Mol Neurobiol (2016) 53:1770–1781
DOI 10.1007/s12035-015-9107-4

Role of Microglial Activation in the Pathophysiology of Bacterial Meningitis

Tatiana Barichello · Jaqueline S. Generoso · Lutiana R. Simões · Jessica A. Goularte · Fabricia Petronilho · Priyanka Saigal · Marwa Badawy · João Quevedo

Received: 30 October 2014 / Accepted: 20 January 2015 / Published online: 7 March 2015

Abstract Bacterial meningitis is a life-threatening infection associated with cognitive impairment in many survivors. The pathogen invades the central nervous system (CNS) by penetrating through the luminal side of the cerebral endothelium, which is an integral part of the blood-brain barrier. The replication of bacteria within the subarachnoid space occurs concomitantly with the release of their compounds that are highly immunogenic. These compounds known as pathogen-associated molecular patterns (PAMPs) may lead to both an increase in the inflammatory response in the host and also microglial activation. Microglia are the resident macrophages of the CNS which, when activated, can trigger a host of immunological pathways. Classical activation increases the production of pro-inflammatory cytokines, chemokines, and reactive oxygen species, while alternative activation is implicated in the inhibition of inflammation and restoration of homeostasis. The inflammatory response from classical microglial activation can facilitate the elimination of invasive microorganisms; however, excessive or extended microglial activation can result in neuronal damage and eventually cell death. This review aims to discuss the role of microglia in the pathophysiology of bacterial meningitis as well as the process of microglial activation by PAMPs and by endogenous constituents that are normally released from damaged cells known as danger-associated molecular patterns (DAMPs).

Keywords Bacterial meningitis · Microglia · DAMPs · PAMPs · Cytokines · Oxidative stress

Abbreviations

17β HSD14	17β hydroxysteroid dehydrogenase type 14
AIM2	Absent in melanoma
AP-1	Activator protein-1
Arg1	Arginase 1
ASC	Apoptosis-associated speck-like protein containing a caspase-recruitment domain
ATP	Adenosine 5′-triphosphate
BBB	Blood-brain-barrier
CLRs	c-type lectin receptors
CNS	Central nervous system
CSF	Cerebrospinal fluid
CX_3CL1	Chemokine (C-X3-C motif) ligand 1
CX_3CR1	Chemokine (C-X3-C motif) receptor 1
DAMPs	Damage-associated molecular patterns
DHEA	Dehydroepiandrosterone
DNA	Deoxyribonucleic acid
ERβ	Estrogen receptor beta
FIZZ1	Found in inflammatory zone 1
GSA-IB4	*Griffonia simplicifolia* isolectin-B4
HMGB-1	High mobility group box-1 protein
HSP	Heat shock protein
Iba1	Ionized calcium binding adaptor molecule 1

T. Barichello (✉) · F. Petronilho · P. Saigal · M. Badawy · J. Quevedo
Center for Experimental Models in Psychiatry, Department of Psychiatry and Behavioral Sciences, The University of Texas Medical School at Houston, Houston, TX, USA
e-mail: tba@unesc.net

T. Barichello · J. S. Generoso · L. R. Simões · J. A. Goularte
Laboratory of Experimental Microbiology, Graduate Program in Health Sciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil

F. Petronilho
Laboratory of Clinical and Experimental Pathophysiology, Graduate Program in Health Sciences, University of South Santa. Catarina, Tubarão, SC, Brazil

J. Quevedo
Laboratory of Neurosciences, Graduate Program in Health Sciences, Health Sciences Unit, University of Southern Santa Catarina, Criciúma, SC, Brazil

IFN	Interferon
IGF-1	Insulin-like growth factor 1
IL	Interleukin
iNOs	Nitric oxide synthase
IRAK-4	Interleukin-1 receptor-associated kinase 4
IRF-3	Interferon-regulatory factor 3
JAK-1	Receptor-Janus Kinase-1
LPS	Lipopolysaccharide
M1	Classical activation phenotype
M2	Alternative activation phenotype
MDA	Malondialdehyde
MIP-2	Macrophage inflammatory protein 2
MyD88	Myeloid differentiation factor 88
NF-κB	Nuclear transcription factor kappa factor B
NLRP3	Nucleotide-binding domain and leucine-rich repeat protein 3
NLRs	Nucleotide binding oligomerization domain-like receptors
NO	Nitric oxide
NODs	Nucleotide binding oligomerization domains
O_2^-	Superoxide anion
$ONOO^-$	Peroxynitrite formation
P2X	P2 purinergic receptor
PAMPs	Pathogen-associated molecular patterns
PRRs	Pattern-recognition receptors
RAGE	Receptor for advanced glycation end products
RLRs	RIG-I-like receptors
STAT-3	Activator of transcription-3
TGF-β	Transforming growth factor beta
TLRs	Toll-like receptors
TNF	Tumor necrosis factor
TRAF	Receptor-associated factor
TRIF	TIR-domain-containing adapter-inducing interferon-β
Ym1	Chitinase-3-like protein 3

Introduction

Bacterial meningitis is a life-threatening disease associated with long-term cognitive impairment in many survivors [1, 2]. Replication of bacteria within the subarachnoid space occurs concomitantly with the release of their compounds, such as peptidoglycan, lipoteichoic acid (a constituent of the cell wall of Gram-positive bacteria), flagellin (a protein in bacterial flagella), lipopolysaccharide (LPS) (a constituent of the cell wall of Gram-negative bacteria), DNA, and cell wall fragments. These compounds are all referred to as pathogen-associated molecular patterns (PAMPs). These PAMPs are recognized by pattern-recognition receptors (PRRs), which are the pivotal components of the innate immune system [3, 4].

The immune system responds to an infection when microbial pathogens are recognised by antigen-presenting cells. This recognition occurs via the binding of PAMPs to PRRs on antigen-presenting cells such as toll-like receptors (TLRs), RIG-I-like receptors (RLRs), c-type lectin receptors (CLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and intra-cytosolic DNA sensors [4, 5]. The interaction between PAMPs and PRRs promotes the release of mediators, including cytokines and chemokines that propagate and regulate the response necessary to remove invasive microorganisms [6]. Innate immune cells are also triggered by endogenous constituents that are normally released from damaged cells including nucleic acids, cytochrome c, uric acid crystals, adenosine 5′-triphosphate (ATP), S100 molecules, histones, heat shock protein (HSP), and high mobility group box-1 protein (HMGB-1). These molecules are known as damage-associated molecular patterns (DAMPs) [7, 8]. Microglia can be activated by many stimuli including PAMPs, DAMPs, or pro-inflammatory mediators to produce cytokines, chemokines, and reactive oxygen and nitrogen species which together are involved in eliminating the invading microorganism. Thus, damage to the central nervous system (CNS) during bacterial meningitis commonly involves pathogenic mechanisms of both bacteria and the innate immune host response [9, 10].

Morphological States and Functions of Microglia

Microglia are the resident macrophages of the CNS parenchyma, they originate from hematopoietic stem cells, and differ from astrocytes in their function, origin, pattern of gene expression and morphological characteristics [11]. Resting microglia morphology exhibits ramified branches that emerge from the cell body and connects with surrounding neurons and glial cells. The extensive surface area allows the microglia to assess and control changes in their environment [12]. Stence and his colleagues (2001) studied the dynamics of microglial cell activation from rat brain tissue slices. The microglia cells converted from a resting ramified morphology to an amoeboid form within several hours in vitro after mechanical injury. The authors suggested that the ramified branches of resting microglia would be incapable of phagocytosis [13]. Another study conducted by Yamada and Jinno (2013) classified reactive microglia into four groups, types I-IV. Type I microglia cells were similar to ramified microglia in a resting state. Type II microglia cells exhibited small cell bodies with thin and short processes. Type III microglia cells were hypertrophied with short thick processes. Type IV "bushy" cells exhibited the greatest process density [14].

Microglia cells maintain cellular, synaptic, and myelin homeostasis during development, normal function of the CNS, and in response to CNS injury. Thus, microglia have been

shown to mediate a myriad of aspects of neuroinflammation, including recognition of pathogens bound to MHC for activation of T lymphocytes, phagocytosis, cytotoxicity through production of cytokines, and secretion of glutamate, aspartate, reactive oxygen, and nitrogen species. Additionally, one of the functions of these cells is CNS repair through the removal of cell debris which facilitates plasticity and synaptogenesis [15]. Activated microglia comprises heterogeneous cells that modify their phenotype depending on the type of stimulus and environment [12].

CX_3C chemokine CX_3CL1 (fractalkine), are found in brain tissue, particularly in neurons and microglia. Microglia binds to CX_3CL1 through CX_3CR1. CX_3CL1 is responsible for many microglial functions including migration, proliferation, inhibition of Fas ligand-induced cell death and glutamate-induced neurotoxicity, and inhibition of pro-inflammatory cytokine production. Therefore, CX_3CL1 has neuroprotective functions against activated microglia-induced neurotoxicity [16].

These various functions are associated with M1 and M2 phenotypes and their multiple receptors that can induce different signaling cascades involved in chemotaxis, phagocytosis, and the production of numerous neurotoxic and anti-inflammatory mediators. Microglial cells polarized to the M1 phenotype are considered to be in a pro-inflammatory state, whereas microglia of the M2 has anti-inflammatory properties. In addition, Mox macrophage that is distinct from conventional M1 or M2 macrophage phenotype induced by oxidized phospholipids and nitrosylated fatty acids. Mox macrophages present elevated levels of reactive oxygen species and heme oxygenase-1, and the transcription factor nuclear erythroid 2-related factor 2 (NRF2) [17, 18]. M1 and M2 surface markers and mediator synthesis are demonstrated in Tables 1, 2, and 3 [33].

Microglia Phenotype 1 Activation and Signaling

Several receptors can trigger the M1 phenotype such as TLRs, RLRs, CLRs, NLRs, the receptor for advanced glycation end products (RAGE), P2X purinergic receptor (P2XR), tumor necrosis factor receptor (TNFR), and macrophage-colony-stimulating factor receptor (CSF1R) as shown in Fig. 1.

TLR signaling complexes generally use an intracellular adapter protein, known as myeloid differentiation factor 88 (MyD88), and a so-called TIR domain-containing adaptor protein which induces IFNβ (TRIF) [34]. MyD88 connects to the TLRs by interaction between TIR domains. After being triggered, receptor-associated kinase (IRAK)-4, IRAK-1, and receptor-associated factor (TRAF)-6 are attracted to the receptor, which induces the union of IRAK-1 and MyD88 by way of the death domains. IRAK-4 transduces inflammatory signals activating IRAK-1 followed by IRAK-2 [35]. The signals are then transmitted to the TRAF6 protein complex which converts factor-β-activated kinase-1 (TAK)-1 into a reactive form. The TAK-1 phosphorylates I-kappa B kinase complex (IKK) leading to the activation of the transcription factor nuclear factor-kappa B (NF-κB) [36]. In experimental meningitis, MyD88-deficient mice had decreased interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and macrophage inflammatory protein 2 (MIP2) in the CNS. Nevertheless, MyD88 deficiency was associated with worsening of disease progression along with severe bacteremia [37]. Another intracellular adapter protein, TIR-domain-containing adapter-inducing interferon-β (TRIF) in microglia, transmits a signal from TLR-3 and TLR-4. This signal activates NF-κB and interferon-regulatory factor 3 (IRF-3) leading to the production of pro-inflammatory mediators and type I interferons (IFN) [11, 38]. These transcription factors are capable of serving as activators and promoters of many pro-inflammatory genes, including genes expressed by the M1 phenotype [11,

Table 1 Gene markers in microglia

Microglial gene markers	M_1 phenotype gene marker	M_2 phenotype gene marker
Ionised calcium binding adaptor molecule 1 (Iba1)	Nitric oxide synthase (iNOS)	Arginase 1 (Arg1)
Alpha M integrin (CD11b)	Tumor necrosis factor alpha (TNF-α)	AT-hook protein of GA feedback 1 (Agf1)
Leukocyte common antigen (CD45)	Interleukin-6 (IL-6)	Glial cell derived neurotrophic factor (GDNF)
Markers for activated microglia (F4/80)	Interleukin-1-beta (IL-1β)	Chitinase-like 3 (Ym1)
Complement component (C1qa)	Chemokine (C-C motif) ligand 2 (Ccl2)	Found in inflammatory zone 1 (FIZZ1)
	Chitinase-3-like 1 (YKL-40)	Transforming growth factor beta (TGFβ)
	Translocator protein (TSPO)	
	Chemokine (C-X3-C motif) receptor 1(Cx_3CR1)	
	Macrophage inflammatory proteins MIP2α (CxCl2)	
	Matrix metalloproteinase (MMP)	
	Taurine pyruvate aminotransferase (tPA)	
	Cyclooxygenase (COX)-2 (COX2)	

Table 2 Protein markers in microglia

Neutral microglia marker	M_1 microglia marker	M_2 microglia marker
CD11b	Ccl2	Arg1
CD45	COX	CD163
CD68	CxCL2	Fizz1
C1qa	CX_3CR1	GDNF
F4/80	IL-6	IGF1
Iba1	IL-1β	TGFβ
	iNOS	Ym1
	MMP	
	TNF-α	
	tPA	
	TSPO	
	YKL-40	

39]. They are also crucial transcriptional activators of various genes involved in the pathogenesis of meningitis [40, 41].

The detection of various pathogens and DAMPS is mediated by a family of cytosolic proteins called the NOD-like receptors (NLR) [42]. After the recognition of bacterial peptidoglycan, the NOD1 and 2 receptors recruit the receptor-interacting protein-2 (RIP-2), as well as cellular inhibitors of apoptosis (cIAP2) and the X-linked inhibitor of apoptosis protein (XIAP). This complex further activates the TAK1/TAB1/TAB2/TAB3 and IKK complex, which phosphorylates IKB resulting in the release of the transcription factor NF-κB and MAPK. Furthermore, these transcription factors translocate from the nucleus and induce the transcription of IL-1 cytokines [43, 44]. Rodents that were found to lack NOD1 were more susceptible to early pneumococcal sepsis and Gram-positive microorganisms [45]. In vitro, primary murine glia with NOD2 mediated an increased inflammatory response to *Streptococcus pneumoniae* [46].

Table 3 Receptors and agonists in microglia

Receptors microglial	Agonist(s)
Adrenoceptor	Noradrenaline
CD45	CD22
CD172a	CD47
CD200R	CD200
CSF1	CSF1
CX_3CR1	CX_3CL1
Dopamine receptor	Dopamine
IL-4	IL-4
IL-10	IL-10
LFA1	ICAM5
P2XR	ATP
TGF-β	TGFβ
TNFR	TNF
TREM2/DAP2	HSP60
TLR1/2	Triacylated lipoproteins, peptidoglycan
TLR2	Lipoproteins, peptidoglycan, HMGB1
TLR3	dsRNA
TLR4	LPS, HMGB1, pneumolysin
TLR5	Flagellin
TLR6/2	Diacylated lipoproteins, zymosan
TLR7	ssRNA
TLR8	ssRNA
TLR9	Non-methylated CpG-containing oligonucleotide DNA

The inflammasome is a large molecular platform that detects pathogenic microorganisms, the exotoxin pneumolysin, bacterial DNA, ATP, membrane disruption (for bacterial toxins and ATP), or phagocytised particles. The inflammasome plays a role in innate immunity by contributing to the production of pro-inflammatory cytokines [47]. The NLRP3 inflammasome is composed of nucleotide-binding and oligomerization domain NOD-like receptors (NLRs), apoptosis-associated speck-like protein containing a CARD (ASC) adaptor, and pro-caspase-1. The NLRP3 inflammasome converts proteolytic caspase-1 into a reactive form. Caspase-1 induces the maturation of two powerful cytokines, IL-1β and IL-18 [48]. Intracisternal administration of recombinant IL-1β in rats induced neutrophil migration into the CSF and resulted in the disruption of the blood-brain barrier (BBB) [49]. Moreover, IL-1 receptor type 1 gene-deficient mice had increased mortality and impaired host defense against pneumococcal meningitis [50]. IL-18 gene-deficient mice were found to have decreased inflammatory infiltrate around the meninges and decreased cytokine and chemokine concentrations in brain tissue resulting in suppressed inflammatory response during pneumococcal meningitis [51].Thus, in experimental pneumococcal meningitis, the ASC or NLRP3 knockout mice had a decreased clinical severity score and brain inflammation [52].

Microglial cells also express P2X receptors that are purinergic receptors and belong to the family of trimeric ion channels which are regulated by extracellular ATP [53]. High levels of ATP are released from necrotic cells during bacterial meningitis. The ATP binds to the P2X receptors, activating the NLRP3 inflammasome and inducing the transcription of pro-inflammatory mediators [48], as shown in Fig. 2.

RAGE is an important receptor that recognizes DAMPs in microglia [54]. After RAGE binds with its ligands, oxidative stress is increased, contributing to neuroinflammation by up-regulation of NF-κB [55]. In vitro, RAGE through HMGB1 mediates chemotaxis, differentiates immune cells, and upregulates TLR4 and RAGE receptors on cell-surface [54].

The CSF1R is a regulator of myeloid lineage cells. The inhibition of CSF1R resulted in the elimination of 99 percent of all microglia within the brain of adult mice, demonstrating that microglia cells in the adult brain are dependent on CSFR1

Table 4 Therapeutic/adjuvant treatments in experimental setting

Method of treatment/target	Outcome	Reference(s)
HMGB1-antagonist ethyl pyruvate or Box A protein	Decreased inflammation and neuronal damage in the brain when combined with ceftriaxone treatment in experimental pneumococcal meningitis.	Hohne et al. [19]
Anti-HMGB1 antibody	Attenuated brain damage in a rat model of experimental brain trauma.	Okuma et al. [20]
Minocycline	Minocycline, risperidone, or both of them prevented microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats.	Zhu et al. [21]
	Minocycline attenuated microglial and neuronal activation in the brain following myocardial infarction.	Dworak et al. [22]
	Minocycline protected the immature white matter against hyperoxia in neonatal rats. Minocycline also blocked changes in microglial morphology and IL-1β release induced by hyperoxia.	Schmitz et al. [23]
	In vitro minocycline suppressed microglial production of IL-1β, IL-6, and TNF-α.	Seabrook et al. [24]
Resveratrol	Rats received resveratrol after acute bacterial meningitis. The calcium intensity, microglial activation, pro-inflammatory cytokine, and malondialdehyde levels were all significantly decreased.	Sheu et al. [25]
Fractalkine	CX_3CL1-CX_3CR1 signaling crucially regulates the development and plasticity of neuronal circuits, brain connectivity, adult hippocampal neurogenesis, learning, and memory.	Paolicelli et al. [26]
	Fractalkine inhibited LPS-induced NO production and TNF-α release in primary neuron-glia cultures and murine microglial cell line.	Mattison et al. [27]
Mesenchymal cells	MSC-mediated induction of the M2 phenotype through upregulation of Ym1 and Arg-1 mRNA levels. Restored neurological functions after experimental brain trauma.	Zanier et al. [28]
IL-10	In vitro, IL-10 has also been shown to augment TGF-β production in astrocyte-microglia co-cultures.	Norden et al. [29]
	IL-10 inhibited the inflammatory immune responses of primary microglia and astrocytes to *Borrelia burgdorferi* and *N. meningitidis*.	Rasley et al. [30]
IL-34	IL-34 activated microglia to rescue neurons by upregulating phagocytosis of toxicants or damaged debris, and producing antioxidant enzymes.	Suzumura [16]
	IL-34 protected blood-brain barrier integrity by restoring expression levels of tight junction proteins.	Jin [31].
Palmitoylethanolamide	Palmitoylethanolamide stimulated phagocytosis of *E. coli* K1 and *S. pneumoniae* by macrophages and increased the resistance of mice against sepsis or meningoencephalitis.	Redlich et al. [32]

signaling [56]. Recognition of IL-34 by CSF1R promotes the development of microglial cells [57]. In contrast, IL-34-deficient mice presented a decrease in microglia cells [58].

Microglia Phenotype 2 Activation and Signaling

The M2 phenotype is associated with the capacity to down-regulate inflammation and promote tissue repair. Several cytokines, such as IL 10, IL 4, IL 6, and transforming growth factor beta (TGF-β) are produced by M2 phenotype which consequently can suppress the M1 phenotype (Fig. 1). The general M2 phenotype has different pathways according to its sub-phenotypes: M2a, M2b, or M2c [59, 60].

M2a phenotype is designed for phagocytosis, and it is induced by IL-4, IL-13, chitinase 3-like 3 (YM1), and arginase-1 (Arg1) [61]. Different markers have been identified as M2a specific, such as the enzymes Arg1 and FIZZ1 (found in inflammatory zone 1) [62]. Microglia skewed to the M2b phenotype clears the reactive oxygen and nitrogen species released during M1 activation. This phenotype expresses the IL-10 and CCL1, and is skewed by immune complexes and TLR or IL-1R agonists. The M2c phenotype is responsible for tissue remodeling and repair. This phenotype is induced by IL-10, TGF-β, or glucocorticoid hormones and expresses CCL16, CCL17, CCL18, CXCL13, CCR2, and CCR5 [15, 62, 63]. It is of interest that polarization of microglia to the M1 state is associated with a decrease in neurotrophic factor synthesis including BDNF, whereas neurotrophic factor expression is upregulated when microglia have acquired the M2 phenotype [59, 60].

TGF-β plays an important role as an anti-inflammatory cytokine. In microglia, this cytokine inhibits phagocytosis and the production of TNF-α, IL-1, and IL-6 [64]. In vitro, treatment of primary microglia with TGF-β resulted in upregulation of the IL4 receptor, showing that TGF-β increases the capacity of microglia for IL-4 signals. Likewise, IL-4 treatment increased the expression and secretion of TGF-β2 in microglia culture [65]. IL-4 treatment also induces upregulation of arginase 1 (Arg1) and chitinase-3-like protein 3 (Ym1) [65, 66]. Arg1 inhibits nitric oxide (NO) by competing with iNOS because both utilize l-arginine as a substrate [67].

IL-10 is probably the most important anti-inflammatory cytokine used for limiting immune reactions [68]. The biological functions of IL-10 are activated via two receptor chains, IL-10R1 and IL-10R2. This further phosphorylates the receptor-Janus Kinase-1 (JAK-1) and tyrosine kinase-2. This phosphorylation subsequently activates signal transducer and activator of transcription-3 (STAT-3), increasing the expression of anti-apoptotic and anti-inflammatory mediators [69,

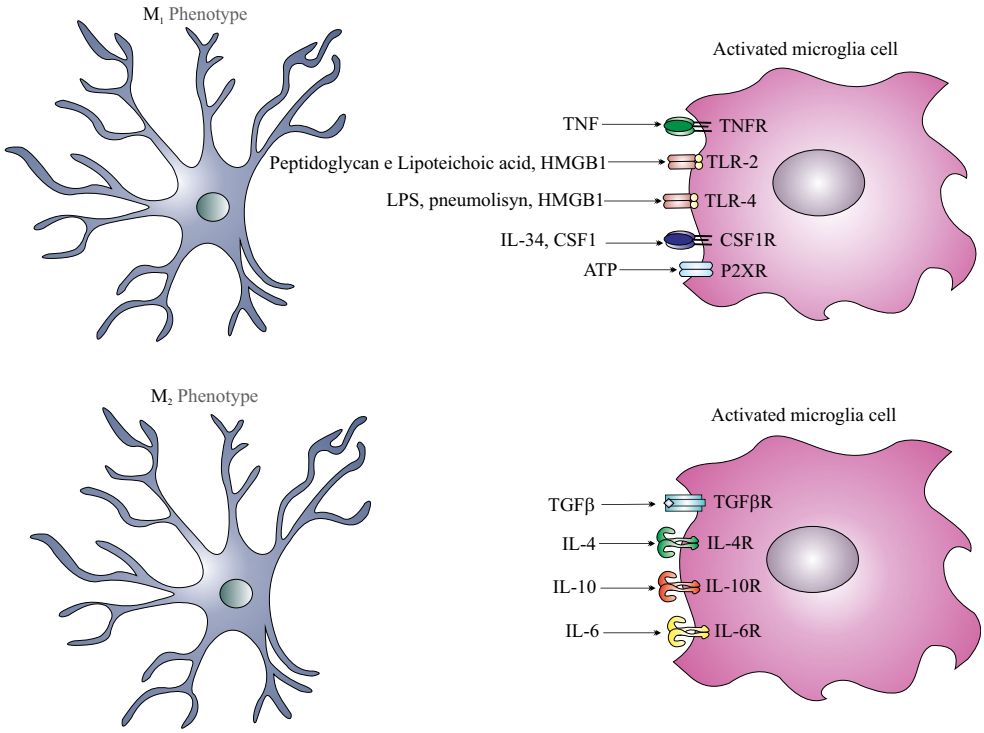

Fig. 1 M1 and M2 phenotypes and their receptors. During bacterial meningitis, the microglia can be activated by peptidoglycan, lipoteichoic acid, lipopolysaccharide (LPS), and pneumolysin which are pathogen-associated molecular patterns (PAMPs), cytokines, and by damage-associated molecular patterns (DAMPs), such as ATP, heat shock protein (HSP), and high-mobility group box 1 protein (HMGB1)

70]. Thus, a role of IL-10 is the inhibition of TNF-α, IL-1β, and colony-stimulating factor (GM-CSF) [71, 72]. IL-10 also upregulates the expression of B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra-large (Bcl-xl) factors and downregulates pro-apoptotic factors such as cytochrome-*c*, caspase-3, and Bax [72]. Another way that IL-10 could suppress the M1-like activation state in microglia could be through 17β-hydroxysteroid dehydrogenase type 14 (17β-HSD14) expression. Moreover, 17β-HSD14 mediates the transformation of dehydroepiandrosterone (DHEA) to 5-androstene-3β,17β-diol, which is an anti-inflammatory ligand of estrogen receptor-β (ERβ) [11], (Fig. 2).

Microglial Activation by Bacterial Meningitis

During bacterial meningitis, resident macrophages, astrocytes, glial cells, and endothelial cells can produce cytokines,

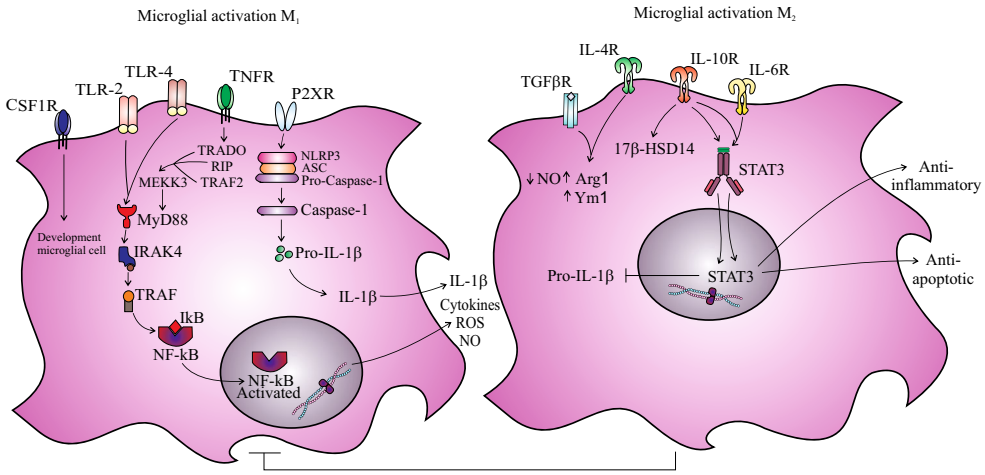

Fig. 2 Classical and alternative microglial activation. The M1 phenotype can be activated through TLRs, RLRs, CLRs, NLRs, HMGB-1, histone, and ATP. TLR-2 and 4 commonly use an intracellular adapter protein myeloid differentiation factor 88 (MyD88) with subsequent release and nuclear translocation of NF-κB leading a production of pro-inflammatory cytokines and reactive oxygen species. ATP binds to the P2XR activating the NLRP3 and inducing the transcription of pro-inflammatory mediators. The M2 phenotype can be activated through IL-10 that leads to 17β-hydroxysteroid dehydrogenase type 14 (17β-HSD14). IL-10-IL-10R activates the phosphorylation of the receptor-Janus Kinase-1 (JAK-1), tyrosine kinase-2, and subsequently transcription of signal transducer and activator of transcription-3 (STAT-3) increasing anti-apoptotic and anti-inflammatory mediators. IL-4 increased TGFβ2 and induces upregulation of arginase 1 (Arg1) and chitinase-3-like protein 3 (Ym1)

chemokines, and other pro-inflammatory mediators in response to infection. This intense inflammatory response contributes to neuronal damage and can be fatal for patients [73, 74]. The concentrations of TNF-α, IL-1β, IL-6, IL-8, IL-10, and IFN-γ are normally enhanced in cerebrospinal fluid (CSF) of patients with bacterial meningitis [75]. In a study of 48 patients with bacterial meningitis, CSF levels of TNF-α correlated with BBB disruption and neuronal damage [76]. Our knowledge of the pathophysiology of bacterial meningitis is based on patient observation and experimental models. In animal models, TNF-α and IL-1β are produced in the hippocampus and cortex during the first 6 to 24 h after meningitis [77, 78]. The treatment with anti-TNF-α antibody blocked the disruption of the BBB and the entrance of circulatory *S. pneumoniae* into the brain of rats, demonstrating that TNF-α has an important role in regulating the BBB [79]. However, TNF-α deficient mice had stronger deficits in spatial memory and increased mortality [80].

In response to invasive microorganisms and pro-inflammatory cytokines, polymorphonuclear leukocytes and other immunocompetent cells are attracted and activated in the brain. This reaction produces reactive oxygen species such as superoxide anion (O_2^-) and NO, thereby causing the formation of peroxynitrite ($ONOO^-$) [81]. Interaction of $ONOO^-$ with biomolecules such as proteins, lipids, and nucleic acid leads to several cytotoxic events including mitochondrial dysfunction and triggering of cell death. Direct nitration and oxidation of invading microorganisms can also lead to destruction of the microorganism [82]. In patients with bacterial meningitis, elevated levels of nitrotyrosine have been detected in the CSF [83]. In vitro, Matata et al. have shown that the production of cytokines by human mononuclear cells is regulated by $ONOO^-$ in a NF-κB-dependent manner [84]. Furthermore, in plasma and CSF of patients with acute bacterial meningitis, the enzymatic antioxidants glutathione and superoxide dismutase levels are usually decreased while the malondialdehyde, nitrite, and protein carbonyl levels are elevated, providing evidence for the production of oxidative stress [4, 85, 86]. The increase of reactive oxygen species and decrease of antioxidant defense are found in experimental meningitis. For example, in neonatal meningitis caused by *Streptococcus agalactiae*, lipid peroxidation and protein carbonyl levels were elevated in the hippocampus [78]. Additionally, oxidative stress was present in the cortex and hippocampus of adult rats affected by pneumococcal meningitis [87]. Moreover, the complex I activity of mitochondrial respiratory chain was inhibited in striatum, hippocampus, and cerebellum after bacterial meningitis [88].

Thus, antioxidants and NOS inhibitors in experimental bacterial meningitis could be a target to prevent neuronal damage. Adjuvant therapy with an $ONOO^-$ scavenger decreased leukocyte levels in the CSF, reduced IL-1β and macrophage inflammatory protein 2 (MIP-2) levels in the rat brain [89], and prevented long-term cognitive impairment in experimental pneumococcal meningitis [90]. The activation of microglia is represented by an increased expression of Griffonia simplicifolia isolectin-B4 (GSA-IB4) and ionized calcium binding adaptor molecule 1 (Iba1) in the CA2 region of the hippocampus of rats. This increase coincided with an intense production of TNF-α, IL-1β, and IL-6 and oxidative damage in experimental *Klebsiella pneumoniae* meningitis [25].

Thus, bacterial meningitis leads to an increase in neutrophil cerebral penetration, a pro-inflammatory state of microglia, oxidative and nitrosative stress production, and subsequently mitochondrial dysfunction, apoptosis, and necrosis resulting in neuronal dysfunction.

Microglial Activation by DAMPs from Bacterial Meningitis

Bacterial meningitis is accompanied by the release of DAMPs, which mediates the inflammatory response and often causes cell injury. In the CSF of pediatric patients with meningitis, HMGB1 (a nuclear protein that is passively released by stressed or damaged cells) has been detected [91]. This protein is recognized by TLR2, TLR4, and RAGE (receptor for advanced glycation end products) further activating the microglial classical pathway and acting as the main propagator of inflammation in pneumococcal meningitis [11, 19]. Under conditions of stress, other molecules such as the intracellular HSPs are also released by the cell provoking the activation of the immune system, many of which have been identified in the CSF of patients with bacterial meningitis [7]. Among the elevated intracellular chaperones were the HSP70 and HSP72 [91, 92]. However, recent data showed that overexpression of HSP70 was associated with anti-inflammatory properties in animal models and in vitro through inhibition of NF-κB. Also, using models of cerebral ischemia-like injury, the overexpression of HSP70 was associated with increased expression of the anti-apoptotic protein, B-cell lymphoma 2 (Bcl-2), and decreased apoptotic cell death. This proposed mechanism may play a possible role in suppression of microglial activation.[93, 94].

The S100 protein family is implicated in a variety of intra- and extracellular regulatory effects. They are localized both in the cytoplasm and in the nucleus of various cells [95]. An increase in S100B and the S100B receptor has been implicated in inflammation, which along with RAGE can activate microglia via NF-κB and AP-1-dependent pathways. Furthermore, an increase in S100B levels in biological fluids is also associated with brain damage [96]. Depending upon the concentration of S100B in the brain, it can exhibit neurotrophic or neurotoxic effects. In normal physiological conditions, low levels of S100B have been shown to decrease microglial activation via the STAT3 pathway with an upregulation of anti-

inflammatory cytokines. Moreover, the clinical severity of bacterial meningitis appears to be related to the high concentration levels of S100B protein in the CSF [97]. The concentration of S100B in children with purulent meningitis was significantly higher than in the control group [98]. In rabbits with pneumococcal meningitis, the S100B protein was elevated and proposed to be a biomarker for the severity of white matter damage and traumatic injury by the authors of this study [99, 100].

Therapeutic Targets Through the Inhibition M1 or Activation M2 Microglia in Bacterial Meningitis

A more complete understanding of the association between bacterial meningitis and it's pathophysiology is important in order to develop new therapeutic targets for the prevention of cognitive impairment [101].

HMGB1-antagonist In a mouse meningitis model, treatment with an HMGB1-antagonist, ethyl pyruvate or Box A protein, decreased inflammation and neuronal damage in the brain when combined with ceftriaxone treatment [19]. Anti-HMGB1 monoclonal antibody also attenuated brain damage in a rat model of experimental brain trauma [20]. Because pro-inflammatory mediators contribute to meningitis-associated brain injury, HMGB-1 may be a promising target for (adjuvant) therapy [19].

Minocycline Minocycline is a semisynthetic second generation tetracycline with anti-inflammatory effects on microglial cells, as well as antioxidant, anti-apoptotic, and neuroprotective properties in rodent models [102]. Its anti-inflammatory properties are represented by downregulation of microglial activity which is associated with decreasing cytokine and cyclooxygenase-2 expression and prostaglandin E2 production [103]. Minocycline has also been shown to reduce microglial and neuronal activation in the brain in experimental myocardial infarction [22] and in neonatal rats that received an intra-hippocampal injection of LPS [21]. Additionally, the activated state of microglia was prevented by minocycline in hypoxic-ischemia and hyperoxia animal models [23].

Resveratrol Resveratrol is a non-flavonoid polyphenol that can attenuate the activation of immune cells through inhibition of NF-κB and activator protein-1 (AP-1) [104]. Resveratrol treatment preserved hippocampal neurons in rats after being infected with bacteria that causes meningitis. Increased microglial expression coincided with intense production of pro-inflammatory cytokines and oxidative damage; however, resveratrol treatment decreased microglial activation through Iba-1 expression which was associated with a decrease in pro-inflammatory cytokine levels and malondialdehyde (MDA) levels in the hippocampus [25].

Fractalkine Fractalkine, or chemokine (C-X3-C motif) ligand 1 (CX_3CL1), is a member of the ∂ (CX_3C) chemokine family, and its receptor, chemokine (C-X3-C motif) receptor 1 (CX_3CR1), is found on the membrane of microglial cells. Fractalkine promotes microglial recruitment to neuronal circuits modulating neuronal survival via the release of trophic factors [26]. In addition, this chemokine activates microglia to rescue neurons by upregulating phagocytosis of toxicants or injured debris and promotes antioxidant enzyme production [16]. In patients with bacterial meningitis, CX_3CR1 levels in the CSF were significantly increased when compared to levels in controls [105]. Alternatively, Fractalkine inhibits LPS-induced NO production and TNF-α release in primary neuron-glia cultures [27]. CX_3CL1 knockout mice had microglial activation in different models of brain disease, including toxic insult by peripheral LPS injections [106].

Mesenchymal Cells Mesenchymal stem or stromal cells (MSCs) are multipotent progenitor cells with regenerative and immunomodulatory properties [107]. MSC transplantation has been observed to attenuate brain damage after neonatal stroke [108]. MSC-mediated induction of the M2 phenotype through upregulation of Ym1 and Arg-1 mRNA levels restored neurological functions after experimental brain trauma [28].

IL-10 The anti-inflammatory cytokine IL-10 is secreted by microglia in the M2b state and is a powerful suppressor of pro-inflammation and is involved in neuronal regeneration and repair [72]; in vitro, IL-10 has also been shown to augment TGF-β production in astrocyte-microglia co-cultures. Inhibition of TGF-β production after LPS administration in mice prolonged sickness behavior and the pro-inflammatory state [29].

IL-34 IL-34 is a cytokine that stimulates the development, survival, and function of microglial cells [109]. This cytokine was identified as a second ligand for CSF-1R [110]. Additionally, IL-34 activates microglia to rescue neurons by upregulating phagocytosis of toxicants or damaged debris, and produces antioxidant enzymes [16].

Palmitoylethanolamide Palmitoylethanolamide is an endogenous lipid produced by neurons, microglia, and astrocytes [111]. Pre-treatment with palmitoylethanolamide increased survival of mice challenged intracerebrally or intraperitoneally with *Escherichia coli* K1. In vitro, stimulation of macrophages with palmitoylethanolamide for 30 min increased the phagocytosis of *E. coli* K1 and *S. pneumoniae* [32, 112]. Palmitoylethanolamide increases phagocytosis of bacteria by

microglial cells in vitro without a measurable pro-inflammatory effect. Therefore, this compound could be a promisor candidate against brain infections [113] (Table 4).

Conclusion

During bacterial meningitis, the severe inflammatory response may lead to neuronal damage and could potentially be detrimental for patients. Many stimuli including PAMPs, DAMPs, and pro-inflammatory mediators are responsible for the activation of microglia cells which further produce cytokines, chemokines, and reactive oxygen and nitrogen species to eliminate the invading microorganism. Therefore, the inhibition of pro-inflammatory mediators or the enhancement of anti-inflammatory mediator production in bacterial meningitis may be a useful strategy to prevent the devastating consequences of the bacterial infection with respect to neuronal damage and function. We propose that inhibition of the activity of DAMPs and/or administration of specific anti-inflammatory agents may lead to lower morbidity and mortality in patients with bacterial meningitis.

Acknowledgments Research from the Center for Experimental Models in Psychiatry (USA) is supported by grants from the Department of Psychiatry and Behavioral Sciences, The University of Texas Medical School at Houston. Research from Laboratorio de Microbiologia Experimental and Laboratório de Neurociências (Brazil) is supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC), and Universidade do Extremo Sul Catarinense (UNESC).

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B (2007) Cognitive outcome in adults after bacterial meningitis. J Neurol Neurosurg Psychiatry 78(10):1092–1096
2. Merkelbach S, Sittinger H, Schweizer I, Muller M (2000) Cognitive outcome after bacterial meningitis. Acta Neurol Scand 102(2):118–123
3. Sellner J, Täuber MG, Leib SL (2010) Chapter 1—pathogenesis and pathophysiology of bacterial CNS infections. In: Karen LR, Allan RT (eds) Handbook of clinical neurology. Elsevier, New York, pp 1–16
4. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D (2011) Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev 24(3):557–591
5. Savva A, Roger T (2013) Targeting Toll-Like receptors: promising therapeutic strategies for the management of sepsis-associated pathology and infectious diseases. Front Immunol 4:387
6. Iwasaki A, Medzhitov R (2010) Regulation of adaptive immunity by the innate immune system. Science 327(5963):291–295
7. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T (2014) Host innate immune responses to sepsis. Virulence 5(1):36–44
8. Lu B, Wang C, Wang M, Li W, Chen F, Tracey KJ, Wang H (2014) Molecular mechanism and therapeutic modulation of high mobility group box 1 release and action: an updated review. Expert Rev Clin Immunol 10(6):713–727
9. Barichello T, Generoso JS, Milioli G, Elias SG, Teixeira AL (2013) Pathophysiology of bacterial infection of the central nervous system and its putative role in the pathogenesis of behavioral changes. Rev Bras Psiquiatr 35(1):81–87
10. Hu X, Liou AK, Leak RK, Xu M, An C, Suenaga J, Shi Y, Gao Y et al (2014) Neurobiology of microglial action in CNS injuries: receptor-mediated signaling mechanisms and functional roles. Prog Neurobiol 119–120:60–84
11. Saijo K, Glass CK (2011) Microglial cell origin and phenotypes in health and disease. Nat Rev Immunol 11(11):775–787
12. Benarroch EE (2013) Microglia: multiple roles in surveillance, circuit shaping, and response to injury. Neurology 81(12):1079–1088
13. Stence N, Waite M, Dailey ME (2001) Dynamics of microglial activation: a confocal time-lapse analysis in hippocampal slices. Glia 33(3):256–266
14. Yamada J, Jinno S (2013) Novel objective classification of reactive microglia following hypoglossal axotomy using hierarchical cluster analysis. J Comp Neurol 521(5):1184–1201
15. Boche D, Perry VH, Nicoll JA (2013) Review: activation patterns of microglia and their identification in the human brain. Neuropathol Appl Neurobiol 39(1):3–18
16. Suzumura A (2013) Neuron-microglia interaction in neuroinflammation. Curr Protein Pept Sci 14(1):16–20
17. Moore KJ, Sheedy FJ, Fisher EA (2013) Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 13(10):709–721
18. Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, Chen J (2015) Microglial and macrophage polarization-new prospects for brain repair. Nat Rev Neurol 11(1):56–64
19. Hohne C, Wenzel M, Angele B, Hammerschmidt S, Hacker H, Klein M, Bierhaus A, Sperandio M et al (2013) High mobility group box 1 prolongs inflammation and worsens disease in pneumococcal meningitis. Brain 136(Pt 6):1746–1759
20. Okuma Y, Date I, Nishibori M (2014) Anti-high mobility group Box-1 antibody therapy for traumatic brain injury. Yakugaku Zasshi 134(6):701–705
21. Zhu F, Zheng Y, Ding YQ, Liu Y, Zhang X, Wu R, Guo X, Zhao J (2014) Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of lipopolysaccharide in rats. PLoS One 9(4):e93966
22. Dworak M, Stebbing M, Kompa AR, Rana I, Krum H, Badoer E (2014) Attenuation of microglial and neuronal activation in the brain by ICV minocycline following myocardial infarction. Auton Neurosci 185:43–50
23. Schmitz T, Krabbe G, Weikert G, Scheuer T, Matheus F, Wang Y, Mueller S, Kettenmann H et al (2014) Minocycline protects the immature white matter against hyperoxia. Exp Neurol 254:153–165
24. Seabrook TJ, Jiang L, Maier M, Lemere CA (2006) Minocycline affects microglia activation, Abeta deposition, and behavior in APP-tg mice. Glia 53(7):776–782
25. Sheu JN, Liao WC, Wu UI, Shyu LY, Mai FD, Chen LY, Chen MJ, Youn SC et al (2013) Resveratrol suppresses calcium-mediated microglial activation and rescues hippocampal neurons of adult rats following acute bacterial meningitis. Comp Immunol Microbiol Infect Dis 36(2):137–148
26. Paolicelli RC, Bisht K, Tremblay ME (2014) Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Front Cell Neurosci 8:129

27. Mattison HA, Nie H, Gao H, Zhou H, Hong JS, Zhang J (2013) Suppressed proinflammatory response of microglia in CX3CR1 knockout mice. J Neuroimmunol 257(1–2):110–115
28. Zanier ER, Pischiutta F, Riganti L, Marchesi F, Turola E, Fumagalli S, Perego C, Parotto E et al (2014) Bone marrow mesenchymal stromal cells drive protective M2 microglia polarization after brain trauma. Neurotherapeutics 11(3):679–695
29. Norden DM, Fenn AM, Dugan A, Godbout JP (2014) TGFbeta produced by IL-10 redirected astrocytes attenuates microglial activation. Glia 62(6):881–895
30. Rasley A, Tranguch SL, Rati DM, Marriott I (2006) Murine glia express the immunosuppressive cytokine, interleukin-10, following exposure to Borrelia burgdorferi or Neisseria meningitidis. Glia 53(6):583–592
31. Jin S, Sonobe Y, Kawanokuchi J, Horiuchi H, Cheng Y, Wang Y, Mizuno T, Takeuchi H, Suzumura A (2014) Interleukin-34 restores blood-brain barrier integrity by upregulating tight junction proteins in endothelial cells. PLoS One 9(12):e115981
32. Redlich S, Ribes S, Schutze S, Nau R (2014) Palmitoylethanolamide stimulates phagocytosis of Escherichia coli K1 by macrophages and increases the resistance of mice against infections. J Neuroinflammation 11:108
33. Gaikwad SM, Heneka MT (2013) Studying M1 and M2 states in adult microglia. Methods Mol Biol 1041:185–197
34. Koedel U (2009) Toll-like receptors in bacterial meningitis. Curr Top Microbiol Immunol 336:15–40
35. Wang Z, Wesche H, Stevens T, Walker N, Yeh WC (2009) IRAK-4 inhibitors for inflammation. Curr Top Med Chem 9(8):724–737
36. Takeda K, Akira S (2007) Toll-like receptors. Curr Protoc Immunol Chapter 14: p Unit 14.12
37. Koedel U, Rupprecht T, Angele B, Heesemann J, Wagner H, Pfister HW, Kirschning CJ (2004) MyD88 is required for mounting a robust host immune response to *Streptococcus pneumoniae* in the CNS. Brain 127(Pt 6):1437–1445
38. Prinz M, Priller J (2014) Microglia and brain macrophages in the molecular age: from origin to neuropsychiatric disease. Nat Rev Neurosci 15(5):300–312
39. Tato CM, Hunter CA (2002) Host-pathogen interactions: subversion and utilization of the NF-kappa B pathway during infection. Infect Immun 70(7):3311–3317
40. Kastenbauer S, Koedel U, Weih F, Ziegler-Heitbrock L, Pfister HW (2004) Protective role of NF-kappaB1 (p50) in experimental pneumococcal meningitis. Eur J Pharmacol 498(1–3):315–318
41. Koedel U, Bayerlein I, Paul R, Sporer B, Pfister HW (2000) Pharmacologic interference with NF-kappaB activation attenuates central nervous system complications in experimental Pneumococcal meningitis. J Infect Dis 182(5):1437–1445
42. Kigerl KA, de Rivero Vaccari JP, Dietrich WD, Popovich PG, Keane RW (2014) Pattern recognition receptors and central nervous system repair. Exp Neurol 258:5–16
43. Damgaard RB, Gyrd-Hansen M (2011) Inhibitor of apoptosis (IAP) proteins in regulation of inflammation and innate immunity. Discov Med 11(58):221–231
44. Kumar S, Ingle H, Prasad DV, Kumar H (2013) Recognition of bacterial infection by innate immune sensors. Crit Rev Microbiol 39(3):229–246
45. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN (2010) Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med 16(2):228–231
46. Liu X, Chauhan VS, Young AB, Marriott I (2010) NOD2 mediates inflammatory responses of primary murine glia to *Streptococcus pneumoniae*. Glia 58(7):839–847
47. Witzenrath M, Pache F, Lorenz D, Koppe U, Gutbier B, Tabeling C, Reppe K, Meixenberger K et al (2011) The NLRP3 inflammasome is differentially activated by pneumolysin variants and contributes to host defense in pneumococcal pneumonia. J Immunol 187(1): 434–440
48. Gombault A, Baron L, Couillin I (2012) ATP release and purinergic signaling in NLRP3 inflammasome activation. Front Immunol 3: 414
49. Quagliarello VJ, Wispelwey B, Long WJ Jr, Scheld WM (1991) Recombinant human interleukin-1 induces meningitis and blood–brain barrier injury in the rat. Characterization and comparison with tumor necrosis factor. J Clin Invest 87(4):1360–1366
50. Zwijnenburg PJ, van der Poll T, Florquin S, Roord JJ, Van Furth AM (2003) IL-1 receptor type 1 gene-deficient mice demonstrate an impaired host defense against pneumococcal meningitis. J Immunol 170(9):4724–4730
51. Zwijnenburg PJ, van der Poll T, Florquin S, Akira S, Takeda K, Roord JJ, van Furth AM (2003) Interleukin-18 gene-deficient mice show enhanced defense and reduced inflammation during pneumococcal meningitis. J Neuroimmunol 138(1–2):31–37
52. Hoegen T, Tremel N, Klein M, Angele B, Wagner H, Kirschning C, Pfister HW, Fontana A et al (2011) The NLRP3 inflammasome contributes to brain injury in pneumococcal meningitis and is activated through ATP-dependent lysosomal cathepsin B release. J Immunol 187(10):5440–5451
53. Samways DS, Li Z, Egan TM (2014) Principles and properties of ion flow in P2X receptors. Front Cell Neurosci 8:6
54. Harris HE, Andersson U, Pisetsky DS (2012) HMGB1: a multifunctional alarmin driving autoimmune and inflammatory disease. Nat Rev Rheumatol 8(4):195–202
55. Tobon-Velasco JC, Cuevas E, Torres-Ramos MA, Santamaria A (2014) Receptor for AGEs (RAGE) as mediator of NF-kB pathway activation in neuroinflammation and oxidative stress. CNS Neurol Disord Drug Targets 13(9):1615–1626
56. Elmore MR, Najafi AR, Koike MA, Dagher NN, Spangenberg EE, Rice RA, Kitazawa M, Matusow B et al (2014) Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron 82(2):380–397
57. Zelante T, Ricciardi-Castagnoli P (2012) The yin-yang nature of CSF1R-binding cytokines. Nat Immunol 13(8):717–719
58. Nakamichi Y, Udagawa N, Takahashi N (2013) IL-34 and CSF-1: similarities and differences. J Bone Miner Metab 31(5):486–495
59. Cherry JD, Olschowka JA, O'Banion MK (2014) Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. J Neuroinflammation 11(1):98
60. Appel SH, Beers DR, Henkel JS (2010) T cell-microglial dialogue in Parkinson's disease and amyotrophic lateral sclerosis: are we listening? Trends Immunol 31(1):7–17
61. Varnum MM, Ikezu T (2012) The classification of microglial activation phenotypes on neurodegeneration and regeneration in Alzheimer's disease brain. Arch Immunol Ther Exp (Warsz) 60(4):251–266
62. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M (2004) The chemokine system in diverse forms of macrophage activation and polarization. Trends Immunol 25(12):677–686
63. Benoit M, Desnues B, Mege JL (2008) Macrophage polarization in bacterial infections. J Immunol 181(6):3733–3739
64. Suzumura A, Sawada M, Yamamoto H, Marunouchi T (1993) Transforming growth factor-beta suppresses activation and proliferation of microglia in vitro. J Immunol 151(4):2150–2158
65. Zhou X, Spittau B, Krieglstein K (2012) TGFbeta signalling plays an important role in IL4-induced alternative activation of microglia. J Neuroinflammation 9:210
66. Wu A, Wei J, Kong LY, Wang Y, Priebe W, Qiao W, Sawaya R, Heimberger AB (2010) Glioma cancer stem cells induce immunosuppressive macrophages/microglia. Neuro Oncol 12(11):1113–1125

67. Pourcet B, Pineda-Torra I (2013) Transcriptional regulation of macrophage arginase 1 expression and its role in atherosclerosis. Trends Cardiovasc Med 23(5):143–152
68. Striz I, Brabcova E, Kolesar L, Sekerkova A (2014) Cytokine networking of innate immunity cells: a potential target of therapy. Clin Sci (Lond) 126(9):593–612
69. Mosser DM, Edwards JP (2008) Exploring the full spectrum of macrophage activation. Nat Rev Immunol 8(12):958–969
70. Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, Dantzer R, Kelley KW (2001) Interleukin-10 in the brain. Crit Rev Immunol 21(5):427–449
71. Genovese T, Esposito E, Mazzon E, Di Paola R, Caminiti R, Bramanti P, Cappelani A, Cuzzocrea S (2009) Absence of endogenous interleukin-10 enhances secondary inflammatory process after spinal cord compression injury in mice. J Neurochem 108(6):1360–1372
72. Thompson CD, Zurko JC, Hanna BF, Hellenbrand DJ, Hanna A (2013) The therapeutic role of interleukin-10 after spinal cord injury. J Neurotrauma 30(15):1311–1324
73. Grandgirard D, Leib SL (2010) Meningitis in neonates: bench to bedside. Clin Perinatol 37(3):655–676
74. van de Beek D, Drake JM, Tunkel AR (2010) Nosocomial bacterial meningitis. N Engl J Med 362(2):146–154
75. Coutinho LG, Grandgirard D, Leib SL, Agnez-Lima LF (2013) Cerebrospinal-fluid cytokine and chemokine profile in patients with pneumococcal and meningococcal meningitis. BMC Infect Dis 13(1):326
76. Sharief MK, Ciardi M, Thompson EJ (1992) Blood-brain barrier damage in patients with bacterial meningitis: association with tumor necrosis factor-alpha but not interleukin-1 beta. J Infect Dis 166(2):350–358
77. Barichello T, dos Santos I, Savi GD, Simoes LR, Silvestre T, Comim CM, Sachs D, Teixeira MM et al (2010) TNF-alpha, IL-1beta, IL-6, and cinc-1 levels in rat brain after meningitis induced by *Streptococcus pneumoniae*. J Neuroimmunol 221(1–2):42–45
78. Barichello T, Lemos JC, Generoso JS, Cipriano AL, Milioli GL, Marcelino DM, Vuolo F, Petronilho F et al (2011) Oxidative stress, cytokine/chemokine and disruption of blood–brain barrier in neonate rats after meningitis by *Streptococcus agalactiae*. Neurochem Res 36(10):1922–1930
79. Tsao N, Chang WW, Liu CC, Lei HY (2002) Development of hematogenous pneumococcal meningitis in adult mice: the role of TNF-alpha. FEMS Immunol Med Microbiol 32(2):133–140
80. Gerber J, Bottcher T, Hahn M, Siemer A, Bunkowski S, Nau R (2004) Increased mortality and spatial memory deficits in TNF-alpha-deficient mice in ceftriaxonetreated experimental pneumococcal meningitis. Neurobiol Dis 16(1):133–138
81. Klein M, Koedel U, Pfister HW (2006) Oxidative stress in pneumococcal meningitis: a future target for adjunctive therapy? Prog Neurobiol 80(6):269–280
82. Radi R (2013) Peroxynitrite, a stealthy biological oxidant. J Biol Chem 288(37):26464–26472
83. Radi R (2004) Nitric oxide, oxidants, and protein tyrosine nitration. Proc Natl Acad Sci U S A 101(12):4003–4008
84. Matata BM, Galinanes M (2002) Peroxynitrite is an essential component of cytokines production mechanism in human monocytes through modulation of nuclear factor-kappa B DNA binding activity. J Biol Chem 277(3):2330–2335
85. Srivastava R, Lohokare R, Prasad R (2013) Oxidative stress in children with bacterial meningitis. J Trop Pediatr 59(4):305–308
86. Barichello T, Generoso JS, Simoes LR, Elias SG, Quevedo J (2013) Role of oxidative stress in the pathophysiology of pneumococcal meningitis. Oxidative Med Cell Longev 2013:371465
87. Barichello T, Savi GD, Silva GZ, Generoso JS, Bellettini G, Vuolo F, Petronilho F, Feier G et al (2010) Antibiotic therapy prevents, in part, the oxidative stress in the rat brain after meningitis induced by *Streptococcus pneumoniae*. Neurosci Lett 478(2):93–96
88. Barichello T, Savi GD, Simoes LR, Generoso JS, Fraga DB, Bellettini G, Daufenbach JF, Rezin GT et al (2010) Evaluation of mitochondrial respiratory chain in the brain of rats after pneumococcal meningitis. Brain Res Bull 82(5–6):302–307
89. Kastenbauer S, Koedel U, Becker BF, Pfister HW (2002) Pneumococcal meningitis in the rat: evaluation of peroxynitrite scavengers for adjunctive therapy. Eur J Pharmacol 449(1–2):177–181
90. Barichello T, Santos AL, Savi GD, Generoso JS, Otaran P, Michelon CM, Steckert AV, Mina F et al (2012) Antioxidant treatment prevents cognitive impairment and oxidative damage in pneumococcal meningitis survivor rats. Metab Brain Dis 27(4):587–593
91. Tang D, Kang R, Cao L, Zhang G, Yu Y, Xiao W, Wang H, Xiao X (2008) A pilot study to detect high mobility group box 1 and heat shock protein 72 in cerebrospinal fluid of pediatric patients with meningitis. Crit Care Med 36(1):291–295
92. Kang R, Cao LZ, Tang DL, Zhang GY, Yu Y, Xiao XZ (2007) Significance of heat shock protein 70 in cerebrospinal fluid in differential diagnosis of central nervous system infection in children. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue 19(6):346–348
93. Tukaj S (2014) Immunoregulatory properties of Hsp70. Postepy Hig Med Dosw (Online) 68:722–727
94. Yenari MA, Liu J, Zheng Z, Vexler ZS, Lee JE, Giffard RG (2005) Antiapoptotic and anti-inflammatory mechanisms of heat-shock protein protection. Ann N Y Acad Sci 1053:74–83
95. Donato R, Cannon BR, Sorci G, Riuzzi F, Hsu K, Weber DJ, Geczy CL (2013) Functions of S100 proteins. Curr Mol Med 13(1):24–57
96. Gazzolo D, Grutzfeld D, Michetti F, Toesca A, Lituania M, Bruschettini M, Dobrzanska A, Bruschettini P (2004) Increased S100B in cerebrospinal fluid of infants with bacterial meningitis: relationship to brain damage and routine cerebrospinal fluid findings. Clin Chem 50(5):941–944
97. Kepa L, Oczko-Grzesik B (2013) Evaluation of cerebrospinal fluid S100B protein concentration in patients with purulent, bacterial meningitis—own observations. Przegl Epidemiol 67(3):415–419, 525-8
98. Zhang LY, Li Y, Jin MF (2014) Diagnostic values of neopterin and S100b for central nervous system infections in children. Zhongguo Dang Dai Er Ke Za Zhi 16(4):380–383
99. Schmidt H, Gerber J, Stuertz K, Djukic M, Bunkowski S, Fischer FR, Otto M, Nau R (2010) S100B in the cerebrospinal fluid–a marker for glial damage in the rabbit model of pneumococcal meningitis. Neurosci Lett 475(2):104–107
100. Vos PE, Jacobs B, Andriessen TM, Lamers KJ, Borm GF, Beems T, Edwards M, Rosmalen CF et al (2010) GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. Neurology 75(20):1786–1793
101. Shin SH, Kim KS (2012) Treatment of bacterial meningitis: an update. Expert Opin Pharmacother 13(15):2189–2206
102. Li C, Yuan K, Schluesener H (2013) Impact of minocycline on neurodegenerative diseases in rodents: a meta-analysis. Rev Neurosci 24(5):553–562
103. Keller WR, Kum LM, Wehring HJ, Koola MM, Buchanan RW, Kelly DL (2013) A review of anti-inflammatory agents for symptoms of schizophrenia. J Psychopharmacol 27(4):337–342
104. Zhang F, Liu J, Shi JS (2010) Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation. Eur J Pharmacol 636(1–3):1–7
105. Kastenbauer S, Koedel U, Wick M, Kieseier BC, Hartung HP, Pfister HW (2003) CSF and serum levels of soluble fractalkine (CX3CL1) in inflammatory diseases of the nervous system. J Neuroimmunol 137(1–2):210–217
106. Cardona AE, Pioro EP, Sasse ME, Kostenko V, Cardona SM, Dijkstra IM, Huang D, Kidd G et al (2006) Control of microglial neurotoxicity by the fractalkine receptor. Nat Neurosci 9(7):917–924

107. Tena A, Sachs DH (2014) Stem cells: immunology and immunomodulation. Dev Ophthalmol 53:122–132
108. van Velthoven CT, Sheldon RA, Kavelaars A, Derugin N, Vexler ZS, Willemen HL, Maas M, Heijnen CJ et al (2013) Mesenchymal stem cell transplantation attenuates brain injury after neonatal stroke. Stroke 44(5):1426–1432
109. Wang Y, Colonna M (2014) Interkeukin-34, a cytokine crucial for the differentiation and maintenance of tissue resident macrophages and Langerhans cells. Eur J Immunol 44(6):1575–1581
110. Lin H, Lee E, Hestir K, Leo C, Huang M, Bosch E, Halenbeck R, Wu G et al (2008) Discovery of a cytokine and its receptor by functional screening of the extracellular proteome. Science 320(5877):807–811
111. Muccioli GG, Stella N (2008) Microglia produce and hydrolyze palmitoylethanolamide. Neuropharmacology 54(1):16–22
112. Redlich S, Ribes S, Schutze S, Czesnik D, Nau R (2012) Palmitoylethanolamide stimulates phagocytosis of Escherichia coli K1 and *Streptococcus pneumoniae* R6 by microglial cells. J Neuroimmunol 244(1–2):32–34
113. Nau R, Ribes S, Djukic M, Eiffert H (2014) Strategies to increase the activity of microglia as efficient protectors of the brain against infections. Front Cell Neurosci 8:138