Journal of Neuroimmunology 278 (2015) 262–270

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Targets for adjunctive therapy in pneumococcal meningitis

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ARTICLE INFO

Article history:
Received 1 August 2014
Received in revised form 10 November 2014
Accepted 13 November 2014

Keywords:
Meningitis
Streptococcus pneumoniae
Targets of adjunctive therapy

ABSTRACT

Pneumococcal meningitis is a severe infectious disease of the central nervous system (CNS) and a significant cause of morbidity and mortality worldwide. The inflammatory reaction to the disease contributes to neuronal injury and involves the meninges, the subarachnoid space and the brain parenchymal vessels. Bacterial pathogens may reach the blood–brain barrier and be recognized by antigen-presenting cells through the binding of Toll-like receptors, triggering an inflammatory cascade. This in turn produces cytokines and chemokines, increases adhesion molecule expression and attracts leukocytes from the blood. This cascade leads to lipid peroxidation, mitochondrial damage and blood–brain barrier permeability. In spite of effective antibacterial treatments, approximately one third of survivors suffer from long-term sequelae, such as hearing loss, cerebral palsy, seizures, hydrocephaly or cognitive impairment. This review summarizes the information on targets of adjuvant treatments of acute pneumococcal meningitis.

Contents

Abbreviations: 3-HAA, 3-hydroxyanthranilic acid; 3-HKYN, 3-hydroxykynureanine; 5HT, 5-hydroxytryptamine; AIF, apoptosis-inducing factor; Apaf-1, apoptosis-activating factor 1; ATM, ataxia telangiectasia mutated; BAK, Bcl-2 antagonist killer; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma extra-large; BDNF, brain-derived neurotrophic factor; CB_2, cannabinoid-2 receptor; CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; CXCL-8, chemokine CXC ligand-8; EPO, erythropoietin; ERK 1/2, extracellular signal-regulated kinase 1 and 2; H_2O_2, hydrogen peroxide; HIF-1, hypoxia-inducible factor-1; ICAM, intracellular adhesion molecule; IRAK4, IL-1 receptor-associated kinase-4; IκB, inhibitor of B kinase; JNK, Jun N-terminal kinase; LFA-1, lymphocyte function-associated antigen; Mac-1, macrophage-1 antigen; MAPKs, mitogen-activated protein kinases; MMP, matrix metalloproteinase; MSCs, human mesenchymal stem cells; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa B; NO, nitric oxide; O_2^-, superoxide anion; $ONOO^-$, peroxynitrite; p38 MAPKs, p38 mitogen-activated protein kinase; PDGFR, platelet-derived growth factor; PIKK, phosphoinositide-3-kinase-related-kinases; ROS, reactive oxygen species; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-α; TRAF6, tumor necrosis factor receptor-associated factor 6-dependent signaling pathway.

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http://dx.doi.org/10.1016/j.jneuroim.2014.11.015
0165-5728/

1. Introduction

Meningitis is a frequent and serious infection of the central nervous system (CNS) affecting the pia mater, the arachnoid and the subarachnoid space (van de Beek et al., 2004). The utilization of conjugate vaccines has modified the epidemiology of bacterial meningitis (Shin and Kim, 2012). However, pneumococcal meningitis continues to be an important cause of mortality and morbidity worldwide, and our incomplete knowledge of its pathogenesis, coupled with the emergence of antimicrobial resistant bacteria and the absence of new targets for adjunctive therapy, contributes to this mortality and morbidity (Mook-Kanamori et al., 2011). The median risk of surviving patients developing at least one sequel, such as cognitive deficits, bilateral hearing loss, motor deficits, seizures, visual impairment and hydrocephaly, is approximately 16.2–35.5% (Edmond et al., 2010). Experimental animal models have demonstrated that the outcome of bacterial meningitis is related to the severity of inflammation and that this outcome can be improved by modulating the inflammation (Mook-Kanamori et al., 2011). Nevertheless, new adjunctive therapies are needed to improve the prognosis of bacterial meningitis. The aim of this review is to summarize the current knowledge of the relevant pathophysiological steps of pneumococcal meningitis and of the new targets for adjunctive therapy.

2. Therapeutic targets in pneumococcal meningitis

2.1. Inhibition of pattern recognition receptors

During pneumococcal development, the concurrent occurrence of autolysis releases bacterial components with extremely immunogenic properties, and these components are recognized by antigen-presenting cells through the binding of Toll-like receptors (TLRs) (Barichello et al., 2012a). These receptors can induce the activation of myeloid differentiation factor 88 (MyD88), which interacts with several protein kinases, including the IL-1 receptor-associated kinase-4 (IRAK4), which is phosphorylated to dissociate from MyD88 (Mook-Kanamori et al., 2011). These compounds also interact with tumor necrosis factor receptor-associated factor 6-dependent signaling pathway (TRAF-6) (Adhikari et al., 2007). This cascade provides a connection nuclear factor kappa B (NF-κB), resulting in the nuclear translocation of NF-κB, which in turn leads to the generation of cytokines, chemokines and other pro-inflammatory molecules in reaction to the pneumococcal stimuli (Tato and Hunter, 2002).

The inhibition of TLR signaling could be a strategy aimed at reducing the severity of disease. The protein tyrosine kinase inhibitor AG126 inhibits the pneumococcal cell wall-induced microglial cytokine generation *in vitro* (Hanisch et al., 2001). In an experimental model of pneumococcal meningitis, AG126 significantly reduced the pneumococcal cell wall-induced leukocyte influx into the cerebrospinal fluid (CSF), decreased tumor necrosis factor-alpha (TNF-α) levels, reduced the increase in regional cerebral blood flow and reduced the increase in intracranial pressure (Angstwurm et al., 2004).

2.2. Inhibition of pro-inflammatory cytokines

Pneumococcal compounds are recognized by TLRs leading to NF-κB activation and to the triggering of the expression of inflammatory cytokines (Klein et al., 2006).

Cytokines, chemokines, reactive oxygen species collaborate to eliminate invading microorganism, however their excessive inflammatory response can have harmful effects on neuronal plasticity, behavior, and cognition (Hu et al., 2014; Barichello et al., 2013a,b). Administration of TNF-α into the CSF induced the expression of matrix metalloproteinases (MMPs) and led to the breakdown of the blood–brain barrier mimicking bacterial meningitis (Rosenberg et al., 1995). However, in a neonatal rat model of pneumococcal meningitis, the administration of the TNF484 inhibitor attenuated the incidence of seizures and decreased TNF-α levels in the plasma and in the CSF (Meli et al., 2004). In contrast, TNF-α-deficient mice had increased of mortality rates and spatial memory deficits in experimental pneumococcal meningitis (Gerber et al., 2004). Inhibition of cytokines is a target treatment, however still it was not possible to demonstrate in experimental meningitis which optimal level of cytokines is necessary to not exacerbate the host immune response and may also eliminate the microorganism.

2.3. Inhibition of leukocyte recruitment

Pneumococcal compounds are pro-inflammatory mediators that induce an immune response triggering the generation of pro-inflammatory cytokines and chemokines (Hirst et al., 2004). Consequently, neutrophils leave the blood and migrate to sites of infection. This is mediated through the binding of Sialyl-Lewis^X on leukocytes to selectins P and E on endothelial cells. This binding becomes stronger when the chemokine CXC ligand-8 (CXCL-8) binds to its specific receptor on neutrophils, which then triggers the production of integrin lymphocyte function-associated antigen (LFA-1) and CX3 (macrophage-1 antigen-Mac-1). Inflammatory cytokines, such as TNF-α, are also necessary to induce the expression of intracellular adhesion molecules 1 and 2 (ICAM-1 and ICAM-2). The link between endothelial cells and ICAM-1 allows for the diapedesis of neutrophils along a concentration gradient of chemoattractant elements (Carlos and Harlan, 1994; Hanna and Etzioni, 2012). Fucoidan, a polysaccharide that inhibits leukocyte rolling, has been shown to attenuate inflammatory responses in experiments of pneumococcal meningitis (Angstwurm et al., 1995). In experimental meningitis induced with bacterial compounds or live bacteria; pretreatment with fucoidan prevented the leukocytes infiltration in the CSF (Granert et al., 1999). However, blocking leukocyte entry into the CNS in animal models of pneumococcal meningitis augmented bacteremia in the CSF and increased mortality rates but did not affect the risk of brain damage (Brandt et al., 2005).

2.4. Inhibition of caspase activation

Streptococcus pneumoniae is the main cause of bacterial meningitis, and it injures the hippocampus by inducing neuronal apoptosis. Live pneumococci induce rapid apoptosis in microglial and neuronal cells (Braun et al., 2001). Pneumococcal cell-wall compounds activate the host inflammatory response in white blood cells. The triggering of the apoptotic actions of p53 requires its phosphorylation by a family of phosphoinositide-3-kinase-related-kinases (PIKKs), which include the ataxia telangiectasia mutated (ATM) protein. ATM acts as an upstream mediator that converges on the mitochondria to initiate the release of cytochrome c. This release is essential in the activation of the