DOI: 10.1002/JLB.4MR1118-419R

JLB JOURNAL OF LEUKOCYTE BIOLOGY

REVIEW

The role of CNS macrophages in streptococcal meningoencephalitis

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Abstract

In the healthy brain, microglia and other CNS macrophages are the most abundant immune cell type. Thus, they form the natural immune cell interface with streptococci, which are the leading cause of bacterial meningitis and encephalitis in infants and young children. In homeostasis, the blood–brain barrier allows for very limited access of immune cells circulating in the periphery. During bacterial meningoencephalitis, however, origin and fate of CNS macrophages are massively altered. This review summarizes the emerging knowledge on the sequence of reciprocal events between streptococci and CNS macrophages leading to host resistance, acute inflammation, changes in resident innate immune cells of the brain, and long-term neuronal damage.

KEYWORDS

meningitis, microglia, *Streptococcus agalactiae*, *Streptococcus pneumoniae*

1 | INTRODUCTION

Bacterial infections of the CNS, bacterial meningitis and encephalitis, inhabit a prominent role among infectious diseases. It is widely accepted that under normal conditions the brain is free from bacteria at any time. In contrast, sporadic bacteremia and thus contact with living bacteria in any other body tissues is common in healthy individuals, for example, after tooth brushing.[1] The sterility of the healthy brain can be at least partially attributed to the blood–brain barrier (BBB), which is very restrictive for the transmigration of both host cells and microorganisms as well as plasma-derived proteins. However, certain bacterial organisms, among which streptococcal species inhabit a prominent role, have the ability to get access to the CNS, and thereby to the resident immune system of the CNS. The beginning of life constitutes a window of susceptibility for these infections, where a cascade of events can transiently severely perturb the separation of the CNS and the peripheral immune system. Thereby, long-term consequences for neurodevelopment might ensue.

Abbreviations: BBB, Blood–brain barrier; CLRs, C-type lectin receptors; CPM, Choroid plexus macrophages; DAMPs, Danger-associated molecular patterns; EMPs, Erythromyeloid progenitors; GBS, Group B streptococcus; LOD, Late-onset disease; MM, Meningeal macrophages; NLRs, Nucleotide-binding oligomerization domain (NOD)-like receptors; NVU, Neurovascular unit; PAMPs, Pathogen-associated molecular patterns; PVM, Perivascular macrophages; WT, Wild-type; YS, Yolk sac

1.1 | Origin and site-specific adaptation of macrophages in the CNS

Macrophage-like cells are the most prevalent immune cell type in the CNS during normal brain development and adulthood. Among these, microglia are exceptional with respect to their specific adaptation to the CNS parenchyma. Microglia are involved in the maintenance of cellular, synaptic, and myelin homeostasis in the resting and challenged CNS,[2] including neuronal guidance and synaptic pruning.[3] Almost 20 yr ago, it was reported that microglia originate from the yolk sac (YS).[4–6] Since then, several fate-mapping studies, particularly those exploiting the high expression of the fractalkine receptor CX_3CR1 in microglia, have been instrumental.[6,7] In embryonic mice, primitive hematopoiesis follows a tight sequence of events. Starting at embryonic day (E) 7.5, multilineage erythromyeloid progenitors (EMPs) are generated in the YS. EMPs enter the neuroepithelium and give rise to microglia, which are present in the brain parenchyma from embryonic

Received: 1 November 2018 | Revised: 14 January 2019 | Accepted: 15 January 2019

day 9.5 onward,[5,8] as well as to other peripheral tissue macrophages.[9] It is reported that a second wave of microglia progenitors, which are distinct by virtue of Hoxb8 expression, migrate from the YS via the aorto-gonad-mesonephros region and the fetal liver and infiltrate the brain at E12.5.[10] Preservation of population density in the subsequently growing brain depends on the remarkable self-renewing potential of microglia.[10,11] In this regard, the CNS differs from organs such as the intestinal tract and the dermis, where a large fraction of resident macrophages is exchanged postnatally by monocytes entering from penetrating capillaries and adapting discretely to the recipient tissue, even under homeostasis.[12]

In humans, the microglia turnover rate has been estimated to be as high as 2% of cells proliferating in any given moment, as indicated by Ki67 staining.[13] However, the calculation of cellular turnover based on cell cycle markers has limitations due to necessary assumptions on cell cycle length and progeny survival. Analysis of atmospheric ^{14}C integration into genomic DNA showed a replacement rate for microglia from the healthy human cortex of 28% per year[14]. Microglia are crucial for maintaining tissue homeostasis by scavenging dying cells, pathogens, and molecules.[8,15] They exhibit multiple features that distinguish them from other macrophage types, such as their "ramified" branches, which extend from the cell body. They permanently scan the environment and communicate with surrounding neurons and other glial cells.[16] Microglia have traditionally been regarded as a rather homogeneous population. However, recent studies in mice have revealed population heterogeneity related to the CNS region.[17,18] In addition, higher turnover rates of microglia were reported from the olfactory bulb, hippocampus, and cerebellum compared to those in the cortex, midbrain, and hypothalamus.[19] Differences in proliferation are probably related to a lower microglia density in the hindbrain.[20] Furthermore, microglia from distinct brain regions display differences in the formation of NO, glutamate uptake, and TNF expression after activation with LPS.[21] Thus, microglial density, renewal rates, and transcriptional programs are spatially organized in the CNS parenchyma.

Recent evidence strongly supports a model, where–next to parenchymal microglia–perivascular and meningeal macrophages (PVM and MM) largely originate from embryonic precursors and are maintained via self-renewal.[22] In contrast, choroid plexus macrophages (CPM), another distinct CNS macrophage population, are derived from embryonic precursors and are replaced over time by myeloid cells from the definitive hematopoiesis.[22] Regarding the presence of PVM, MM, and CPM, respectively, their location at the CNS barriers indicates a role in immunosurveillance by bridging "inside" and "outside." The transcriptional regulator PU.1 is essential for the development of all YS-derived CNS macrophages,[5,22] whereas c-Myb, as the necessary transcription factor for fetal monocytes and definitive hematopoiesis,[7] is dispensable in this context.[22] Discrepancies between very recent and previous studies, which were based on bone marrow transplantation models and found definitive hematopoiesis to contribute to all nonparenchymal CNS macrophages,[23,24] probably originate in the perturbation of the BBB by irradiation or chemotherapy, resulting in CNS infiltration of circulating monocytes.[22]

CNS macrophages show specific features, which might be in part explained by anatomic and functional needs and may be used to determine their identity. Although PVM exhibit similarities to microglia both with respect to the expression of surface markers, for example, CX_3CR1, CSF1R, Iba1, and CD11b, they are different in their morphology and transcriptional profile. In accordance with their location between the bloodstream and the CNS, they appear to be particularly important when the relative immune privilege of the brain is disturbed, that is, when circulating leukocytes are recruited to the brain during disease.[25] MM originate, like PVM and microglia, from the YS.[22] The meninges as resident site of the MM form an important part of the CSF–brain barrier. They are composed of three layers of connective tissue, the dura (the most external part, facing the skull), the arachnoid, and the pia mater (leptomeninges). The immunologic anatomy of the meninges is further characterized by a dedicated lymphatic system draining into deep cervical lymph nodes.[26] The exact impact of the meningeal lymphatic system on the CNS immunity and its functional role in brain infections is currently unclear.[26] Moreover, the connection of MM and the aforementioned lymphatic system has not been clarified.

The choroid plexus is composed of epithelial cells, fibroblasts, neural stem cells, telocytes, as well as circulating lymphocytes and resident macrophages.[27] CPM originate from the YS, but are constantly replaced by bone marrow-derived monocytes.[22]

1.2 | The blood–brain barrier

More than one hundred years ago, Paul Ehrlich and Edwin Goldman discovered that the CNS and the peripheral circulation are separated by what was later called the BBB or hematoencephalic barrier.[28] The BBB is anatomically represented by the cerebral microvascular endothelium, which is interconnected by tight junctions and lacks fenestrations, by pericytes, astrocytes, and a basal membrane.[29] The crosstalk between these cells is commonly known as the neurovascular unit (NVU).[30] The neonatal BBB is conventionally regarded as immature and therefore "leaky".[31] Nonetheless, it has been shown that BBB development starts with the angiogenic phase as early as E9.0-E10.5 of the embryonic development in mice.[32] A pivotal characteristic of blood endothelial cells is the formation of tight junctions already early in brain vascularization.[33,34] It has been shown that the tight junctional proteins claudin 5 and occludin are present soon after blood vessel formation in the brain.[35] Moreover, recruitment of pericytes and astrocytes to the new blood vessels occurs during the differentiation phase between E15.5 and E18.5 in mice.[36] Therefore, it is conceivable that the BBB is functional to some degree in the early phases of the development.

The BBB permeability can be affected by a plethora of factors such as viral and bacterial infection, traumatic brain injury, poisoning, or hypertension.[37–41] Interestingly, it seems that factors from the gut microbiota can also affect BBB permeability, because germ-free or antibiotic-treated mice show an increased BBB permeability and altered expression of tight junction proteins.[42] With respect to immune cells, PVM functionally contribute to the BBB. They are located in perivascular spaces, between endothelial and glial basement membranes[43] and are involved in sampling debris and dying cells, the maintenance of endothelial cells, the BBB and capillaries, and

the regulation of vascular constriction.[44,45] Moreover, $CD31^+F4/80^+$ macrophages, which are derived from embryonic hematopoiesis, differentiate into a subset of cerebrovascular pericytes,[46] which impact on BBB function.[47,48] Studies using transgenic mice with different degrees of pericyte deficiency showed that pericytes inhibit the expression of molecules that increase vascular permeability.[47,48]

The BBB is anatomically complemented by the blood–CSF barrier. Like the BBB, it comprises three layers: choroidal epithelial cells, which are interconnected by tight junctions, a basal membrane, and fenestrations containing endothelium of the pia mater capillaries. The blood–CSF barrier indirectly connects to the CNS parenchyma via the CSF-brain barrier, which is lined by ependymal cells with gap junctions in the mature brain. In the adult, these gap junctions do not restrain diffusion between the brain and the CSF, whereas during development so-called "strap" junctions of neuroepithelial and later radial glial cells limit the exchange of different sized molecules.[49] On the other hand, the blood–CSF barrier appears to be somewhat leaky at the beginning of life, as indicated by the presence of leukocytes in the normal neonatal CSF.[50]

1.3 | Pattern-recognition receptors in microglia and nonparenchymal macrophages

Innate immune cells have the capability to recognize pathogen compounds such as glycolipids, lipoproteins, cell wall fragments, and nucleic acids.[25] These so-called pathogen-associated molecular patterns (PAMPs) are, together with endogenous products of tissue damage (danger-associated molecular patterns, DAMPs), recognized by pattern recognition systems such as TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs), scavenger receptors, and intra-cytosolic DNA and RNA sensors.[30] Activation of PRRs leads to production of inflammatory mediators like chemokines and cytokines.

Although microglia are largely sheltered by the BBB from contact with foreign material, the pattern recognition machinery allows them to respond to the spurious presence of microbial components. Accordingly, microglia are easily activated by microbial components, leading to the formation of cytokines, for example, TNF, IL-1β and IL-18, and NO .[29] Microglia express all TLRs identified so far, both on the cell membrane and at the endosome.[51,52]

The first TLR to be studied in the context of meningitis was TLR2, which is constitutively expressed in microglia.[53,54] The importance of MyD88-dependent TLR signaling was demonstrated in a *S. pneumoniae* meningitis model that displayed a lack of inflammatory response and severe bacteremia in MyD88-deficient mice.[55]

NLRs are involved both in pathogen detection and the inflammatory response by forming inflammasomes. Although different types of inflammasomes are described in the CNS, NLRP3 in microglia has been investigated most extensively.[56–58] In contrast to NLRs, the role of cytosolic helicases such as RIG-I in microglia is somewhat controversial. RIG-I controls the response to RNA viruses via recognition of double-stranded RNA carrying a 5′-triphosphate (3pRNA). In RIG-I-deficient mice, cytokine production is almost entirely abolished in microglia and astrocytes when infected with the model neurotropic RNA virus, indicating that RIG-I plays an important role in RNA virus infection.[59] However, to our best knowledge, a role of RIG-I-like helicases in bacterial meningitis and encephalitis has not been identified yet.

One of the exclusive microglial markers in the CNS is P2Y12, a purinergic receptor for nucleotides like ATP, which are released upon cellular injury.[60,61] P2Y12 is expressed in human microglia already in steady state.[62] Microglial recognition of pathogens can have both favorable and unfavorable consequences.[63] The combination of PAMPs, DAMPs, and cytokines elicits distinct activation cascades that allow for an antibacterial response, but at the same time cause collateral damage to immune and nonimmune cells. In the healthy state, this is prevented, because the brain is separated from the microbial environment by several layers of defense, starting with the mucocutaneous interfaces where bacteria reside in healthy individuals, the subepithelial tissues, the circulating cellular and acellular immune elements, the BBB, and the blood–CSF barrier. Accordingly, antimicrobial defense to protect the brain is mostly executed far away from the brain. According to the situation in other tissue resident macrophages, it has been attempted to classify microglia in a polarized system containing classically activated, inflammatory "M1"-like cells and alternatively activated or regulatory M2 microglia.[64] The ligand-receptor pair of the chemokine CX_3CL1 (fractalkine) and CX_3CR1 (fractalkine receptor), which is highly expressed by microglia appears to negatively affect M2 polarization of microglia.[65] However, in view of the recently unveiled microglia heterogeneity,[18,19] it seems probable that a system with two or few polarization states oversimplifies the multitude of microenvironmental niches and activation states in the CNS.[66]

The specificity and the differences between microglia and other CNS macrophages have not been exhaustively investigated, as the discrimination of these distinct populations has been challenging.[22] Therefore, not a lot is known about pattern recognition receptors that are specific for nonparenchymal macrophages, with the notable exception of CD36 and CD206. CD36, a member of the class B scavenger receptor family, mediates recognition and phagocytosis of apoptotic cells and oxidized lipids.[67] It has been connected with β-amyloid fibril binding and a consecutive inflammatory response in an Alzheimer disease model[68] and with a reparative role during the resolution of inflammation in ischemic stroke.[69] In the mouse brain, PVM, MM, and CPM also express the mannose receptor (CD206).[22] CD206 is involved in pathogen recognition and phagocytosis, because many pathogenic microbes express mannose-containing structures. Examples for pathogens recognized by the mannose receptor are *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, and *Candida albicans*.[70] Interestingly, expression of CD206 in the CNS is strictly limited to nonparenchymal macrophages and is not present in microglia.[71,72] However, the functional significance of this expression pattern has not been explored yet. In general, CD206-deficient mice did not show an increased susceptibility to *Candida albicans*,[73] but had a higher fungal burden and died more rapidly in pulmonary infection with *Cryptococcus neoformans*.[74] This indicates a site- and pathogen-specific importance of CD206 expression.

CD163, a membrane glycoprotein belonging to the scavenger receptor cysteine-rich superfamily group B, has also been referred to

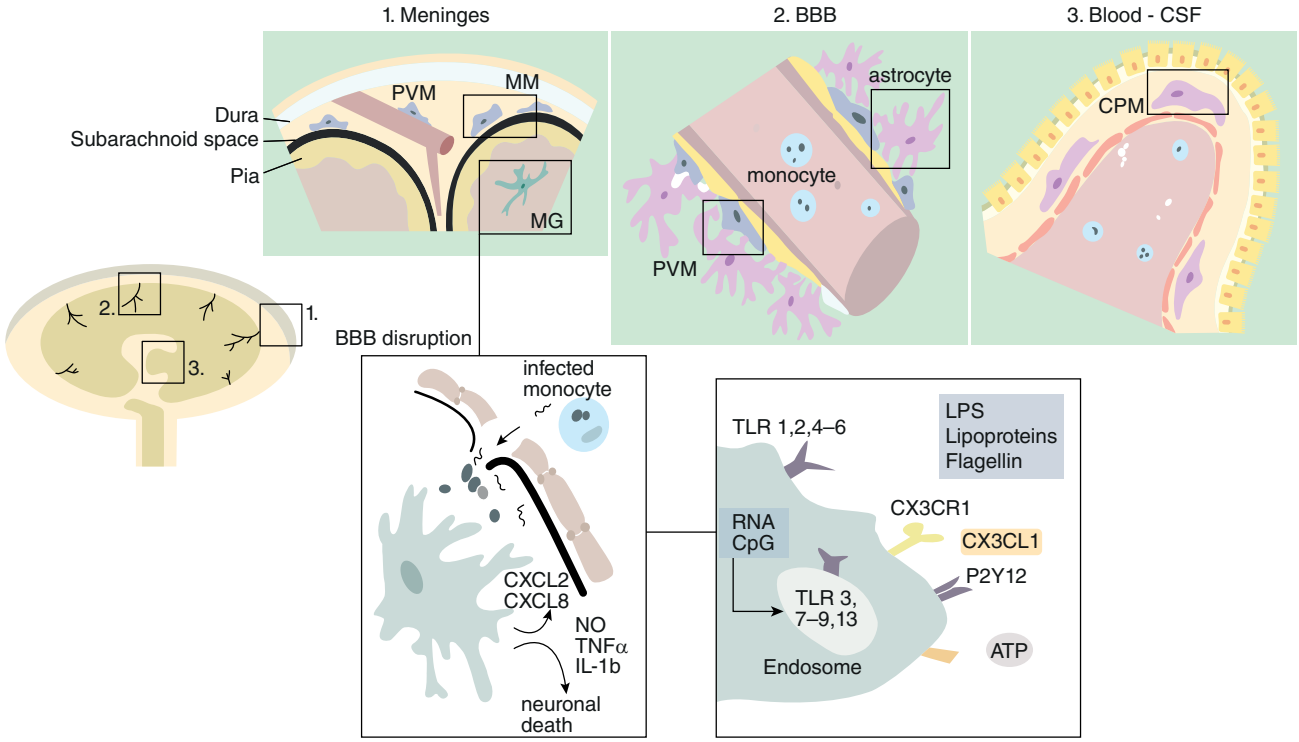

FIGURE 1 **Representation of distinct macrophage populations localized at different CNS interfaces**. BBB disruption causes the infiltration of bacteria into the brain parenchyma and consequent microglial sensing. Microglia produce chemokines that attract the circulating monocytes, which could possibly serve as a Trojan horse for the bacterial dissemination. On the other hand, microglia produce cytokines and NO as an antibacterial response which can also lead to unfavorable consequences such as neuronal death

as a specific marker for nonparenchymal macrophages.[75] However, microglia may up-regulate CD163 in diseases such as multiple sclerosis and Alzheimer's disease.[72,76]

Microglia as well as nonparenchymal macrophages have antigen-presenting and thus T cell-activating potential, as indicated by their expression of MHC class II.[72,77] Microglia–T cell interactions have predominantly been studied in pathologic conditions such as viral infections and multiple sclerosis. In homeostasis, T cells are rarely found in the brain parenchyma.[78,79] However, in lymphocytic choriomeningitis virus infection, antiviral T cells are recruited to the CNS, which promote CD11c expression, proliferation, antigen presentation, and chemokine formation in microglia.[80] Mice infected intracerebrally with *S. pneumoniae* showed the recruitment of B cells, $CD4^+$, $\gamma\delta$, and natural killer T cells to the brain. Moreover, $Rag1^{-/-}$ mice lacking functional B and T cells died earlier compared to the wild-type (WT) control and had less proliferating microglia, indicating the importance of lymphocytes in bacterial meningitis.[81] In contrast to the brain parenchyma, T cells reside in the choroid plexus, the perivascular space and in meninges already in homeostatic conditions, which suggests a role in immunologic CNS surveillance.[82] It appears that central memory T cells, that is, antigen-experienced $CD4^+$ or $CD8^+$ T cells, play an essential functional role in this context.[83] However, virtually nothing is known about the interactions between nonparenchymal macrophages and T cells.

1.4 | Bacterial meningoencephalitis

It is a conclusive model that in bacterial meningoencephalitis bacteria are usually disseminated via the bloodstream and enter the brain via blood vessels.[84] Three distinct blood–CNS interface systems allow blood-derived bacteria to reach the CNS: first the parenchymal vessels of the BBB, second the meningeal blood vessels, and third the choroid plexus vessels. In all cases, bacteria need to penetrate through the luminal side of the endothelial barrier (Fig. 1).

Certain pathogens can penetrate the BBB and gain entry into the CNS, either via direct invasion, or in an opportunistic fashion, if permeability of the BBB is increased. The factors perturbing BBB restriction for bacterial and cellular penetration in meningitis are incompletely resolved. Bacterial effectors and toxins may induce BBB permeability directly or via induction of cytokines, chemokines, arachidonic acid metabolites, and reactive nitrogen and oxygen species.[85] In the context of this review, mechanisms underlying the BBB breakdown are important for several reasons. First, microbial factors that activate peripheral cells may get access to the CNS and thus interact with microglia. Furthermore, bacteria appear to use phagocytes as Trojan horses to get access to the brain,[86] although the evidence for this is very limited. As an example, injection of *L. monocytogenes*-infected bone marrow myeloid cells more efficiently causes brain infection than the injection of bacteria alone.[87] Similar effects have been observed in mice for *S. pneumoniae*, where inflammatory monocytes appeared to serve as vehicles.[88] It appears that the dominant paths for transmigrating leukocytes lead via the outer meningeal spaces, where the vasculature lacks tight junctions, and via the lymphatic system rather than directly across the BBB.[86]

Further mechanisms, which are employed by bacteria to overcome the BBB, involve vacuoles as envelopes (transcytosis) and squeezing through intercellular junctional spaces.[85] Depending on the site

of penetration, the bacteria get in contact with macrophage subsets, which are distinct concerning origin and function.[22] Bacteria invading from vessels, which are penetrating the CNS parenchyma, interact with PVM in the Robin-Virchow spaces,[77] before they are confronted with parenchymal microglia. In case they reach the inner and outer CSF spaces, CPM and MM form dynamic interaction partners. The most important bacteria causing meningitis, for example, streptococci, meningococci, and *Haemophilus influenzae*, cohabitate with humans as their nearly exclusive hosts. However, bacterial meningitis is a catastrophic event that essentially threatens the coexistence. Thus, it seems safe to assume that contact of the brain immune system with bacteria is, in contrast to dermis, lamina propria, or even the liver, not a planned or frequent interaction. In other words, any activation of the CNS monophagocytic system likely induces a state of immunopathology.

It is a critical question, which microbial and host factors allow for these interactions to take place. In the pathogenesis of meningitis, penetration of bacteria through the BBB initiates activation of brain endothelia and leads to leukocyte recruitment and release of inflammatory mediators. Subsequently, the subarachnoidal inflammation stimulates astrocytes, microglia, and neurons to produce cytokines and chemokines.[89] Clearly, certain bacterial species have a relatively high probability to reach the CNS once they have become invasive, in particular group B streptococci, *Listeria monocytogenes*, and *Neisseria meningitis*. On the other hand, *S. pneumoniae*, which is the most common cause of bacterial meningitis in many areas of the world, far more frequently causes bacteremia and pneumonia in children.[90] Finally, *L. monocytogenes* can directly enter the brain via the olfactory epithelium and spread along the sensory neurons to the CNS in neonatal mice,[91] similar to what has been shown for pneumococci.[92]

1.5 | Streptococcal meningoencephalitis

Streptococcus spp. are responsible for a large portion of bacterial meningoencephalitis cases, in particular in areas where vaccinations against *Haemophilus influenzae* type B and *Neisseria meningitis* have been successfully implemented. Under these circumstances, *S. pneumoniae* (pneumococcus) and group B streptococcus (*S. agalactiae*, GBS) are leading and in many respects paradigmatic causes of bacterial meningoencephalitis. GBS is the most frequent cause of bacterial meningitis in small infants when both the macrophage system and the microbiota undergo the biggest changes.[93] Next, whereas GBS is a common mucocutaneous colonizer in 10–30% of all infants, older children and adults, it rarely causes invasive disease in infants. If so, however, it results in meningitis in over 50% of cases, if it occurs after postnatal day 3.[94] Finally, GBS meningitis is a clonal disease in many areas of the world.[95] Whereas GBS mainly causes meningitis in neonates and in patients with immunosuppression, *Streptococcus pneumoniae* is the major cause of meningitis in older children and adults.

1.6 | The problem of the developing immune system: group B streptococcal meningoencephalitis

GBS is a Gram-positive encapsulated bacterium that often colonizes the gastrointestinal and genital tracts of humans. It has been isolated from the vagina and/or the rectum of 15–40% of pregnant women.[96] Neonatal GBS meningitis typically occurs in the frame of the so-called late-onset disease (LOD), between day 4 and 90 of life.[96] Perinatal antibiotic prophylaxis, which has been introduced in many countries to prevent early GBS sepsis, has not decreased the incidence of GBS meningoencephalitis.[97,98] Next to the lethality of GBS meningoencephalitis (5–10%), long-term neurologic impairment of variable degrees affects up to 30 to 70% of surviving infants.[99,100] GBS has been cultured from breast milk of the nursing mother and the intestinal tract of individual infants before onset of LOD and meningitis in individual cases,[101–106] which suggests that GBS is acquired through the intestinal route, yet this model remains somewhat speculative. The concept that GBS dissemination happens from the intestine to the CNS is supported by the study of Poyart et al., where intestinal GBS colonization in mice in the first three weeks of life led to CNS invasion and meningoencephalitis.[107] It is notable in this context that the consumption of raw freshwater fish in Singapore caused a large outbreak of severe GBS infections including meningoencephalitis in adults.[108] This outbreak was linked to the sequencing type (ST) denominated 283 GBS, although two-thirds of cases were due to other types.

GBS interacts with CNS immune and nonimmune cells via various mechanisms.[109–111] As an example, GBS was found to cross the microvascular endothelium by utilizing the surface-anchored serine-rich protein Srr-1.[112] Other GBS proteins interacting with microvascular endothelial cells are laminin-binding protein Lmb,[113] fibrinogen-binding protein FbsA[114] and PilB, which is necessary for the pilus formation.[115] However, most of these studies were performed in vitro. In order to study the effects of GBS infection on CNS macrophages, a proper animal model of GBS-induced meningitis that mimics the human GBS infection is necessary. A recent paper by Andrade et al. described a mouse model in which GBS strain BM110 is transmitted to the offspring from vaginally colonized pregnant females, which represents a natural route of infection.[116] Under these conditions, an increased number of Ly6C$^{int/low}$ monocytes in the brains of the infected pups was observed and microglia morphology was switched toward a reactive phenotype, leading to neuronal apoptosis and reactive astrogliosis. Sequelae in surviving mice showed different neuronal impairments such as reduced exploratory activity, impairment in memory, and learning as well as altered levels of neurotransmitters, for example, glutamate, dopamine, and 3,4-diydroxyphenylacetic acid.[116]

The pathways, which mediate microglia activation by GBS, thus initiating and terminating inflammation and leading to neurologic damage, have been partially resolved. GBS is recognized by mouse microglia via TLR2 and endosomal TLRs, most likely TLR13, leading to discrete signaling programs.[117] In contrast to endosomal TLRs, which are dominating the TNF response, the surface-expressed TLR2 primarily mediates NO formation, resulting in the loss of neurons cocultured with microglia.[109] Yet, at the same time, TLR2 triggers caspase-8-dependent apoptosis induction in microglia, thereby potentially limiting neuropathology resulting from microglia activation.[118] Whereas these ex vivo data allow for some insights into the interaction of GBS with the CNS immune system, data regarding the CNS immune response to GBS in vivo, in particular in the context of

neonatal meningoencephalitis, are lacking. First, it remains elusive, how GBS overcomes the layers of defense, in particular tissue macrophages, at colonizing sites and myeloid cells in the bloodstream. Secondly, whereas the available studies focus on microglia, the role of MM, PVM, and CPM in GBS infection is virtually unknown. Notably, microglia as well as PVM and MM show an age-related decline in their phagocytic capacity for bacteria such as *E. coli*,[119] yet this age-related development appears not to directly result in a change in susceptibility for streptococcal meningoencephalitis.[120]

1.6.1 | *Streptococcus pneumoniae*

Streptococcus pneumoniae is the major cause of meningitis in adults. Despite antimicrobial therapy and critical care medicine, the mortality remains as high as 28%.[121] In addition, 50% of the survivors have neurologic sequelae, indicating postinflammatory damage.[122] In contrast to GBS, *S. pneumoniae* is a frequent colonizer of the nasopharynx. It expresses various adhesion factors, such as the Pneumococcal adherence and virulence factor A (PavA). Pneumococci may enter the brain via adhesion to laminin receptors on brain microvascular cells.[123] The neuraminidase NanA is another pneumococcal virulence factor that allows *S. pneumoniae* to invade human brain microvascular endothelial cells.[124] In the pathogenesis of meningitis, bacterial penetration through the BBB initiates activation of brain endothelia and leads to leukocyte recruitment and release of inflammatory mediators. Subsequently, the subarachnoidal inflammation stimulates astrocytes, microglia, and neurons to produce cytokines and chemokines.[89]

Host invasion and bacteremia with *S. pneumoniae* are relatively frequent events. In unclassified small children that report with fever to the emergency department, around 1% show bacteremia with pneumococci, and many will clear them without any sequels.[125] However, although almost everybody is at least transiently colonized and many are invaded, very few will go on to develop meningoencephalitis.[126] During pneumococcal meningitis, microglia can recognize components of *S. pneumoniae* via TLRs.[55] Upon intracisternal infection, TLR2$^{-/-}$ mice showed a moderate increase in disease severity and succumbed to infections faster than WT mice, which was associated with reduced bacterial clearance.[127] In addition to TLR2, TLR4 was found to contribute to pneumococcal detection in meningitis. Compared to WT mice, TLR2/4$^{-/-}$ mice displayed less pleocytosis and reduced expression of inflammatory cytokines in advanced pneumococcal infection.[128]

It has been demonstrated that in pneumococcal meningitis neuronal injury results from the local inflammatory response. IL-1β and IL-18 are increased in the CSF of patients with bacterial meningitis and are inversely correlated with the disease outcome. In mice with pneumococcal meningitis, NLRP3 appears to mediate bacterial killing in the brain early in infection. NLRP3 deficiency was furthermore associated with increased CNS inflammation later in disease.[129]

It is intriguing that microglia change their morphology to an activated phenotype with increased expression of MHC class II, CD40 and CD86 already a few hours after streptococcal infection.[130,131] Additionally, they form chemokines such as CXCL2 and CXCL8, thereby recruiting immune cells to the brain. Furthermore, it appears that IFN-γ-dependent induction of NO production mediates pathology in pneumococcal meningoencephalitis and that CNS-resident myeloid cells including microglia are the most probable NO source.[132]

In contrast to the recruitment of monocytes, which occurs already relatively early after meningitis onset, the engraftment of macrophages into the CNS parenchyma happens during later stages, that is, during tissue repair.[130] Ly6C^{high}CCR2^{+} monocytes, as well as Ly6G^{+}CCR2^{-} granulocytes, are efficiently recruited into the meninges, but the depletion of this monocyte population or the chemokine receptor CCR2 did not affect bacterial clearance and clinical outcome in a pneumococcal meningitis model.[133] Animals with depleted Ly6G^{+}CCR2^{-} cells, on the other hand, died earlier and had higher bacterial burdens compared to the controls.[133] This suggests that among myeloid cells originating from definitive hematopoiesis, granulocytes are key players in pneumococcal meningitis.

Limited data is available on the specific roles of PVM and MM in pneumococcal meningitis. Intraventricular injection of clodronate liposomes to largely deplete MM and PVM in experimental pneumococcal meningoencephalitis caused worsening of clinical symptoms, an increased bacterial burden, impaired recruitment of granulocytes, and other leukocytes and enhanced levels of inflammatory mediators in CSF and blood.[25] These data indicate that MMs and PVMs play an important and protective role in this disease.

1.7 | CNS macrophages in and after inflammation

Resolving the discrete contributions of resident versus recruited immune cells to host resistance and neuropathology in bacterial meningoencephalitis is an obvious research goal with translational potential. In this context, it remains an ongoing debate whether the macrophage origin, that is, YS versus bone marrow, imprints a differentiation and activation program onto macrophages. Currently, most of the available evidence suggests that bone marrow-derived macrophages adapt to a new site with very distinct functional demands. As an example, peritoneal macrophages transplanted into the lung are, after 4 mo of adaptation, partially reprogrammed by the new tissue microenvironment and transcriptionally resemble YS-derived alveolar macrophages.[134,135] Moreover, monocyte-derived parenchymal CNS macrophages cannot be safely discriminated from YS-derived microglia. As an example, one of the most sophisticated microglial functions, the so-called "synaptic pruning," by which superfluous and defective synapses are eliminated, particularly in the developing brain, can be executed by ontogenetically distinct HoxB8 positive and negative microglia subsets.[10] On the other hand, the plasticity of tissue macrophages has limitations. Very recent data show that although macrophages from non-CNS tissues generally express microglial genes in the brain after transplantation into the CNS, only those of YS origin fully attain microglial identity.[136] Moreover, in a chronic microglia depletion model, repopulating macrophages were reported to retain a distinct functional and transcriptional identity as compared to YS-derived microglia.[137]

In addition, germ-free mice show alterations in both morphology and transcriptional program of microglia,[138] thus highlighting how general changes in activation and potentially myeloid cell dynamics may impact on microglia identity.[3]

1.8 | Concluding remarks

Microglia and nonparenchymal CNS macrophages are important for CNS development and demarcation from body fluids and peripheral blood cells. CNS macrophages are equipped with an elaborate sensing machinery to detect spurious bacterial components already in homeostasis, for example, those originating from the microbiota, which contributes to neurodevelopment. In contrast, it remains an ongoing puzzle, whether the in part pathogen-specific potent activation of resident CNS macrophages by streptococci breaching the BBB and blood–CSF barriers executes effective host defense, or whether this predominantly relies on recruited myeloid cells. In contrast, the role of CNS macrophages in neuronal damage seems beyond doubt. Given the immense health burden of the disease, it constitutes an important translational research goal to decipher the particular contribution of resident and infiltrating myeloid cell subsets to the long-term outcome in streptococcal meningoencephalitis.

AUTHORSHIP

All authors contributed equally to this work.

ACKNOWLEDGEMENTS

The work was sponsored by the German Ministry of Education and Research (01EO0803, 01GL1746A and 535 01EK1602A to P.H.) and by the German Research Council (SFB/TRR167 to D.E. and P.H., HE3127/9-1 and HE3127/12-1 to P.H.).

DISCLOSURES

The authors declare no conflicts of interest.

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How to cite this article: Gres V, Kolter J, Erny D, Henneke P. The role of CNS macrophages in streptococcal meningoencephalitis. *J Leukoc Biol*. 2019;1–10. https://doi.org/10.1002/JLB.4MR1118-419R