The diverse cellular responses of the choroid plexus during infection of the central nervous system

Alexa N. Lauer, Tobias Tenenbaum, Horst Schrotten, and Christian Schwerk
Department of Pediatrics, Pediatric Infectious Diseases, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
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Lauer AN, Tenenbaum T, Schrotten H, Schwerk C. The diverse cellular responses of the choroid plexus during infection of the central nervous system. Am J Physiol Cell Physiol 314: C152–C165, 2018. First published October 25, 2017; doi:10.1152/ajpcell.00137.2017.—The choroid plexus (CP) is responsible for the production of a large amount of the cerebrospinal fluid (CSF). As a highly vascularized structure, the CP also presents a significant frontier between the blood and the central nervous system (CNS). To seal this border, the epithelium of the CP forms the blood-CSF barrier, one of the most important barriers separating the CNS from the blood. During the course of infectious disease, cells of the CP can experience interactions with intruding pathogens, especially when the CP is used as gateway for entry into the CNS. In return, the CP answers to these encounters with diverse measures. Here, we will review the distinct responses of the CP during infection of the CNS, which include engaging of signal transduction pathways, the regulation of gene expression in the host cells, inflammatory cell response, alterations of the barrier, and, under certain circumstances, cell death. Many of these actions may contribute to stage an immunological response against the pathogen and subsequently help in the clearance of the infection.

blood-cerebrospinal fluid barrier; cellular response; central nervous system; choroid plexus; pathogens

INTRODUCTION

The choroid plexus (CP; also known as plexus choroideus) plays an essential role in the homeostasis of the central nervous system (CNS). This highly vascularized and specialized structure of the brain is responsible for producing approximately 500 ml of cerebrospinal fluid (CSF) a day in healthy adults (50, 142). It is localized at the blood-CSF interface in the lateral, third, and fourth ventricles of the brain. Not only is it key in regulating CSF homeostasis, it also functions as an important barrier to the sterile CSF and brain parenchyma. As illustrated in Fig. 1, the CP endothelial cells are fenestrated and line the capillaries, which are surrounded by connective tissue called the stroma. The stroma contains immune cells, such as dendritic cells and macrophages. A basement membrane surrounds the stroma, to which the CP epithelium adheres. CP epithelial cells consist of a single layer of cuboidal cells and are connected via tight junctions (TJs).

Attached to the apical side of the CP epithelium are the macrophage-like epiplexus cells, also called Kolmer cells (50). Another important morphological feature of CP epithelial cells is the microvilli protruding from the apical side of the cell, which allow a greater surface area for the large volume of CSF secretion into the ventricles (50, 142). This overall cell arrangement comprises the blood-CSF barrier (BCSFB), which is one of the major barriers to the CNS (70, 142). Another major barrier is the blood-brain barrier (BBB), which is formed by microvascular endothelial cells in conjunction with astrocytes and pericytes at the brain capillaries (for a comprehensive review please refer to Refs. 1 and 81).

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The consequences caused by these pathogens infecting the CNS can be meningitis, encephalitis, and/or meningoencephalitis (21).

Meningitis and encephalitis refer to inflammation of the meninges, the membrane surrounding the brain, and the brain parenchyma, respectively (21). In broad terms, an inflammatory reaction is described as the body’s innate immune response to invading pathogens or tissue trauma to limit the severity of damage to the organism. In relevance to pathogen induced inflammation, a sequence of events has to occur. During, for example, bacterial meningitis, this includes colonization of the host, invasion to the host’s circulatory system, survival against host defenses, and dissemination through the bloodstream to selective sites, where replication and infection can occur (17).

During the infection process of the CP, the pathogen encounters a variety of host cells that it has to either avert (immune cells) or overcome (CP endothelial or CP epithelial cells) (17). There is generally a better understanding of pathogen interaction at the BBB than BCSFB. However, previous studies have provided evidence that pathogens not only use the BBB to invade the CNS, but that some mainly utilize the BCSFB (109). The cells at the BCSFB were shown to respond to infection on a transcriptional level, by recruiting and activating immune cells, as well as changing their secretome, signaling cascades, and even necrosis and induced cell death.
(apoptosis) have been observed; all of which will be covered in this review.

THE CHOROID PLEXUS AS AN ENTRY GATE FOR PATHOGENS INTO THE CNS

The CP is a highly vascularized tissue, which provides a significant interface between the bloodstream and the ventricular system of the CNS (118). To prevent uncontrolled access of unwanted substances, including toxins, pharmaceutically active agents, as well as pathogens to the CNS, the BCSFB employs several mechanisms to seal the blood from the CNS at the CP.

The apically located TJ proteins connecting neighboring cells of the CP epithelium hinder a paracellular passage between CP epithelial cells by forming a “physical barrier.” A transcellular progress of substances through single cells of the epithelium is also impeded by a low pinocytotic activity and a “biochemical barrier.” The biochemical barrier consists of the presence of different transporters on the CP epithelium’s apical and basolateral side, and functions via concentration and osmotic gradients to keep the homeostasis of the CSF. Furthermore, the BCSFB presents an “immunological barrier” by controlling immune cell trafficking into the CNS (70, 110, 142).

To enter the CNS via the CP, pathogens need to overcome these barriers provided by the CP epithelium. The CP has been described as entry gate for a multitude of pathogens, including bacteria, viruses, fungi, and parasites (21, 109). Still, it should be noted that in many cases entry to the CNS might not solely occur through the CP route, but instead does, often possibly even more commonly, proceed via the BBB (53). For crossing of host cell barriers, pathogens can apply a set of different strategies. For paracellular transmigration between the CP epithelial cells they can induce opening of the TJs, thereby overcoming this “roadblock.” Alternatively, pathogens are able to invade into host cells by different mechanisms for a transcellular pathway directly through the epithelial cells. A third strategy involves crossing of the barrier inside of infected host immune cells by a “Trojan horse” route (21, 53, 93). An overview of selected pathogens, for which evidence of the BSCFB as entry site into the CNS has been provided, is given in Table 1.

The most frequent cause for aseptic meningitis, encephalitis, and meningoencephalitis are viral infections, constituting threefold more cases than bacterial meningitis (97). Young children (including neonates and infants), the immunocompromised, and elderly people tend to be most susceptible to viral infection of the CNS. Involvement of the CP during viral infection has previously been observed with members of the non-polio enterovirus group, most notable being Echovirus 30 (EV30) and Coxsackievirus B3 (CVB3), and human immunodeficiency virus (HIV) (see Table 1). Virus infiltration utilizing the CP was shown for Chikungunya virus and Maedi-Visna virus (MVV), a lentivirus that infects sheep (16, 40). Further evidence exists that cytomegalovirus (CMV), mumps virus, hepatitis E virus (HEV), herpes simplex virus 1 (HSV-1), and lymphocytic choriomeningitis virus utilize the CP during viral CNS infection (15, 52, 111, 112, 144).

Following viral infections, the second common source for infection of the CNS is caused by bacteria. Though not as common as viral infections, bacterial infections tend to be more severe and patients are more likely to suffer from long-lasting sequelae, including hearing loss, as well as intellectual and cognitive impairment (43, 44). Pathogenesis of several bacteria has been implicated with the CP. Bacteria, for which clear evidence of the CP involvement has been provided, include Neisseria meningitidis, Listeria monocytogenes, Hemophilus influenzae type b (Hib), and the zoonotic pathogen

Table 1. Examples for pathogens utilizing the BCSFB as an entry gate into the CNS

| Pathogen                  | Symptoms and Disease                        | Traversal Mechanisms Across the CP | Reference No. |
|---------------------------|---------------------------------------------|----------------------------------|---------------|
| **Viruses**               |                                             |                                  |               |
| Echovirus 30              | Meningitis                                  | Transcellular                    | (104)         |
| Coxsackievirus B3         | Aseptic meningitis, encephalitis, pancreatitis, myocarditis | Transcellular, paracellular, “Trojan horse” | (38, 120) |
| Human immunodeficiency virus | Encephalitis, AIDS                        |                                   | (55)          |
| Feline immunodeficiency virus | Feline AIDS                              | “Trojan horse”                   | (7)           |
| Simian immunodeficiency virus | Simian AIDS                              | “Trojan horse”                   | (14, 61)      |
| Herpes simplex virus 1    | Encephalitis, benign mucosal disease        |                                  | (112, 135)    |
| **Bacteria**              |                                             |                                  |               |
| Neisseria meningitidis    | Septicemia, meningitis                     | Transcellular                    | (46, 91, 107) |
| Listeria monocytogenes    | Listeriosis, meningitis, meningoencephalitis | “Trojan horse”, transcellular   | (5, 45, 90)   |
| Haemophilus influenzae    | Meningitis                                  |                                  | (22, 114)     |
| Streptococcus suis        | Meningitis, septicaemia                    | “Trojan horse”                   | (83, 148)     |
| **Fungus**                |                                             |                                  |               |
| Cryptococcus neoformans   | Meningitis, choroid plexitis               |                                  | (57, 59)      |
| **Parasites**             |                                             |                                  |               |
| Angiostrongylus cantonensis | Angiostrongyliasis, Eosinophilic meningitis, eosinophilic meningoencephalitis | ? | (132) |
| Trypanosoma brucei        | African sleeping sickness, meningoencephalitis, heart failure | ? | (2, 105) |
| Toxoplasma gondii         | Meningoencephalitis, encephalitis          | ?                                | (36)          |

STSLS, streptococcal toxic shock-like syndrome; AIDS, acquired immunodeficiency syndrome.

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Streptococcus suis (see Table 1 for references and for a recent review see Ref. 109). Additional evidence exists, which suggests that Streptococcus agalactiae (Group B Streptococcus) and Escherichia coli K1 may also exploit the CP as entry gate into the brain (83, 121, 148).

For fungi, the most common CNS-infection causing pathogen is Cryptococcus neoformans, which affects immunocompromised patients. Past in vivo studies in the murine model demonstrated that C. neoformans utilized the BBB as an entry into the CNS, not the CP (11). Still, there have been rare instances of choroid plexitis observed during magnetic resonance imaging (MRI) (57, 59).

Lastly, although rare, eukaryotic parasites are also capable of infecting the CNS. Angiostrongylus cantonensis is often found to cause parasitic CNS infections, leading to eosinophilic meningitis or meningoencephalitis (133). Additionally, Trypanosoma brucei, Toxocara canis, Toxoplasma gondii, as well as Schistosoma species (spp.) have been shown to be associated with the CP following infection (2, 36, 69, 73, 87, 141).

PATHOGEN-HOST CELL INTERACTIONS AT THE CHOROID PLEXUS

It is well known that infection of the CNS involves diverse host-pathogen interactions (21, 29). During the traversal of the CP, pathogens undergo extensive interactions with cells of the host organism, including immune cells and the cells comprising the CP. Whether viral, bacterial, fungal, or parasitic, each pathogen is equipped with a unique set of outer or transmembrane structural proteins involved in physical interaction between the pathogen and the surface of host cells. This physical interaction can then lead to activation of mechanisms enabling pathogen invasion and transmigration.

The Coxsackie and adenovirus receptor (CAR) is a TJ-associated protein and is expressed at the CP epithelium (79, 120). Analyzing infection with CVB3 in a mouse model, Tabor-Godwin and colleagues (120) suggest that virions bind to CAR at the CP epithelium, where they recruit and infect a myeloid cell population that traverses across the CP into the CSF, a process that assists dissemination of the virus. A role for CAR was also shown during Echovirus 6 (E6) infection in a recombinant CHO cell model. Here, CAR functioned as a coreceptor for the E6 receptor decay-accelerating factor during infection with some E6 strains (98). Recently, by applying a murine HSV-1 infection model, the specific susceptibility of newborns compared with adults was demonstrated. Interestingly, the presence of the IFN-α/β receptor played a crucial role in the susceptibility of the CP during HSV-1 infection (135). Nectin-1 was also demonstrated to be a potential receptor of HSV-1 at the CP (112). In a murine model for CMV, high-level β1 integrin-expressing cells of the CP were, among other brain cells with the same receptor profile, highly susceptible to CMV infection (52). CP epithelial cells and ependymal cells, in both murine and human brains, were shown to express high levels of human and avian influenza virus receptors, respectively (54). Lastly, glycosaminoglycans and heparan sulfate proteoglycans may play a role in West Nile virus (WNV) entry into the CP (80).

Bacterial examples of CP cell interaction have been demonstrated for E. coli, N. meningitides, Hib, S. suis, and the facultative intracellular bacteria, L. monocytogenes. The latter has been shown to use its surface receptors Internalin (InlA) and InlB to interact with the host receptors E-cadherin and tyrosine kinase Met receptor, respectively, to initiate cell uptake (88). In an in vitro model, the requirement for InlA and InlB has been confirmed for invasion of L. monocytogenes in human CP epithelial cells (45). Furthermore, the entry of L. monocytogenes into sheep CP epithelial cells can be mediated by the interaction between the listerial immunogenic surface protein C and an unknown receptor (131).

Gram-negative bacteria possess certain threadlike surface structures, termed fimbriae or pili, which can undergo interactions with target cells. Some data exist concerning the role of E. coli fimbriae during infection, where it has been shown that recombinant E. coli expressing S fimbiae bound to the epithelial lining of the CP. Furthermore, examining cryostat sections from rat brains showed that these E. coli adhered to the ventricles (83).

For other bacteria, which involve the CP during the course of disease, e.g., Hib, N. meningitidis, and S. suis, the molecular partners mediating interactions with cells of the CP are not yet defined. Interestingly, it was observed for certain bacteria, including N. meningitidis and S. suis, that invasion into host cells is attenuated by the presence of a capsule (107, 125). This observation suggests that capsule downregulation contributes to expose bacterial surface proteins involved in adhesion and invasion.

During parasitic infections, it has been suggested that trypanosomes express a membrane-bound metalloproteinase, which in a first step opens the basal lamina underlying both the CP endothelium and the epithelium (141). In a second step, to overcome the TJs sealing the CP epithelium, it was proposed that trypanosomes may interact with the BCSFB-specific TJ protein claudin-11, but the exact mechanism of TJ opening is not understood (77, 78).

Not only surface proteins, but also factors secreted by pathogens can interact with host cells and add to the progress of infection. For example, hemolysins of streptococcal species with different roles in virulence can have important functions (4). Along these lines, in primary porcine CP epithelial cells, S. suis strains expressing the hemolysin siliusin displayed higher cytotoxicity compared with siliusin-negative strains (122, 123).

It should be noted that in polarized cell layers like the CP epithelium, receptors can be differently distributed at the basolateral and the apical side, which supports a polar invasion of pathogens from a specific direction. This is exemplified by the selective basolateral invasion of L. monocytogenes into human epithelial CP papilloma (HIBCPP) cells due to the basolateral localization of E-cadherin and Met. This polar localization of host cell target receptors can elicit specific host responses, which are dependent on the direction of pathogen-host cell interaction (27, 45).

Pathogens can also undergo more indirect interactions with the CP when entering the CNS via the Trojan horse mechanism. This strategy is employed by several viruses (20), as well as by certain bacteria. For example, several studies point to CNS entry via L. monocytogenes-infected monocytes (30, 31, 48).
HOST RESPONSE AT THE CHOROID PLEXUS

The interactions of a pathogen with host cells at the CP lead to diverse host cell responses that can either help the host organism to protect itself against the microorganism or contribute to the pathogenesis of the disease. Examples for the response of the CP epithelium to pathogens are depicted in Fig. 2. Typically, the host cells respond with the activation and regulation of intracellular signal transduction pathways that initiate a multitude of cellular responses including the activation of inflammatory response genes and the production of proteins, several of which are secreted. Furthermore, cell death is often initiated subsequent to challenge of host cells with pathogens, which, when located at host cell barriers as the BCSFB, can lead to loss of barrier integrity.

Signal Transduction

In order for the host cell to adapt to a changing environment, communication between the extracellular space and the cell’s nucleus has to occur. During infection, extracellular physical interaction between a pathogen-associated molecular pattern and a host’s pattern recognition receptor results in a chain of signal transduction events within the host cell. One important class of receptors playing a role in the host’s innate immunity and microbial pattern recognition is the Toll-like receptor (TLR) family (101). TLRs are divided into different groups depending on their ligand-specificity, which subsequently results in a downstream signal transduction cascade to induce a proinflammatory response (51). The signal transduction cascade occurs through a series of protein modifications, most commonly via phosphorylation, which ultimately leads to activation of transcription factors (TFs) responsible for gene regulation. It is especially important for inflammatory response genes to be transcribed, in order for the host cell to combat and clear the environment of the foreign invader. However, the signal transduction cascade can be manipulated by some pathogens to support their survival (58, 128).

During viral CNS disease, TLR7 was shown to regulate the innate immune response to retroviral and WNV infections, and

![Signal transduction processes in CP epithelial cells in response to pathogens. Bacteria (Streptococcus suis, Neisseria meningitidis, Listeria monocytogenes), virus (Echovirus), and parasites (Angiostrongylus cantonensis) can interact with adhesion molecules and receptors on the CP epithelium, including Toll-like receptors (TLRs). The host-pathogen interactions lead to the activation and regulation of signal transduction pathways [MAPK, NF-κB, phosphatidylinositol 3-kinase signaling (PI3K)]. Regulation of signal transduction may assist during host cell invasion by the pathogen or lead to the activation of target genes causing the production of, e.g., cytokines and chemokines or matrix metalloproteinases (MMPs). Whereas cytokines and chemokines contribute to the activation and attraction of host immune cells (neutrophils, eosinophils), MMPs are implicated in degrading extracellular matrix components and causing barrier breakdown. These processes can lead to the traversal of immune cells across the blood-cerebrospinal fluid barrier. For more detailed information please refer to the text of this review.](image-url)

Fig. 2. Signal transduction processes in CP epithelial cells in response to pathogens. Bacteria (Streptococcus suis, Neisseria meningitidis, Listeria monocytogenes), virus (Echovirus), and parasites (Angiostrongylus cantonensis) can interact with adhesion molecules and receptors on the CP epithelium, including Toll-like receptors (TLRs). The host-pathogen interactions lead to the activation and regulation of signal transduction pathways [MAPK, NF-κB, phosphatidylinositol 3-kinase signaling (PI3K)]. Regulation of signal transduction may assist during host cell invasion by the pathogen or lead to the activation of target genes causing the production of, e.g., cytokines and chemokines or matrix metalloproteinases (MMPs). Whereas cytokines and chemokines contribute to the activation and attraction of host immune cells (neutrophils, eosinophils), MMPs are implicated in degrading extracellular matrix components and causing barrier breakdown. These processes can lead to the traversal of immune cells across the blood-cerebrospinal fluid barrier. For more detailed information please refer to the text of this review.
TLR9 was implicated in mediating the innate immune response to HSV-1 infections in the brain, although involvement of the CP was not further investigated (68, 115). In a newborn murine model, stimulation with the TLR9 agonist cytosine-phospho-guanosine oligodeoxynucleotide (CpG-ODN) was able to induce inflammation at the CP after intracerebroventricular inoculation. The analysis of gene expression of isolated CP revealed the expression of TLR9, myeloid differentiation primary response gene 88, also known as Myd88, and IFN regulatory factor 7 mRNA at comparable levels to those observed with astrocytes, indicating that these cells may be directly responding to CpG-ODN stimulation (10).

One of the most important TFs activated during pathogenic induced inflammation is NF-κB (82). Its activation is associated with an early expression of proinflammatory cytokines and chemokines (see below), supporting host defense. In an in vitro human CP epithelial model, HIBCPP cells infected with *N. meningitides* mounted a strong proinflammatory response involving NF-κB, which was possibly activated by the heterodimerization of TLR2 and TLR6 (6). TLR2 heterodimerization with TLR1 or TLR6 was shown to occur to expand ligand recognition (37). However, the induction of NF-κB does not always lead to a positive outcome for the host. As demonstrated by Chiu and Lai (13) using the murine in vivo model, infection with the parasitic *A. cantonensis* leads to NF-κB activation and results in the expression of matrix metalloproteinase (MMP)-9 (see below), subsequently leading to the breakdown of the BCSFB.

In contrast to helping the host cell respond to infection, intracellular signal cascades can be utilized or manipulated by pathogens to their own advantage. As mentioned previously, *L. monocytogenes* can be taken up in HIBCPP cells in vitro. Its interaction with CP cells was shown to activate MAPK signaling, especially the ERK 1 and 2 and the p38 pathway. Possibly due to the polar distribution of E-cadherin and Met, activation of ERK1/2 and Met preferentially occurred following basolateral infection. Furthermore, a combined inhibition of the ERK1/2 and p38 signaling pathways resulted in decreased infection of HIBCPP cells, and it was therefore concluded to be required for efficient infection with *L. monocytogenes* (27). ERK1/2 activation was also observed following infection of primary porcine CP epithelial cells (PCPEC) with *S. suis* in vitro (124). A further signal transduction pathway that was found to be manipulated by bacterial pathogens to gain entry into host cells is phosphatidylinositol 3-kinase (PI3K). Normally this signal transduction pathway is active at a basal level or needs to be activated in order for some bacteria to enter host cells (58). In vitro PCPEC infections with *S. suis* demonstrated that inhibition of PI3K decreases bacterial translocation through the CP epithelial cells (125).

Generally speaking, these signal transduction pathways exist in order for the cell to respond to its changing external environment and regulate cell survival. However, these pathways cannot always lead the cells to adapt to external stress, especially during infection. For example, activation of the ERK1/2 pathway of the MAPK family normally results in cell proliferation and survival, whereas the p38 signaling pathway stimulation can end in induced cell death (145).

**Cell Death**

A common response to infection and interaction with pathogens is the death of host cells. These cell death phenomena can occur in different forms, including necrosis and apoptosis. Apoptosis, or programmed cell death, can be the direct result of activation of apoptotic signaling following interaction of pathogens with host cell receptors (60). Cell death processes occurring at the CP epithelium in response to pathogens are illustrated in Fig. 3.

Following the interaction with pathogens, cells of the CP can undergo cell death during the course of infection. For example, during viral disease involving the BCSFB it was observed in murine models that infection with CVB3 caused an increase of apoptotic cells in the CP. A consequence of this cell death could be detrimental brain function failure. In this regard, the hypothesis was put forward that hydrocephalus, which was observed as a result of infection with CVB3 in mice, could be caused by dysfunction of the CP due to apoptosis (92, 99, 120). Apoptosis has also been implicated in the pathogenesis of the lentivirus MVV. MVV, whose pathological alterations in the CNS include infiltration of the CP, causes apoptosis in vitro following infection of sheep CP cells, thereby involving the activation of apoptotic caspases (32).

In vivo evidence for cell death at the CP has also been provided for bacterial pathogens causing CNS disease. Infection of infant primates with Hib revealed histopathologic lesions at the CP early during disease (22, 114). Furthermore, during meningitis caused by *S. suis*, lesions were observed at the CP of naturally and experimentally infected pigs (72, 102, 136). These lesions could be elicited by different kinds of cell death. In an in vitro model of the BCSFB built on PCPEC, both necrotic and apoptotic cell death was described following infection with *S. suis*. Additionally, a significant overrepresentation of genes involved in programmed cell death was found (106, 123). Further supporting this observation, treatment of PCPEC with the proinflammatory cytokine tumor necrosis factor-α (TNF-α), which is overexpressed following challenge with *S. suis*, led to the induction of apoptotic and necrotic mechanisms (108). Interestingly, expression of proinflammatory cytokines including TNF-α and degeneration of ependymal cells of the CP was also observed following infection with trypanosomes in murine models (2, 95).

Cell death processes at the CP can lead to loss of barrier function at the BCSFB, as has been demonstrated in in vitro experiments (108, 123, 149). PCPEC challenged with *S. suis* in vitro exhibited a dislocation of the TJ proteins occludin, claudin-1, and zonula occludens 1, subsequently resulting in the actin loss on the apical cell surface and stress fiber formation on the basolateral cell pole. This consequently led to compromised barrier integrity in this model system. Such a loss of barrier function can contribute to CNS entry of pathogens as well as reseeding from the brain into the blood by microorganisms that had previously crossed into the CNS.

**Regulation of Host Cell Genes**

The activation of host cell signaling pathways in response to challenge with pathogens often leads to the regulation of target genes, which can be up- as well as downregulated. These genes can encode surface proteins and receptors, but also secreted proteins like MMPs or cytokines and chemokines. Not all, but
many of the regulated gene products play an important role in orchestrating the immune response of the infected host organism.

Surface Proteins

Membrane-bound proteins expressed on the surface of target cells are exposed for contact with extracellular pathogens or other cells, such as immune cells. These interactions can be involved in engaging host cell signaling pathways or can serve during cellular invasion of the pathogens.

As already mentioned, TLRs are an important class of receptors for microbial recognition. Since TLRs are part of the host’s innate immunity, basal expression can be detected in multiple cell types, including CP cells. It was reported that in vivo stimulation of mice with the Gram-negative bacterium-derived endotoxin lipopolysaccharide (LPS) resulted in a rapid and robust transcription of TLR2, which has a substrate-specificity towards microbial components, at the murine CP (62, 63). This response was speculated to occur due to TLR4 expression, which possesses ligand-specificity towards LPS. Rivest (101) suggested that TLR4 recognized the circulating LPS, which resulted in a downstream upregulation of proinflammatory cytokines and TRL2. In a mouse model of infection, stimulation with the Gram-positive bacteria S. suis demonstrated fast upregulation of TLR2 and the cluster of differentiation (CD) 14 receptor, which is involved in binding bacterial cell wall components (28, 65). Lastly, amoeba of the Acanthamoeba spp. likewise induced an upregulation of TLR2 and TLR4 in the CP of infected mice (140).

Further surface proteins regulated by the CP epithelium in response to infection include the adhesion molecules ICAM1, VCAM1, mucosal addressin cell adhesion molecule, P-selectin, and E-cadherin (76, 116). These membrane-bound proteins can facilitate the interaction with immune cells during infection, but also during immune surveillance of the CNS (76). Along these lines, transcriptome analysis of PCPEC found a significant upregulation of ICAM1 and VCAM1, and a downregulation of claudin-2, a protein present in the TJ of CP epithelial cells of mice, following S. suis infection in vitro (106, 143), and N. meningitides caused upregulation of ICAM-1 in HIBCPP cells in vitro (6). Upregulation of ICAM-1 and VCAM-1 on the CP epithelium was also found in experimental murine Toxoplasma encephalitis (25).

An additional adhesion molecule, nectin-4, was found to be expressed by CP epithelial cells. In an experiment studying the interaction of canine distemper virus (CDV) of dogs succumbed to the virus, Pratakpiriya and colleagues (89) found that CDV utilized the host’s nectin-4, thus increasing neurovirulence.

Matrix Metalloproteinases

MMPs are a family of proteinases that are either secreted from- or anchored to the cell membrane by different types of tissues in response to, among other things, inflammation, and have even been demonstrated to modulate inflammation (84, 149). Currently, there are 24 different MMPs found in mammals, which are divided based on their substrate-binding specificity (84). Due to their destructive nature, regulation of MMPs is essential (18). MMPs have been implicated in the breakdown of the BBB and BCSFB during inflammation by degrading components of the extracellular matrix, but also in neurological sequelae following bacterial meningitis (67, 129, 149). Additionally, the CSF of patients suffering from viral, bacterial, fungal, and parasitic meningitis was found to contain a higher concentration of MMPs (41, 56, 74, 127).

The BSCFB is not only affected by MMPs, but CP epithelial cells have been demonstrated to be a source of secreted MMPs. Proteomic analysis revealed that primary murine CP epithelial
cells secreted MMP-2 and MMP-3 in vitro upon LPS stimulation (126). Furthermore, in vivo LPS stimulation in mice resulted in an increase of transcription and translation of MMP-8 (129) and increased mRNA expression of MMP-12 (3) localized to the CP, which corresponded to a MMP-dependent BCSFB leakage. In PCPEC infected with S. suis in vitro, upregulation of MMP-3 on a mRNA level was also observed (106, 124). In the three latter examples, BCSFB leakage could be diminished upon applying a MMP inhibitor or the corticosteroid dexamethasone. Dexamethasone usage has been applied as adjunctive therapy in clinical settings to improve disease outcome by reducing potential neurological sequelae caused during infection and the inflammatory response (75). Furthermore, the usage of MMP inhibitors was suggested to be applied as adjunctive therapy during bacterial meningitis, since promising results were shown in experimental murine meningitis models (71, 100).

A few investigations examining the relationship of MMPs in the CNS following infection with the parasitic A. cantonensis using in vivo murine models have also been carried out. Previous studies correlated an increase of MMP-9 in the CNS following infection with A. cantonensis (12, 13, 64, 66). Shyu and colleagues (113) were able to demonstrate that MMP-9 was localized to the murine CP epithelium, and that MMP-9 processed fibronectin, a glycoprotein part of the extracellular matrix and essential for homeostasis of the CNS, therefore weakening the BCSFB. Again, application of a MMP-blocker was able to attenuate damage to the BCSFB (113).

Lastly, MMP activity was likewise shown to contribute to proinflammatory cytokine induced-damage to the BCSFB. Using the in vitro PCPEC model, Zeni and colleagues (149) showed that MMP activity was modulated by TNF-α. Furthermore, utilizing primary rat CP epithelial cells in vitro, stimulation with different proinflammatory cytokines elicited MMP-9 and MMP-2 release in a polar manner, dependent on the cytokine (119).

Cytokines and Chemokines

During inflammation, signaling molecules termed cytokines are released into the extracellular space by multiple types of cells to attract immune cells to the site of infection, inflammation, or trauma. They can be divided into different groups depending on their origin and function (150). Furthermore, these signaling molecules can be divided into pro- and anti-inflammatory cytokines, as well as chemokines, which induce chemotaxis of immune cells. Proinflammatory cytokines play a role in the upregulation of the inflammatory response, whereas anti-inflammatory cytokines control the proinflammatory cytokine response. However, the production of cytokines is not always to the advantage of the host; instead it is possible that these molecules can contribute to pathogenesis of the disease.

Previous transcriptome and proteome investigations demonstrated that the CP contributes to the inflammatory response by producing and releasing cytokines during infection and inflammation. During bacterial meningitis, the proinflammatory cytokines interleukin (IL) 1β, IL-6, IL-8, and TNF-α have been demonstrated to play an important role, and are frequently found in the CSF of patients suffering from meningitis (26). In vivo murine studies found that early transcriptional activation of inflammatory cytokines occurred in the CP following S. suis infection (28). By applying in situ hybridization, Domínguez-Punaro and colleagues (28) were able to demonstrate that mRNA transcripts of IL-1β and TNF-α could be localized to the murine CP. Additionally, the MMP-12 activated monocyte chemotactic protein 1, a chemokine implicated in attracting T lymphocytes and monocytes to the site of inflammation, was also found to be upregulated (28). Similar observations were made when the in vitro transcriptional response of apically (“CSF” side) infected PCPEC with S. suis was investigated (106). Using microarray analysis, regulation of genes belonging to the gene ontology (GO) term “cytokine activity” was found to be overrepresented. Strong upregulation of TNF-α, IL-1β, IL-6, and IL-8 expression was detected on the mRNA level, and for the two latter cytokines, secretion into culture supernatants was confirmed (106). Comparable results were demonstrated in HIBCPP cells infected with N. meningitides and L. monocytogenes, which showed an upregulation of IL-6 and IL-8. Additionally, N. meningitides-challenged cells were found to upregulate chemokine C-X-C motif ligands (CXCL) 1–3, and L. monocytogenes-challenged cells also demonstrated an upregulation of CXCL-3 (6, 27).

Furthermore, viral meningitis is known to elicit cytokine and chemokine release following infection. For example, Sato and colleagues (103) found that during the acute phase of enterovirus meningitis, high concentrations of the proinflammatory cytokines IL-6, IL-8, and interferon-γ were detected in the CSF of the patients, and in a mouse model expression of C-C motif ligand 12 (CCL12) was detected in the CP after infection with CVB3 (120). In an in vitro human BCSFB model studying the effects of EV30 infection, CP epithelial cells transcribed and secreted the chemokines CXCL 1–3, CCL5, and the proinflammatory cytokine IL-8 (104). In a further study that applied the same human in vitro model, chemokines CCL20, CXCL3, and CXCL10 and cytokines IL-8 and macrophage colony-stimulating factor were found to be secreted in significantly high concentrations towards the basolateral (“blood”) side (19). Interestingly, IL-7, a cytokine functioning as a T lymphocyte modulator, was secreted in high concentrations from the apical (CSF) side of the human CP epithelial cells (19).

In patients with HIV-associated neurocognitive disorders, elevated levels of IL-8, CCL2, CXCL10, and granulocyte colony-stimulating factor were measured in the CSF, which may have originated in the CP (147). Furthermore, an interesting observation was made by de Almeida and colleagues (23), who found that 44% of HIV-positive patients in their study suffered from a dysfunctional BCSFB, and that a higher cytokine level was present in the CSF compared with the serum. Similarly, induction of the proinflammatory mediators CXCL9 and CCL2 was found in the CSF of simian immunodeficiency virus (SIV)-infected macaques. SIV infection of the CP could be found via immunofluorescent analysis of brain sections (14). In the murine brain, following retroviral infection, elevated levels of CCL2–5 and CXCL10 were detected (86).

Additionally, parasitic meningitis is associated with the release of cytokines and chemokines. Patients suffering from eosiophilic meningitis were found to have elevated levels of IL-5, IL-10, and IL-13 in their CSF, playing a role in attracting eosinophils, a non-phagocytic immune cell implicated in parasitic infections, and regulating the cytokine response during angiostrongyliasis (47). Furthermore, in vivo A. cantonensis
infection in a murine model demonstrated that the cytokines and chemokines formed a complex network, which affected the development of inflammation during eosinophilic meningitis (146). However, no in vitro and in vivo studies have been performed to localize the origin of these cytokines during parasitic CNS infection.

Although it was previously shown that increased cytokine levels in the CSF can lead to a disruption of the BCSFB, proper cytokine and chemokine response is essential during infection (129). The production of cytokines and chemokines by the CP can significantly contribute to orchestrating the immune response initiated by a host organism when infected with a pathogen that enters the CNS.

IMMUNE RESPONSE OF THE HOST ORGANISM

When challenged by a pathogenic microorganism, the host stages an immunological response to battle the infection. Cells of the immune system play a major role during this response upon being activated and attracted to the sites of infection by cytokines and chemokines. In healthy individuals, the total number of immune cells present in the CNS is ~450,000 immune cells (76). The major immune cells associated with the CNS are microglia cells [resident myeloid cells within the CNS parenchyma (55)], ependymal cells associated with the apical surface of the CP epithelium, and other immune cells present between the CP stroma and blood patrolling the CNS (34, 76).

Immune cell entry is differently regulated at the BBB compared with the BCSFB. The BCSFB was suggested to function as a “controlled” gate that allows an immunosurveillance of the CSF in the healthy state, whereas the BBB is considered as a “true” immunological barrier, which blocks entry of leukocytes during this state (34, 110). Previous research indicates that the BBB is primarily utilized when a proinflammatory stimulus is present, and that sequential transmigration steps for T cells across the BBB was described to occur via rolling, capture, crawling, and crossing (34). Immune cell crossing through the BCSFB from the CP stroma to the CNS has yet to be fully elucidated.

During infectious diseases of the CNS, immune cells are recruited to this site. The CP was shown to be involved in regulating immune cell traffic for not only surveillance of the CNS, but also during infection. Interactions of integrins expressed on immune cells with certain host cell surface proteins are important during this process. In this regard, the CP epithelium expresses the adhesion molecules VCAM-1, ICAM-1, P-selectin, and E-cadherin, suggesting that immune cell trafficking through the CP is controlled by the epithelium rather than the endothelium (76). Whereas entry of immune cells at the BBB is associated with inflammation and tissue damage, the trafficking across the BCSFB under inflammatory conditions might be involved in an immunomodulatory fashion (110).

Host immune cells have been found in the CP during infections involving the CNS (20, 138). For example, polymorphonuclear and mononuclear leukocyte infiltration of the CP was detected following infection with L. monocytogenes (5, 85, 90). Results obtained from infection of mice with CVB3 suggested that a myeloid cell population infected with the virus traverses across the CP into the brain (120), and in Mongolian gerbils infected with HEV, massive lymphocyte infiltration, especially in the CP and perivascular area, was observed (111).

Furthermore, cells infected with SIV colocalized with monocytes and macrophages to the CP stroma, thereby indicating a Trojan horse mechanism for CNS invasion (14).

In vitro, immune cell transmigration was investigated following challenge of porcine or human CP epithelial cells with bacterial and viral pathogens. Migration of neutrophil granulocytes was increased in PCPEC after infection with S. suis, or in HIBCPP cells with N. meningitidis (117, 134). In contrast, monocyte transmigration across HIBCPP cells was attenuated by N. meningitidis (117). Viral infection of HIBCPP cells with EV30 increased trafficking of neutrophil granulocytes and naïve CD3+ T lymphocytes, and in a feline CP epithelial cell model challenged with feline immunodeficiency virus (FIV) the transmigration of both macrophages and peripheral blood mononuclear cells was enhanced (19, 76, 104).

In a murine influenza vaccination model, using pregnant mice, it was demonstrated that stimulation with influenza A (H1N1) led to the recruitment of T lymphocytes directed to the CP to promote hippocampal neurogenesis and working memory T cells. Furthermore, adhesion molecules and chemokines, such as VCAM-1, ICAM-1, CXCL9–10, and CCL5, capable of recruiting T cells, were found to be increased at the CP (94).

During the pathogenesis of HIV in the CNS, migration of CD14+CD16+ monocytes through the BCSFB and BBB was found to be mediated by CCR2/CCL2 (14, 137).

Importantly, depending on the causative pathogen, the immune cell presence can vary. For example, viral meningitis was shown to be associated with ~39% CD4+ T cells, 6% CD8+ T cells, 3% monocytes, and ~4% neutrophils of the total white blood cell count in the CSF. Bacterial meningitis on the other hand is associated with ~8% CD4+ T cells, 5% CD8+ T cells, 4% monocytes, and ~87% neutrophils in the CSF (33, 76). In contrast, parasitic meningitis is usually associated with a high amount of at least 10% eosinophils of the total leukocytes in the CSF (42).

Neutrophil granulocytes can act antimicrobial by the formation of neutrophil extracellular traps (NETs), which consist of released nuclear DNA and associated factors with antimicrobial function (9, 39). Interestingly, NET formation has been shown in the CSF of piglets infected with S. suis (24). In vitro, NETs and S. suis entrapment were demonstrated in a model system consisting of HIBCPP cells, neutrophil granulocytes, and S. suis strains. In this experimental setup, expression of the NET-stabilizing cathelicidin LL-37 was increased in HIBCPP cells following neutrophil transmigration. Additionally, piglets with meningitis showed increased expression of the cathelicidin PR-39, which colocalized with NETs (24). These observations show an intricate interplay between the host immune cells and the CP following CNS infection.

CONCLUSION AND FUTURE OUTLOOK

From the compiled literature it is apparent that the CP is not just a passive player during infection of the CNS but contributes actively during the course of disease by providing several responses. These include direct and indirect interactions with pathogens, as well as cellular responses, such as the production of surface proteins and secreted factors or a progress into cell death leading to changes in the barrier function.
Despite effective therapeutic agents available today, mortality rates still remain unacceptably high, especially for bacterial, fungal, and parasitic CNS infections. As mentioned earlier in this review, adjunctive therapies employing dexamethasone and MMP inhibitors can result in positive disease outcome. A further immunomodulatory therapeutic agent involving the inhibition of complement component 5 in murine pneumococcal meningitis has been shown to improve disease outcome, especially in combination with dexamethasone (49, 139). However, this form of therapy has not yet been applied in the clinical setting.

Still, the most effective “treatment” against these infections would certainly be prevention by vaccination. Therefore, a major focus of future research should concentrate on generating immunization protocols, for example, by immunizing expectant mothers to prevent the incidences of neonatal meningitis. In industrialized countries, vaccine availability for the most common bacterial meningitis-causing agents exists; nevertheless, this is more of a challenge in developing countries, for example, along the African meningitis belt. In the event that disease develops, early diagnosis and efficient treatment strategies should be in place to increase chances of a better outcome. However, a major problem in treating infections of the CNS is drug delivery into this specific environment. In this aspect, research on pharmacological agents designed for crossing either the BBB or the BCSFB, to allow a directed delivery into the CNS, should be supported. For this, understanding the transporter systems at the BBB versus the BCSFB could be advantageous. Additionally, the differences in the immunological response at the BBB and BCSFB should be further investigated. It should be conceivable to target immunomodulatory therapeutic substances with beneficial effects selective to either the BBB or the BCSFB, similar to what is being applied in the treatment of multiple sclerosis (MS), where lymphocytes are blocked via monoclonal antibodies from transmigrating across the BBB (8).

A better understanding of the host-pathogen interactions at the CP would certainly be helpful for developing treatment options and predicting disease outcome. At this point it should be noted that the CP, and its cellular responses, has an important role during other afflictions of the CNS, such as MS and cancer metastasis. We believe that intense research should be dedicated to this small structure of the brain that seems to have a large impact on the CNS.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS
A.N.L. prepared figures; A.N.L. and C.S. drafted manuscript; A.N.L., T.T., H.S., and C.S. edited and revised manuscript; A.N.L., T.T., H.S., and C.S. approved final version of manuscript.

Glossary

- **BBB**: Blood-brain barrier
- **BCSFB**: Blood-cerebrospinal fluid barrier
- **CAR**: Coxackie- and adenovirus receptor
- **CCL**: C-C motif ligand
- **CD**: Cluster of differentiation
- **CDV**: Canine distemper virus
- **CMV**: Cytomegalovirus
- **CNS**: Central nervous system
- **CP**: Choroid plexus
- **CSF**: Cerebrospinal fluid
- **CVB3**: Coxsackievirus B3
- **CXCL**: C-X-C motif ligand
- **FIV**: Feline immunodeficiency virus
- **HEV**: Hepatitis E virus
- **Hib**: *Haemophilus influenzae* type b
- **HIBCPP**: Human epithelial CP papilloma
- **HIV**: Human immunodeficiency virus
- **HSV**: Herpes simplex virus
- **Inl**: Internalin
- **LPS**: Lipopolysaccharide
- **MMP**: Matrix metalloproteinase
- **PCPEC**: Primary porcine CP epithelial cells
- **PI3K**: Phosphatidylinositol 3-kinase
- **SIV**: Simian immunodeficiency virus
- **TF**: Transcription factor
- **TJ**: Tight junction
- **TLR**: Toll-like receptor
- **TNF-α**: Tumor necrosis factor-α
- **WNV**: West Nile virus

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C165

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