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Ependymal cells: roles in central nervous system infections and therapeutic application

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Abstract

Ependymal cells are arranged along the inner surfaces of the ventricles and the central canal of the spinal cord, providing anatomical, physiological and immunological barriers that maintain cerebrospinal fluid (CSF) homeostasis. Based on this, studies have found that alterations in gene expression, cell junctions, cytokine secretion and metabolic disturbances can lead to dysfunction of ependymal cells, thereby participating in the onset and progression of central nervous system (CNS) infections. Additionally, ependymal cells can exhibit proliferative and regenerative potential as well as secretory functions during CNS injury, contributing to neuroprotection and post-injury recovery. Currently, studies on ependymal cell primarily focus on the basic investigations of their morphology, function and gene expression; however, there is a notable lack of clinical translational studies examining the molecular mechanisms by which ependymal cells are involved in disease onset and progression. This limits our understanding of ependymal cells in CNS infections and the development of therapeutic applications. Therefore, this review will discuss the molecular mechanism underlying the involvement of ependymal cells in CNS infections, and explore their potential for application in clinical treatment modalities.

Key points

- Ependymal cells play an important role in the maintenance of CSF homeostasis and CNS health by forming physical and immune barriers against pathogen invasion.
- PPRs signaling pathways, cilia and intercellular junctions, cytokine secretion or senescence of ependymal cells can lead to dysfunction, which in turn is involved in the onset and progression of CNS infection.
- We propose potential therapeutic applications including gene transfer and novel biomarkers.
- Studies of ependymal cells have provided new ideas for pathophysiology and treatment, but further research is needed to fully understand their role in CNS infection and evaluate therapeutic effect.

Keywords Ependymal cell, Central nervous system infections, Molecular mechanism, Clinical treatment

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Introduction

Ependymal cell

Ependymal cells are glial cells that form an epithelium lining the inner surfaces of the brain ventricles and the central canal of the spinal cord [1, 2]. They are located at the interface between cerebrospinal fluid (CSF) and brain parenchyma, playing a crucial role in the formation of the brain-CSF barrier [3]. They provide significant mechanical support and sensory functions, facilitating the transport of substances between CSF and parenchyma to maintain the composition of CSF while isolating damaging agents to protect the central nervous system (CNS). The apical ciliary clusters of ependymal cells beat in a coordinated manner to regulate the unidirectional flow of CSF. Moreover, ependymal cells can secret cytokines and other signaling molecules, providing nutritional support and contributing to immune and metabolic regulation. Reports indicate that ependymal cells can be activated under pathological conditions, such as spinal cord injury (SCI), exhibiting robust proliferative capacity and multipotent responses to injury, positioning them as potential endogenous stem cells [4] (See Fig 1). The heterogeneity of ependymal cells has been widely explored. Recent studies have identified different subgroups of ependymal cells according to their different localizations and morphologies, including multiciliated E1, biciliated E2 and uniciliated E3 [5, 6]. They possess distinct molecular markers and regeneration characteristics, playing varying roles in neurodevelopment, homeostasis maintenance, and damage response [7]. Among them, the E1 is the major subgroup, playing a key role in the brain homeostasis. In this review, we put emphasis on the multiciliated ependymal cells.

Ependymal cell and CNS diseases

Due to the critical role of ependyma integrity and CSF homeostasis in regulating normal CNS activity, ependymal cells are implicated in the pathogenesis of various CNS disorders [6] (See Fig 1). Numerous studies have focused on the relationship between ependymal cells and hydrocephalus, identifying mechanisms such as ciliary dysfunction and loss of ependymal integrity caused by impaired cell junctions, both of which are considered to be the mechanisms of hydrocephalus [8, 9]. In addition, ependymal cell abnormality is found in the early pathological stages of neurotrauma. For example, after traumatic brain injury (TBI), there is a dramatic reduction in ependymal cilia, as well as DNA damage in cells, potentially affecting the barrier function and disrupting CSF composition, circulation, and waste clearance [10]. Dysfunction of ependymal cells may heighten the risk of further neuropathology and disease, particularly neurodegenerative disorders. Evidence of ependymal dysfunction has been noted in several neurodegenerative diseases, including multiple sclerosis (MS), Alzheimer's disease (AD) and other neurodegenerative diseases. In autoimmune demyelinating diseases, after exposure to autoantibodies, such as IgG against Aquaporin-4 and GlialCAM, it can induce changes in the substance expression and morphology of ependymal cells and lead to lesions in the periventricular area [11, 12]. Though whether ependymal cells could serve as a potential origin

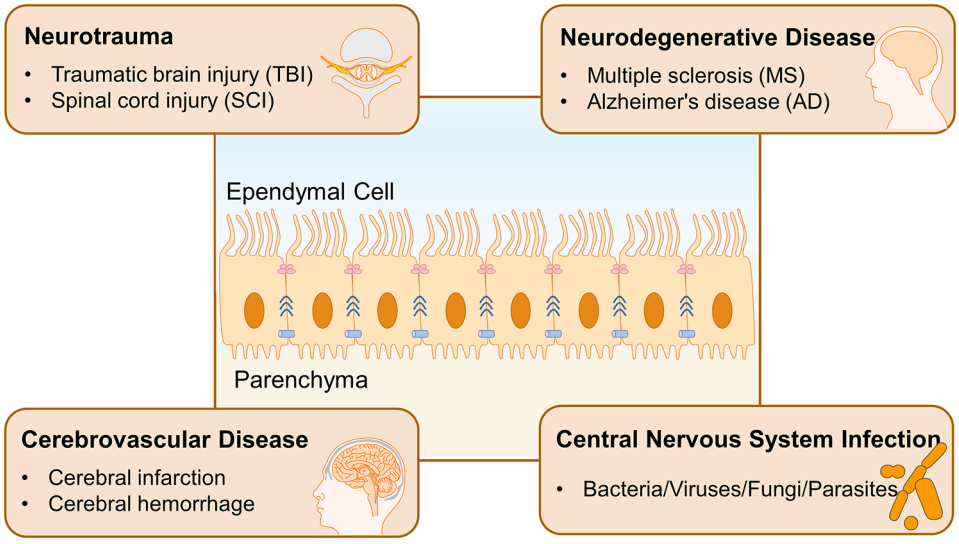

Fig. 1 The structure, location and roles of ependymal cells Multiciliated ependymal cells are located at the interface between CSF and CNS parenchyma, participating in the brain-CSF barrier formation. Their cilia beat in a coordinated manner to regulate the unidirectional flow of CSF. There exist tight junctions, gap junctions, and adhesion junctions between cells, which maintain ependymal integrity and permeability and isolate harmful substances to protect the CNS. Ependymal cells are involved in the onset and progression of many CNS diseases, including neurotrauma, neurodegenerative diseases, cerebrovascular diseases, and CNS infections

of these diseases remains to be further explored [13]. However, ependymal cells also participate in the restrictive repair and prognosis. In the later stages of SCI, ependymal cells can actively promote neurological recovery by activating proliferation and differentiation, as well as providing neurotrophic support and limiting secondary injury [14]. The CNS can be infected by various pathogens, including viruses, bacteria, fungi, and parasites, which invade neural tissue, meninges, and vasculature, resulting in CNS infections with diverse pathological changes. Among them, ependymal cells are also susceptible to infections. It is worth mentioning that Stratton, J. A. and her team have carried out detailed and comprehensive work on ependymal cells. They also wrote a review to update the biology and pathology of ependymal cells in the adult brain, introducing the role of multiciliated ependymal cells in homeostasis and in response to CNS pathologies and aging [2].

While the significance of ependymal cells in CNS disorders is recognized, little is known about their molecular mechanisms in disease progression, particularly in infectious diseases. Recently, several reviews and articles have discussed and hypothesized about ependymal cells in the pathogenesis of SCI [15, 16], AD [13, 17], hydrocephalus [3, 18], autoimmunity [11, 12] and neurodegenerative diseases [13, 19]. Nevertheless, their involvement in CNS infection has received scant attention. In Stratton, J. A.'s latest review, a summary table regarding recent studies on ependymal cells in infections was presented in Supplementary Table 4 [2]. This review describes the mechanism by which ependymal cells are involved in CNS infections and their potential application in clinical practice. These findings will help clarify the role of ependymal cells in CNS infections and may encourage targeted therapies for CNS diseases based on ependymal cell function (See Fig 1).

Ependymal dysfunction in infections

Ependymal cells can be invaded or affected by various pathogens. Receptors for coxsackie-adenovirus, measles virus [20] and the poliovirus [21] are present on ependymal cell surface. Nectin, expressed on the ependymal cells, functions not only as an adhesion molecule but also as an entry receptor for some viruses [22, 23]. For the newly emerging pathogen SARS-CoV-2, low-level expression of both angiotensin-converting enzyme-2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2), necessary for viral entry, has been observed in human choroid plexus (CP) and ependymal cells [24, 25]. There are plaques that are immunopositive for the prion protein (PrP) in ependymal cells and around the base of adjacent vessels [26–28] following prion infection. Interactions between cells and prions lead to the formation and production of scrapie PrP amyloid filaments, along with the synthesis of PrP mRNA in ependymal cells [29], suggesting that ependymal cells may serve as one of the targets of prions [30]. HSV-1 infection shows a tropism for the ependyma, resulting in a loss of ciliated ependymal cells, lateral ventricular enlargement, and increased intracranial pressure during acute infection [31]. However, during latency, the expression of HSV-1 lytic genes is detected in the ependyma, correlating with a sustained dysfunctional response from resident T cells [32]. Ependymal cell dysfunction after infection is associated with various pathological changes in the CNS.

Ependymal dysfunction and post-infectious hydrocephalus

Ependymal ciliary dysfunction, inflammation, and increased intercellular space may contribute to hydrocephalus. In malaria, ependymal cells display varying degrees of damage, including ciliary thickening or loss, increased intercellular space, and dissociation of the ependymal layer. These alterations may enhance the permeability of the CSF-brain barrier [33]. In a model of Streptococcus pneumoniae meningitis, ependymal cells exhibit structural and functional ciliary abnormalities [34]. Zika virus's NS5 protein causes severe ciliopathy through interacting with cilia in ependymal cells, which may be associated with microcephaly [35, 36]. Ciliary dysfunction may contribute to the neuropathological changes following CNS infections, especially hydrocephalus. In neurocysticercosis (NCC) caused by the larval form of Taenia Solium, ependymal and arachnoidal inflammation, along with the obstruction of the CSF pathway can lead to hydrocephalus, the most common cause of hydrocephalus in adults in endemic regions [37] (See Fig 2).

In fact, post-infectious hydrocephalus is the leading cause of hydrocephalus in children worldwide, and hydrocephalus resulting from tuberculous meningitis (TBM) imposes a considerable burden in regions with a high tuberculosis prevalence [38]. Different reovirus serotypes mediate infectious tropism and pathogenesis: serotype 1 infects ependymal cells, leading to hydrocephalus, while serotype 3 targets neurons, resulting in encephalitis [39, 40]. This suggests that ependymal cell injury during infection may be a key pathophysiological mechanism underlying post-infectious hydrocephalus [41]. On the one hand, in the acute phase, ongoing damage to choroidal epithelial cells, ependymal cells, and brain tissue coupled with inflammation, may impair CSF resorption. On the other hand, in the chronic phase, ependymal scarring leads to intraventricular obstruction. In both instances, they account for the pathophysiologic mechanism of post-infectious hydrocephalus [38, 41]. In addition, microglia are also involved in the damage and death of ependymal cells. Intracerebroventricular (ICV) injection of recombinant HIV-1 tat protein can

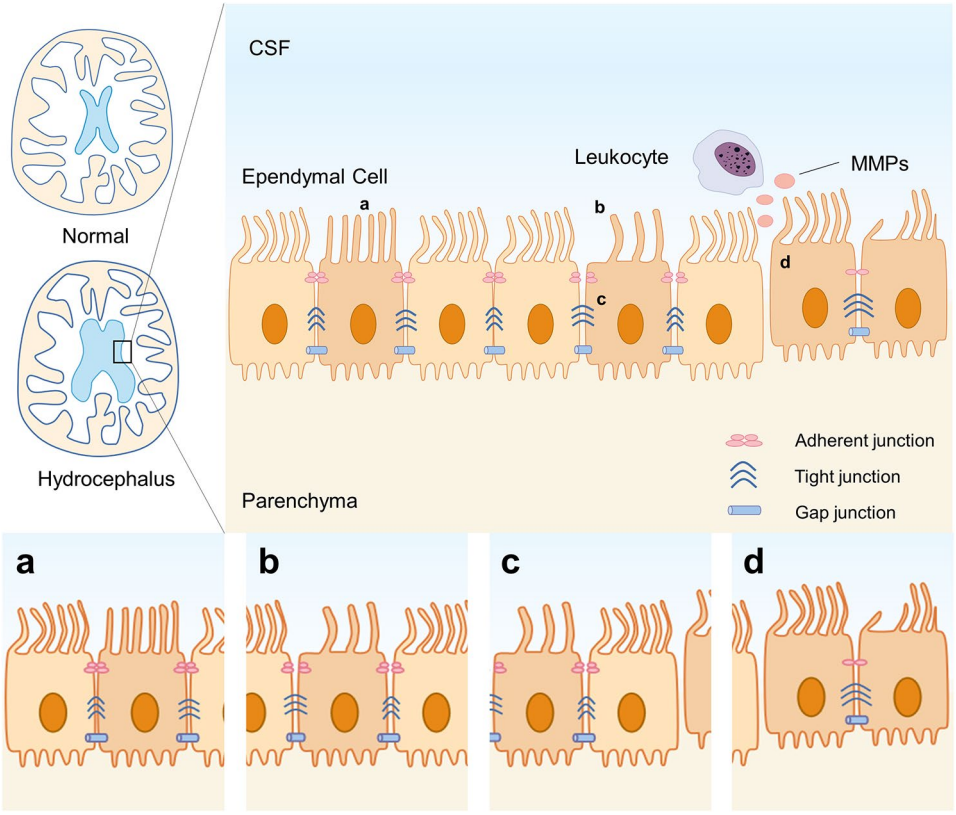

Fig. 2 Hydrocephalus and ependymal cell dysfunction Hydrocephalus often occurs after infection, with structural and functional abnormalities in ependymal cells: **(a)** a decreased ciliary beating frequency; **(b)** an increased intercellular space, with junctions changing or disappearing; **(c)** cilia thickening or loss; **(d)** ependymal denudation. Besides, leukocytes express active MMPs that allow them to cross the ependymal barrier and infiltrate the ventricles. MMPs: matrix metalloproteinases

lead to ependymal damage and activate subependymal microglia. These microglia phagocytose ependymal fragments and migrate and infiltrate into the periventricular area and parenchyma, thereby causing inflammation [42]. VPS35 is highly expressed in ependymal cells and is involved in ependymal cell differentiation and ciliogenesis. In mice with VPS35 specifically knocked out in ependymal cells, hydrocephalus is observed, accompanied by damaged ependymal cells and local activation of microglia. After depletion, an alleviation in hydrocephalus and a restoration of ependymal cell homeostasis are observed [43].

Ependymal barrier dysfunction and pathogen invasion

Significant structural features of ependymal cells are the apical ciliary cluster and the tight junctions, gap junctions and adhesion junctions between them [44–46]. Together, they maintain ependymal integrity and permeability, regulate CSF circulation and ion transport, and form the brain-CSF barrier, which is crucial for maintaining CSF homeostasis. In CNS infection, ependymal cells present with ciliary loss, decreased beating frequency, and ultrastructural disruption, making neurons more likely susceptible to bacterial toxins [34], accompanied by hydrocephalus. Some pathogens, such as cryptococcus, enter the CNS through the blood-CSF-brain pathway. Following intracerebral inoculation, the virus initially spreads in the CSF and extensively infects ependymal cells before entering the brain parenchyma to infect neurons and glial cells [47, 48], thereby establishing a pathway for encephalitis development [49]. Cytomegalovirus (CMV) is the most common opportunistic viral pathogen in immunocompromised adults. It preferentially affects ependymal cells, and then expands to the parenchyma [50]. Additionally, SARS-CoV-2 can induce neurological symptoms and complications, and its staining is observed in CP and ependymal cells [51]. SARS-CoV-2 exhibits tropism for CP epithelial cells, accompanied by increased cell syncytia and increased cell death. And RNA-seq reveals heightened inflammatory cellular responses and downregulation of genes related to transport, cilia, and cell junctions, resulting in impaired barrier and secretory functions [52, 53]. And as for neurocysticercosis (NCC) infection, Alvarez proposes a fourth route from blood to the CSF through the disrupted ependymal layer via internal leptomeninges vessels [54]. Notable structural changes and loss of junction proteins occur in ependymal cells adjacent to the internal leptomeninges, correlating

with active matrix metalloproteinases (MMPs) expressed by leukocytes, which facilitate their infiltration into the ventricles [54–56]. In malaria, the observed intercellular dissociation of ependymal cells appears to enhance the paracellular permeability of the CSF-brain barrier, making inflammatory mediators and toxins to enter the brain and cause injury [33]. In early bacteremia of tuberculosis, Mycobacterium tuberculosis (Mtb) deposits in the subpial or subependymal region of the brain and remains dormant for a long time. When the lesion expands and ruptures into the ventricle or subarachnoid space [57], it can lead to TBM. Mtb can also cross the ependymal layer or CP to enter the brain parenchyma [58]. Similarly, pathogens can invade the blood-CSF barrier and penetrate CP epithelium via the Trojan horse strategy, resulting in barrier breakdown and subsequent CNS infection [59].

In summary, ependymal cells may serve as a route for the entry of pathogens and inflammatory mediators into the brain. This occurs via the transcellular pathway through receptors, the paracellular pathway that disrupts with ependymal cell junctions, and leukocyte infiltration [53]. In addition to pathogens, tumors, immune cells, antibodies and cytokines can also access the brain parenchyma through the blood-CSF-brain pathway (See Fig 2).

The mechanism of ependymal cells in CNS infection

Pattern-recognition receptors are involved in inflammatory signaling

Intraventricular administration of lipopolysaccharide (LPS) induces a robust inflammatory response at the periventricular margin of the cerebral cortex. The inflammatory signaling in the brain may involve two pathways: local diffusion of LPS/inflammatory molecules across the meninges and ependyma, as well as signaling through cerebral blood circulation [60]. During CNS infection, ependymal cells at the blood-CSF barrier and CSF-brain barrier function as both a physical and immunological barrier. Pattern-recognition receptors (PPRs) on these cells, including Toll-like receptors (TLRs), CD14 and C-type lectin PRR, can recognize pathogens prior to their entry into the parenchyma and participate in inflammatory signaling transduction.

The expression of TLRs on ependymal cells increases upon infection, such as TLR4, TLR7, TLR8, and TLR13. TLR-mediated innate immunity plays a crucial role in recognizing pathogens such as bacteria, viruses, fungi and parasites, and facilitates interactions between immune cells and CNS cells [61–63]. The downstream of signaling of TLR4 involves the signaling molecules myeloid differentiation factor 88 (MyD88), nuclear factor kappa B (NF-κB) and inflammatory factors interleukin-1β (IL-1β) and tumor necrosis factor α (TNF-α). These factors not only induce the release of inflammatory factors, and apoptosis of phagocytic cells but also mediate persistent brain inflammation and neurological tissue damage during endotoxemia [60, 64]. Additionally, the ependyma also expresses the scavenger receptor CD14, which interacts with TLR4 to promote the phagocytosis of apoptotic neutrophils in CSF, thereby reducing the severity of inflammation [65].

In addition, unmethylated CpG motifs in bacteria are highly immunogenic and activate TLR9 signaling, leading to damage and subsequent activation of periventricular microglia, ependymal destruction and reactive astrocyte proliferation. This cascade may result in impaired neurological function, neuroinflammation, and even neurodegeneration [66], suggesting a potential association among infection, innate immunity and neurodegeneration. Pituitary adenylate cyclase-activating polypeptide (PACAP) can inhibit LPS-induced TLR4 signaling and its downstream responses, reducing the secondary inflammatory response and indicating a neuroprotective role [67]. Meanwhile, the regulation of TLRs can help maintain balance within the innate immune system, preventing excessive antimicrobial inflammatory response that could lead to secondary brain damage. TLRs may serve not only as targets for immunomodulation in CNS infection, but also for improving the prognosis of nerve injury and neurodegenerative conditions. Further research on TLRs is essential to elucidate how infections and innate immunity influence the onset and progression of neurodegenerative disorders.

Indeed, CNS infection can disrupt ependymal ciliary status and motility through the TLR/MyD88/NF-κB signaling pathway, contributing to acquired hydrocephalus [68]. In the presence of inflammatory factors and chemokines such as TNF-α and IL-1, NF-κB activation and pro-inflammatory mediators lead to macrophage recruitment and inhibition of ciliogenesis [69]. Furthermore, the NF-κB-independent inhibitor of kappa B kinase 2 (IKK2) stabilizes Foxj1, whereas some viruses such as HSV-1 and growth factors can inhibit IKK, resulting in Foxj1 degradation, dedifferentiation of ependymal cells, and progression to hydrocephalus [70]. On the other hand, cilia length and function may regulate TLR4-mediated NF-κB signaling activation and pro-inflammatory cytokine expression [71], suggesting that the interactions between the NF-κB signaling pathway and cilia in neuroinflammation and innate immune responses warrant further investigation. As mentioned earlier, ependymal cilia are crucial for maintaining CSF homeostasis and undergo pathological changes during infection. Ciliogenetic genes are highly expressed in ependymal cells and are tightly regulated by a complex network of transcription factors, with Foxj1 serving as the central transcription factor of ciliogenesis in the network [72] (See Fig 3). Additionally, there is a strong connection between ciliogenesis and cell

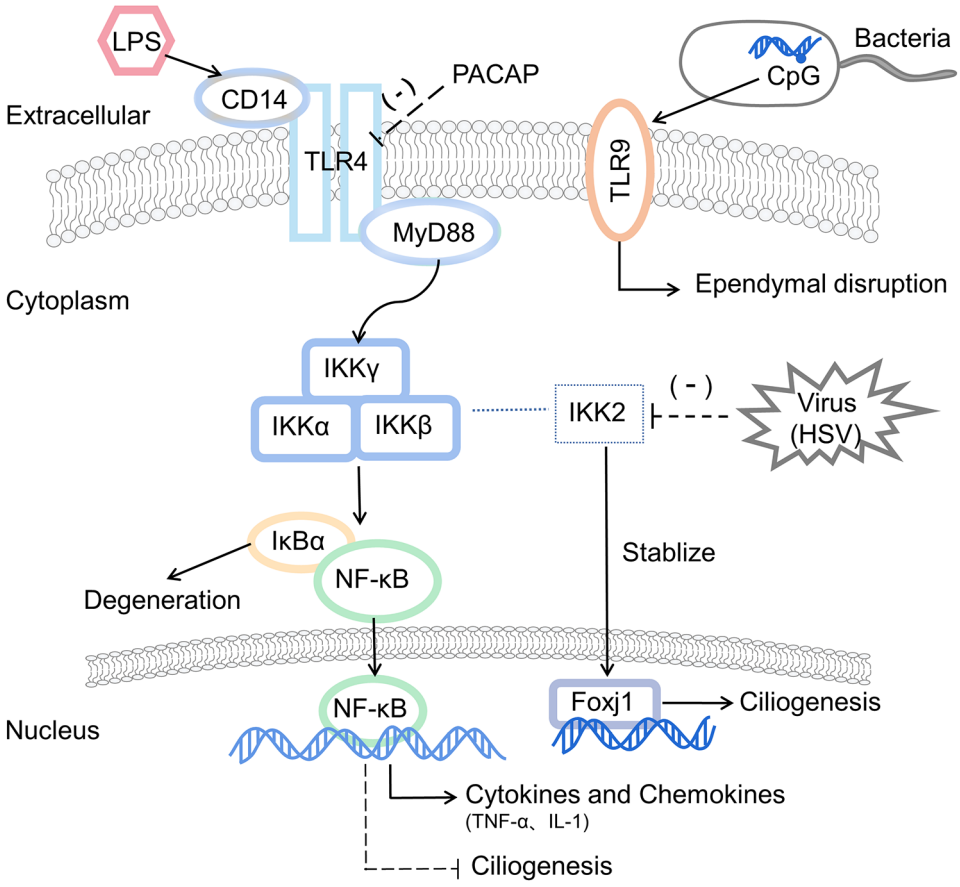

Fig. 3 Pattern recognition receptors on ependymal cells are involved in inflammatory signaling The TLR4/MyD88/NF-κB signaling pathway induces the release of inflammatory cytokines like IL-1β and TNF-α, while promoting phagocytic apoptosis. This mediates persistent brain inflammation and neurological tissue damage. Activation of NF-κB and pro-inflammatory mediators facilitates macrophage recruitment and inhibits ependymal ciliogenesis. NF-κB-independent IKK2 can stabilize Foxj1, while some viruses such as HSV-1 and growth factors can inhibit IKK, which in turn strongly induces Foxj1 degradation and subsequently leads to hydrocephalus. Besides, unmethylated CpG in bacteria relies on TLR9 signaling to mediate damage and induce ependymal destruction. LPS: lipopolysaccharide; TLR: toll-like receptor; PACAP: Pituitary adenylate cyclase-activating polypeptide; NF-κB: nuclear factor kappa B; IKK: inhibitor of kappa B kinase

cycle regulation. After SCI, the expression of cilia-related genes in ependymal cells may be suppressed due to increased cell proliferation and downregulation of Foxj1 expression [72]. The axoneme, the fundamental structure of cilia, comprises microtubules and ATP-driven dynein motors [73], enabling cilia to beat synchronously in a rhythmic, wave-like manner through gap junctions or innervation. However, structural and functional abnormalities within the cilia may impair intraciliary transport, ciliary maintenance, material transport, and CSF regulation [9], leading to ventricular enlargement and hydrocephalus. Mutations or defects in cilia-related genes and proteins can result in compromised ciliary motility and failure of mucosal clearance [68], resulting in primary ciliary dyskinesia (PCD) [74]. PCD is a hereditary and clinically heterogeneous syndrome characterized by recurrent respiratory infections, infertility and early postnatal hydrocephalus [75]. At least 40 genes have been found to be associated with PCD [76–80]. Consequently, hydrocephalus can arise from the production of structurally abnormal cilia that cause dyskinesia and disrupt normal CSF flow.

Inflammatory cytokines and neurotrophic support

Ependymal cells are also involved in immune regulation and inflammatory responses through cytokines. Interferon (IFN) is a cytokine involved in antiviral, antitumor and immunomodulation activities, particularly in viral encephalitis and autoimmune diseases within the CNS. Following viral infection, ependymal cells produce IFN-α/β, which strongly inhibits viral transmission [81, 82]. Additionally, IFN-γ induces ependymal cells to express chemokines that recruit T cells into the CNS synergizing with peripheral infection stimulation [83]. Loss of myelin is a prominent pathological hallmark of MS and viral infection in humans. Defects in IFN-γ signaling are linked to enhanced oligodendrocyte tropism and delayed virus clearance but do not significantly impact the extent

or distribution of demyelination [84, 85]. Interferon regulatory factor 3 (IRF3) is selectively expressed in brain cells, with particularly strong expression in ependymal cells [86]. Upon activation, IRF3 induces IFN-β production and antiviral immunity, effectively inhibiting viral replication [86]. For example, during CNS infection with coronaviruses, the interplay between IFN I-related innate immunity and the cleavage of the viral spike glycoprotein by host protease contribute to reduced neurovirulence and control of neural invasion [87], highlighting two potential antiviral targets. In the absence of functional IFN I, the Semliki Forest virus exhibits rapid and widespread infection with tropism, affecting ependymal cells, meningeal cells, and oligodendrocytes, resulting in viral encephalitis. JC polyomavirus (JCPyV) infection can also cause encephalitis and induce progressive multifocal leukoencephalopathy [82]. In a CNS infection model with Mouse polyomavirus (MuPyV) to mimic JCPyV infection, STAT1 is involved in IFN receptor signaling and collaborates with CD8 T cells to alleviate MuPyV encephalopathy and control viral replication [88]. Additionally, by inducing acute neuroinflammation through the application of LPS and IFN-γ both in vivo and in vitro, ependymal cells can be triggered to exhibit reactive characteristics, manifested as the increased expression of GFAP and STAT1 and closely related to some genes associated with cellular reorganization and immune regulation. The same applies to chronic neuroinflammation [89]. Macrophage migration inhibitory factor (MIF), present in ependymal cells and choroidal epithelial cells [90, 91], serves as a key upstream mediator of host innate and adaptive immunity, functioning as immunomodulators and pro-inflammatory cytokines that facilitate pathogen clearance and enhance host defenses [92].

The TLR pathway has been established as a crucial mediator of inflammatory signal recognition, with TNF-α and IL-1-mediated acute inflammatory response playing important roles in the initiation of inflammatory response to CNS infection. Following both HSV viral encephalitis and bacterial meningitis, induction of TNF-α was observed in the ependyma, alongside elevated levels of pro-inflammatory factors and chemokines in the CSF, such as IL-1β, IL-6, CXCL1, and CXCL10 [31, 93, 94]. In infant rats infected with Streptococcus pneumoniae, ependymal cells and CP express cathelin-related antimicrobial peptide, which are induced by IL-1β and TNF. Furthermore, the expression of the antimicrobial peptide LL-37 has also been detected in the CSF of patients with bacterial meningitis [95].

Moreover, ependymal cells likely consistently express receptors for IL-1 and TNF-α. In acute aseptic neuroinflammation induced by neuraminidase (NA) injection, activated microglia are contribute to ependymal injury in the ventricles, with IL-1β likely serving as the mediator [96]. This mechanism may explain how neurological infections, such as those caused by Streptococcus pneumoniae, lead to ependymal cell death and hydrocephalus. However, it is also evident that NA can partially induce ependymal damage in vitro, indicating that its role should not be discounted. Additionally, IL-1 signaling is directly or indirectly involved in the changes of the blood-CSF barrier. High levels of IL-1β in CP enhance the activity of MMPs, which degrade substrates and junction proteins, increasing barrier permeability and inducing edema. This process also facilitates the release of chemokines and leukocyte trafficking [97]. Activating transcription factor 3 (ATF3) acts as a negative regulatory transcription factor in TLR pathways [98], thereby reducing the expression of genes encoding inflammatory cytokines such as IL-1β, IFN-γ and TNF-α during infection and injury [99, 100]. Quiescent ependymal cells express ATF3; while activated in vitro or after SCI, ATF3 expression is upregulated, accompanied by the migration of ependymal cells [101]. Inhibiting ATF3 suppresses the migration of ependymal cells and upregulates the expression of inflammatory factors. These data suggest that ATF3 may contribute to the survival of motor neurons and the maintenance of axonal connections in the zebrafish SCI model by regulating the inflammatory response. ATF3 is proposed as a novel dynamic marker of ependymal derived stem/progenitor cell (epSPC) [101], and the upregulation of ATF3 after SCI acts as a negative regulator of proinflammatory cytokines, promoting motor recovery and axonal regeneration [102].

Interestingly, ependymal cells can also express immunomodulatory proteins, including GPI-anchored molecules and immunoglobulin superfamily molecules, to regulate excessive immune responses in both health and disease, thereby modulating innate immune responses in the CNS [103]. In meningitis, there is upregulation of complement activators in ependymal cells and choroidal epithelial cells, such as strong CD46 and CD35 staining, which helps balance anti-inflammatory and protective responses. This expression renders ependymal cells resistant to complement-mediated attacks during strong activation of the complement pathway in the infected CNS, thereby mitigating innate complement-mediated inflammatory damage. Notably, some viruses can exploit this mechanism to gain immune privilege [104].

It is worth noting that ependymal cells can also secrete neurotrophic factors that promote neurogenesis and angiogenesis, regulate local inflammation, and protect neurons from death. During the recovery from TBI and cerebrovascular disease, the CP/ependyma upregulate the expression of growth factors and neurotrophic factors, including brain-derived neurotrophic factor (BDNF), nerve growth factor, vascular endothelial growth factor (VEGF), transforming growth factor and

so on. These factors are released into CSF through endocrine-like mechanisms and then transmitted to injured areas [105], potentially activating similar signaling pathways that protect neurons and improve the neurogenesis niche [106]. This process is modulated by inflammatory cytokines.

Ependymal cells and changes in innate immunity-related genes

Changes in the expression of innate immunity-related genes have been observed in ependymal cells. Exposure to LPS significantly increases the expression of inflammation-related genes [65]. In ependymal cells from NCC-infected mice, genes associated with the innate immune response, antigen presentation, and leukocyte infiltration are upregulated, including MHC-II and various chemokines [56]. Meanwhile, a recent study has reported significant transcriptional alterations of ependymal cells in a Bacillus Calmette-Guerin-induced model of TBM, revealing a significant enrichment of genes related to metal ion and protein transport, as well as antigen presentation and processing, as detected by single-cell RNA sequencing. Notably, a reduced expression of the FERM structural domain 4 A (Frmd4a) may correlate with clinical symptoms of hydrocephalus and neurodegeneration [107]. Additionally, another study has identified miRNAs that are associated with changes in gene expression, particularly targeted mRNAs focusing on ion and protein transport. MiR-21a-3p is one of miRNAs involved in the miRNA-mRNA network of ependymal cells and neurons [108], which targets several components in the network that work in the innate immune response. Furthermore, it has been shown that miR-21a-3p targets IFN-γ mRNA, negatively regulating anti-mycobacterial immune responses [109]. These evidences suggest that ependymal cells play a role in innate immunity and material transport in TBM.

Potential applications implicating ependymal cells in clinical treatment

Gene transfer in ependymal cells

Due to the blood-brain barrier, the efficacy of some drugs targeting the CNS is limited. As brain-CSF barrier, ependymal cells are considered as promising targets for enzyme replacement therapies to improve neurological metabolic disorders and for delivering cytokines or drugs through ventricular, subarachnoid, and perivascular spaces. Therefore, non-replicating viral vectors carrying therapeutic genes have been engineered to effectively infect ependymal cells, facilitating the synthesis and secretion of transgenic therapeutic products into CSF to target neurons and achieve sustained transgene expression without significant toxicity. This approach holds potential for treating various CNS diseases [110]. Among these, adeno-associated virus (AAV) vectors enable ependymal-specific transduction and transgene expression in the CNS, making them suitable for local intracerebral gene therapy [111–113] (See Fig 4). Comparative studies have shown that AAV2/5 and AAV2/8 display remarkable infections in the CP, while AAV2/1 infects both ependymal cells and cells in the CP. In contrast, lentivirus vectors demonstrate low infection intensity in the CP. Therefore, serotype-specific AAVs 5 and 8 are promising tools for ICV gene delivery [112].

Batten disease is caused by a deficiency of the soluble lysosomal enzyme tripeptidyl peptidase 1 (TPP1) due to mutations in the TPP1 gene. Transduction of recombinant AVVs expressing the TPP1 gene into ependymal cells, which have high TPP1 expression and secrete the enzyme into the CSF, has been shown to halt disease

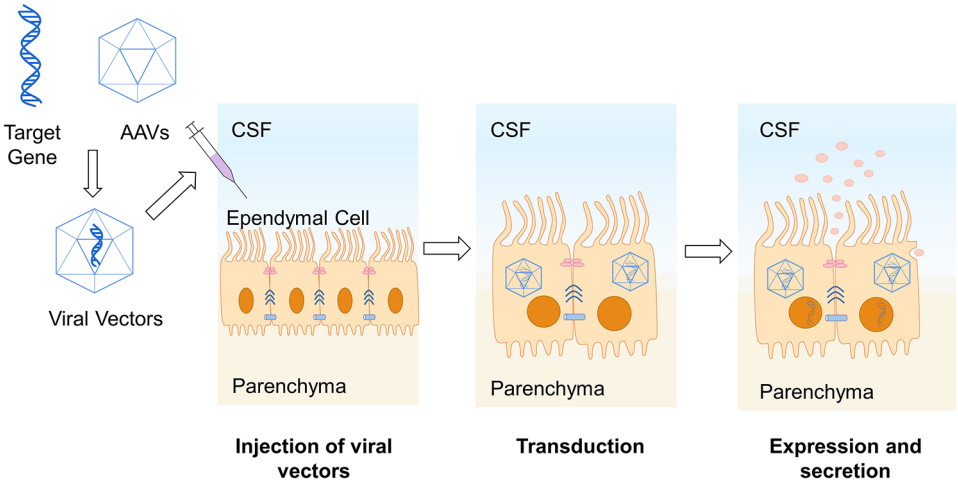

Fig. 4 Gene transfer application in ependymal cell Design non-replicating viral vectors containing therapeutic genes. These vectors are injected into CSF through lumbar puncture. They effectively infect ependymal cells for long-term therapeutic gene expression. The resulting products are secreted into CSF, providing potential treatments for neurodegenerative diseases and metabolic disorders. AAVs: adeno-associated virus

progression and rectify neuropathological features in TPP1-deficient dogs [114]. Additionally, the feasibility of ICV injection of self-complementary (sc) AAV to treat metachromatic leukodystrophy (MLD), caused by functional deficiency in human arylsulfatase A (hASA), has been reported. However, controlling the immune response to prevent antibody production remains a challenge for long-term therapeutic application [115, 116]. Beyond enzyme replacement therapy, AAV-mediated gene therapy can be applied for the delivery of cytokines and neurotrophic factors. For example, AAV4-mediated expression of insulin-like growth factor-1 (IGF-1)/VEGF in the ependymal lining, CP and central canal of the spinal cord, significantly delays exercise decline and extends survival in amyotrophic lateral sclerosis (ALS) mice [106]. Enhancer-based HB-EGF delivery by AAV improves axon densities in neonatal crush SCI, suggesting a potential strategy to improve spinal cord repair in mammals [117].

Several studies have demonstrated that intrathecal or intraventricular injection of AAV vectors can achieve extensive and prolonged, though not permanent, expression of exogenous genes in ependymal cells [118]. In addition to the effective and stable sustained secretion [115, 119], this approach facilitates high-level and wide delivery in the CNS, showing noteworthy benefits for aging and several diseases. Furthermore, the transduction of cytokine genes can achieve high levels in the CNS without affecting the peripheral immune system [120]. Recently, Carrell and his colleagues have identified a promoter for ependyma-derived transgene expression, derived from the VWA3A gene, demonstrating its functional utility in diseases and aging, and its cross-species function in both mice and rhesus macaques. This strategy enhances safety and continuity while leading to higher protein secretion for better therapeutic applications [121].

Given the accessibility of the ventricles, gene transduction therapy through the ependymal pathway using viral infection presents a promising alternative for treating neurodegenerative and neuropathic metabolic diseases. Notably, ependymal cells are susceptible to viral infections. Currently, lysosomal viruses that selectively target cancer cells require thorough evaluation for CNS safety and their potential to infect and damage ependymal cells [122, 123]. The sigma 1 sequence of echoviruses determines the tropism for infecting specific cells, suggesting a direction for rational design and improvement [39, 40]. However, current research still focuses on in vitro experiments and animal experiments, and has not yet obtained sufficient data to support for clinical application. Thus, its safety and feasibility need to be carefully evaluated by more studies.

Ependymal cells and novel biomarkers

Ependymal cells play crucial barrier and secretory roles in maintaining CSF composition and homeostasis, while abnormalities in CSF often reflect CNS lesions or diseases. Evaluation of CSF can identify immune cells, tumor cells, or microorganisms indicative of disease spread in CSF, as well as biomarkers therein that reflect parenchymal changes [124]. However, due to the temporal and spatial variation of CSF parameters, definitive diagnosis of CNS infection using routine clinical chemistry or cytology parameters remains challenging. It still relies on identifying causative pathogens by culture, antigen detection or molecular methods such as polymerase chain reaction (PCR) and next-generation sequencing (NGS) [125]. Nevertheless, recent advances in novel biomarkers and molecular methods could open new ways for future definitive diagnosis of CNS infections and disease evaluation.

Surfactant proteins (SP) are crucial for regulating CSF flow and CNS innate immunity, similar to their function in the lung. Surfactant proteins A, B, C and D exhibit immunoreactivity in the CP and in the ependymal cell layer of the CNS, playing a role in host defense, regulating inflammation and maintaining CSF flow. In patients with CNS infections, the level of both SP-A and SP-D in CSF is statistically significantly decreased compared to healthy individuals. Considering their known functions, they are assumed to participate in the clearance of pathogens and apoptotic polymorphnuclear neutrophils [126]. Additionally, SP-G, a recently identified surfactant protein, is produced by ependymal cells and CP and secreted into CSF. Its concentration significantly increases in children with intraventricular hemorrhage or CNS infection, indicating its potential as a novel CSF biomarker for reflecting the CNS innate immune response and dynamic parameter changes of CSF components [127].

Levels of non-LTA4H-dependent cytokines in TBM affect the therapeutic efficacy of dexamethasone [128, 129]. Ependymal cells secrete cytokines such as IL-1, TNF, and IFN into CSF following infection, which affects cytokine levels. A deeper understanding of the mechanisms governing cytokine secretion by ependymal cells and how cytokines affect infection treatment, utilizing gene transduction in ependymal cells for expressing and secreting cytokines may provide new insights to guide clinical treatment and prognosis. Additionally, a meta-study of CSF cytokines in TBM provides a reference set of cytokines as a potential adjunct to the diagnosis of TBM and to differentiate it from other etiologies of meningitis [130].

In addition, correlation of imaging findings with biomarkers can be used for clinical management. Ventricular tuberculosis shows ependymal enhancement, swelling, and enhancement of CP and intraventricular

tuberculomas on magnetic resonance imaging (MRI) [131]; some patients with TBM shows enplaque-like ependymal granulomas associated with the ventricular ependymal lining on computed tomography (CT) [132]. Guerini proposed an empirical review of periventricular ependymal enhancement characteristics on MRI to reflect etiological types, such as neurological infection or tumor, based on the patient's immune status, type of enhancement, and treatment response [133]. The release of brain-derived proteins such as GFAP and neurofilament light chain (NFL) into the CSF indicates a disruption of the brain-CSF barrier [124]. In HIV patients with cryptococcal meningoencephalitis, correlating MRI imaging findings with NFL, which reflects axonal damage, and sCD27, a predictor of intrathecal T-cell-mediated inflammation, can serve as a measure of severity and an individualized guide to treatment. Results indicate that brain MRI ependymitis is the best predictor of higher sCD27 levels, while choroidal plexitis is the best predictor of higher NFL levels [134]. Additionally, intraventricular debris and stranding, and an irregular and echogenic ependyma in cranial sonography are highly indicative of ventriculitis. Sonography is also capable of detecting post-infectious hydrocephalus and parenchymal involvement from cerebritis or early abscess [135]. Therefore, imaging changes in the ependyma provide an effective, noninvasive method for reflecting inflammatory biomarkers, assessing inflammatory immune activation, and facilitating subpopulation management, follow-up, and prognostic evaluation.

Summary and prospects

In CNS infections, relevant molecules and receptors, expressed by glial cells and neurons, are involved in immune recognition, defense and clearance of pathogens and toxic cellular components, which serve as innate immunity [136]. Ependymal cells constitute a vital physical and immune barrier essential for maintaining CNS health, with dysfunction often evident in the early stages of the disease. Current research on ependymal cells has been progressively advanced from cellular studies to molecular mechanisms, exploring interactions among signaling pathways such as TLR/MyD88/NF-κB, various cytokines, cilia and intercellular junctions, through in vivo/vitro experiments, single-cell sequencing and other techniques. Notably, single-cell sequencing technology facilitates the precise identification of specific gene expression profiles and allows for a detailed analysis of underlying molecular mechanisms, paving the way for future investigations into the roles and mechanisms of ependymal cells in CNS infections.

Due to the special location of ependymal cells between CSF and parenchyma, they broaden our perspective for detecting, diagnosing and managing CNS infections, and provide an important manipulable target for the treatment of CNS diseases. The application of viral vectors containing therapeutic genes for long-term expression in ependymal cells is promising, extending beyond CNS infections to encompass injuries [117], neurodegeneration [106] and cerebrovascular diseases [137]. However, their potential application in infectious diseases, such as antibiotic delivery, requires further exploration. Additionally, the specificity and sensitivity of the proposed novel biomarkers above are currently low, and the imaging findings are often based on empirical observations, necessitating further research and validation. Further studies on ependymal cells may lead to develop innovative therapeutic strategies aimed at enhancing neurological recovery and functional improvement in CNS infections, particularly by leveraging the neural stem cell characteristic of ependymal cells. However, it is important to note that ethical considerations and accessibility issues have limited most studies on ependymal cells to animal models, predominantly adult specimens, leaving a gap in our understanding of age-related responses in ependymal cells. Therefore, the therapeutic potential observed in animal models should be approached with caution [138].

In conclusion, ependymal cells play a significant role in CNS infections by resisting pathogen invasion, activating innate immunity, participating in inflammatory signaling and secreting cytokines and chemokines. As infection progresses, pathogens penetrate the parenchyma, leading to structural alterations, dysfunction, and necrosis of ependymal cells, often resulting in hydrocephalus as a clinical manifestation. These processes offer insights for clinical diagnosis and treatment, particularly through the detection of biomarkers in CSF and producing therapeutic proteins into CSF.

Abbreviations

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
AVV	Adeno-associated virus
BDNF	Brain-derived neurotrophic factor
CNS	Central nervous system
CP	Choroid plexus
CSF	Cerebrospinal fluid
CT	Computed tomography
epSPC	Ependymal derived stem/progenitor cells
HSV	Herpes simplex virus
IFN	Interferon
IKK	NF-κB-independent inhibitor of kappa B kinase
IL	Interleukin
IRF3	Interferon regulatory factor 3
JCPyV	JC polyomavirus
LPS	Lipopolysaccharide
MARCKS	Myristoylated alanine-rich C kinase substrate
MIP	Migration inhibitory factor
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
Mtb	Mycobacterium tuberculosis
MuPyV	Mouse polyomavirus

MyD88	Myeloid differentiation factor 88
NA	Neuraminidase
NCC	Neurocysticercosis
NF-κB	Nuclear factor kappa B
NFL	Neurofilament light chain
NGS	Next Generation Sequencing
PACAP	Pituitary adenylate cyclase-activating polypeptide
PCD	Primary ciliary dyskinesia
PCR	Polymerase chain reaction
PPR	Pattern-recognition receptor
PrP	Prion protein
SCI	Spinal cord injury
SP	Surfactant proteins
TBI	Traumatic brain injury
TBM	Tuberculous meningitis
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor α
TPP-1	Tripeptidyl peptidase 1
VEGF	Vascular endothelial growth factor

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Declarations

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