaging ECs	By sponging miR-26b and increasing unc-51 like kinase 2	[86]	
	lncRNA Snhg8	Improving TJs	By increasing ZO-1 and Occludin	[87]	
	Glioma	lncRNA GS1-600G8.5	Impairing TJs		[89]
		miR-181c	Impairing TJs	By degrading PDPK1	[90]
miR-509		Impairing TJs	by promoting secretion of TNF- α	[91]	
miR-181a		Impairing TJs	By reducing ZO-1, occludin, and claudin-5 expression and targeting KLF6	[92]	
miR-18a		Impairing TJs	By binding to MEF2D	[93]	
miR-144		Impairing TJs	By binding to HSF2	[94]	
miR-140		Impairing TJs	By binding to NFYA	[95]	
miR-181d-5d		Impairing TJs	By binding to SOX5	[96]	
miR-137		Impairing TJs	By binding to USF1	[97]	
miR-148b-3p		Impairing TJs	By binding to ZO-2 and FOXC1	[98]	
lncRNA NET1		Impairing TJs	By targeting SOX5	[96]	
lnc00462717		Improving TJs	By interacting with polypyrimidine tract binding protein	[99]	
lncRNA TUG1		Improving TJs	By reducing ZO-1, occludin, and claudin-5 expression	[100]	
lncRNA XIST		Improving TJs	By reducing ZO-1, occludin, and claudin-5 expression	[97]	
piR-DQ5900/D327/miR-17HG	Impairing TJs	By binding to FOXR2	[101]		
Traumatic brain injury	circRNA_001160	Impairing TJs	By binding to miR-195-5p	[102]	
	circRNA DENND4C	Impairing TJs	By binding to miR-577	[103]	
	miR-21-5p	Protecting ECs	By suppressing apoptosis, Akt signaling, inflammatory cytokines and NF- κ B signaling	[58]	
	miR-21	Protecting TJs and ECs	By resisting apoptosis and improving the expression of the angiogenesis-related molecule VEGF and the Ang-1/Tie-2 axis	[107]	
	miR-21	Protecting TJs	By reducing the loss of claudin-5 and occludin	[108]	
	miRNA-9-5p	Protecting TJs and ECs	By stimulating the Hedgehog pathway and inhibiting the NF- κ B/MMP-9 pathway	[110]	
Alzheimer's disease	miR-212/132	Protecting TJs	By targeting tight junction-associated protein 1, the junction protein claudin-1, and junctional adhesion molecule 3	[111]	
	miR-107	Impairing TJs	By decreasing endophilin-1 expression by regulating ZO-1, occludin, and claudin-5	[113]	
	miR-224-5p/miR-497-5p	Protecting TJs	By increasing ZO-1, occluding, and claudin-5 expression	[115]	
	miR-501-3p	Impairing TJs	By binding to the 3'UTR of ZO-1 mRNA	[116]	
Multiple sclerosis	LINC00662	Improving TJs	By promoting the degradation of ELK4 mRNA by SMD pathway	[117]	
	miR-155	Impairing TJs	By reorganizing vinculin and ZO-1 and binding to the DOCK-1, syntenin-1, claudin-1, and annexin-2 genes	[119]	
	miR-125a-5p	Improving ECs	By regulating claudin-5 and ZO-1	[120]	
	miR-126	Impairing TJs	By weakening the adherence of monocytes and T cells to human ECs and decreasing the level of E-selectin and VCAM1	[121]	
	miR-98	Reducing leukocyte adhesion	By binding to CCL2 and CCL5	[122]	
	miR-22/miR-29a	Impairing TJs	By regulating the VCAM-1 and ICAM-1 of the BBB	[123]	
Parkinson's disease	miR-22/miR-29a	Impairing TJs	By regulating the VCAM-1 and ICAM-1 of the BBB	[123]	
	Brain infection	circ_2858	Reducing TJs	By binding to miR-93-5p	[124]
		miR-1303	Improving ECs	By degrading the junction proteins claudin-4, claudin-5, VE-cadherin, and ZO-1 by binding to MMP-9	[125]
	miR-155	Damaging ECs	By targeting the Ang/Tie2 axis	[126]	

major emphasis as a key pathological feature [4]. The loss of tight junction proteins and the accumulation of A β protein result in disruption of the function of the BBB [25,112].

Liu et al. demonstrated that the increase in miR-107 expression eliminated A β -induced disruption of the BBB by decreasing the expression of endophilin-1, which was associated with the regulation of ZO-1, occludin, and claudin-5 [113]. Moreover, Kim et al. found that induction of ABCA1 caused by the downregulation of microRNA-33 expression not only improved the lipidation of brain ApoE but also decreased A β levels [114]. Moreover, enhanced miR-224-5p or miR-497-5p binding to endophilin-1 led to an increase in ZO-1, occludin, and claudin-5 levels, which contributed to damage to BBB permeability [115]. Similarly, the

inflammation and apoptosis attributed to miR-501-3p in vascular dementia had a negative influence on the TJs of the BBB via binding to the 3'-UTR of ZO-1 mRNA [116]. Besides, LINC00662 was found by Liu et al. to promote the degradation of ELK4 mRNA by SMD pathway, leading to the up-regulation of tight junction-related protein of BBB, which explained the BBB breakdown in early AD [117].

2.1. Multiple sclerosis (MS)

Multiple sclerosis is an immune-mediated chronic inflammatory demyelinating disease of the central nervous system. The most common sites of multiple sclerosis are periventricular, proximal cortex, optic

nerve, spinal cord, brainstem and cerebellum. The main clinical features of multiple lesions are dissemination of lesions in space and in time. The main clinical features of the disease are scattered white matter of the central nervous system in multiple lesions and recurrence, spatial symptoms and signs and temporal progression of the disease course [118].

MiR-155 has been proven to reorganize the formation of vinculin and ZO-1 to protect BBB integrity by combining with the DOCK-1, syntenin-1, annexin-2 genes, and claudin-1 [119], and miR-125a-5p has been proven to increase brain endothelial cell barrier function [120]. Moreover, the decrease in miR-126 levels strengthened the adherence of monocytes and T cells to human ECs and increased the levels of E-selectin and VCAM1 [121] when miR-98 reduced leukocyte adhesion by binding to CCL2 and CCL5 [122].

2.2. Parkinson's disease (PD)

Parkinson's disease is a dyskinesia that manifests as relaxation of voluntary movement, resting tremor, muscle rigidity and postural and gait disorders. In PD patients, upregulation of the expression of inflammatory factors such as VCAM-1, miRNA-22, and miRNA-29a resulted in an increase in proinflammatory cytokines such as TNF- α and IL-1 β , which exacerbated neuroinflammation by regulating VCAM-1 and ICAM-1 in the BBB [123].

2.3. Brain infection

Regarding brain infection, one study demonstrated that a newly identified circRNA, circ_2858, after meningitis induced by *Escherichia coli* infection competitively binds miR-93-5p to downregulate the expression of tight junction proteins, contributing to changes in BBB permeability [124].

Coxsackie virus A16 is another highly neurotropic virus that infects children. Recently, Song et al. found that miR-1303 increased the permeability of the BBB of human umbilical vein ECs, which is related to the degradation of claudin-4, claudin-5, VE-cadherin and ZO-1 [125].

Barker determined that the activation of endothelial cells triggered by miR-155 contributed to the leakage of the BBB in cerebral malaria [126].

Amjad et al. demonstrated that *Neisseria meningitidis* crosses the BBB of the host, resulting in a significantly enhanced signal of brain microvascular colorectal miR-19b-3p/TNFAIP3/NF- κ B, which causes further inflammatory damage to the central nervous system of the host [127].

5. Conclusion

In conclusion, ncRNAs are versatile regulatory molecules that regulate the integrity and permeability of the BBB through different mechanisms, thus playing an important role in the pathophysiology and therapeutic prognosis of CNS diseases. First, ncRNAs are involved in regulating the biological processes of inflammation, necrosis, and apoptosis of the cells that constitute the BBB, aggravating or reducing the dysfunction of the BBB. Second, they affect the translational dysfunction of proteins that constitute the BBB structure, interfering with the physiological function of the BBB. In addition, they can exert effects on the TJs of the BBB and change its permeability and integrity, which is the most common and most important among all methods.

Major progress has been made in elucidating the mechanism of ncRNAs' effects on the BBB in CNS disease, which provides innovative methods for the treatment of many diseases. For example, the regulation of related lncRNAs increases the permeability of the BTB, which is conducive to the drug treatment of glioma. For example, miR-based drug and recanalization of endovascular thrombotomy may provide a new prospect for the treatment of ischemic stroke. However, the role of ncRNAs in BBB function is still unclear and remains to be determined.

There are still many problems to be solved, such as avoiding the degradation caused by RNases and the potential off-target effects. A comprehensive and detailed understanding of the mechanism by which ncRNAs regulate the structure and function of the BBB will not only help discover biomarkers for the early diagnosis of diseases but also lay a solid foundation for the development of effective drugs for the treatment of CNS diseases.

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