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Review article

Cellular damage in bacterial meningitis: An interplay of bacterial and host driven toxicity

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Abstract

Bacterial meningitis is still an important infectious disease causing death and disability. Invasive bacterial infections of the CNS generate some of the most powerful inflammatory responses known in medicine. Although the components of bacterial cell surfaces are now chemically defined in exquisite detail and the interaction with several receptor pathways has been discovered, it is only very recently that studies combining these advanced biochemical and cell biological tools have been done. Additional to the immunological response direct bacterial toxicity has been identified as an important contributor to neuronal damage. A detailed understanding of the complex interaction of bacterial toxicity and host response may generate opportunities for innovative and specific neuroprotective therapies.

Keywords: Meningitis; Innate immunity; Neuronal damage; Cell death; Microglia

Contents

1. Background

> "*Increased power to destroy the diplococcus is not associated necessarily with an equally increased power to resist the toxic effects of the intracellular poison. This fact must have an important bearing upon a specific therapy of diplococcus meningitis.*" (Flexner, 1907)

100 years ago, it was recognized that killing bacteria did not arrest the progression of the pathophysiology of meningitis. Bacterial meningitis is still an unresolved problem in clinical medicine. Although highly effective antibiotics kill bacteria efficiently, mortality rates of up to 34% are still reported (van de Beek et al., 2006) and up to 50% of the survivors suffer from long term sequelae (Schuchat et al., 1997; Bohr et al., 1984; de Gans and van de Beek, 2002; Weisfelt et al., 2006). These values are no better than those obtained by opsonic serum 100 years ago (Flexner, 1913). Then in the last years, two landmark studies suggested an approach to improve outcome by decreasing inflammation using dexamethasone as an adjunctive treatment to antibiotics (Odio et al., 1991; de Gans and van de Beek, 2002). This has set the tone for current work to

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implement therapies derived from an understanding of the molecular basis of the disease so as to increase the cure rate, particularly in view of new upcoming challenges such as increasing resistance to currently used antibiotics (Whitney et al., 2000; Doern et al., 2001; Richter et al., 2002). Sophisticated animal models as well as cell culture systems and new molecular techniques, provide an exciting area of research that will teach how bacteria communicate with the brain in general and hopefully create new opportunities for neuroprotection.

2. Bacterial entry and inflammation of the blood–brain barrier (BBB)

The specific sites of bacterial entry into the CNS are controversial. It is generally assumed, that high grade bacteremia precedes meningitis and that bacteria traverse from blood into the ventricular or subarachnoidal space. Direct access to the CNS through the olfactory bulb (van Ginkel et al., 2003) or dural defects, e.g. after neurosurgery, trauma or due to local infections, is also described. More commonly, the successful invasive pathogen carries effective tools in order to invade and replicate within the CNS. Some evidence generated in the monkey model suggests that the choroid plexus may be the site of invasion (Daum et al., 1978). Meningococci have been found in the choroid plexus as well as in the meninges (Pron et al., 1997). Animals developing pneumococcal meningitis after systemic challenge show inflammatory infiltration mostly around the leptomeningeal blood vessels supporting subarachnoidal and arachnoidal vessels as potential entry sites (Rodriguez et al., 1991; Zwijnenburg et al., 2001). Taking these few data from different models together, the anatomical site of bacterial entry into the cerebrospinal fluid (CSF) and the brain may be diverse.

Historically, the majority of bacterial meningitis is caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b, and, in the newborn, by group B *streptococcus* and *Escherichia coli K1* (Durand et al., 1993). Whether the bacteria enter the CSF by crossing the choroid plexus epithelium or the vascular endothelium, they must engineer passage despite the presence of tight junctions. This is a two step process involving tropism of circulating bacteria to the cerebral endothelium followed by transcellular transit via receptor mediated uptake and transcytosis within a vacuole. Models to study these mechanisms at the molecular level have been developed specifically using brain microvascular endothelium cells (BMEC, primary or cell lines) (Stins et al., 1997; Blasig et al., 2001). *E. coli* (Huang et al., 1995), *Listeria* (Parida et al., 1998; Wilson and Drevets, 1998), meningococci (Pron et al., 1997), streptococci (Nizet et al., 1997) and pneumococci (Ring et al., 1998) transmigrate across human BMEC *in vitro*. Just recently the interaction of pneumococci and meningococci with the BBB has been shown *in vivo* (Mairey et al., 2006; Fillon et al., 2006). The mechanisms of BMEC transit involve unique molecular pairings of a given bacteria with a cognate human cell receptor. This process is governed by a set of general operative features shared by all the pathogens:

- an adhesion step is specified by a ligand/receptor interaction that brings the pathogen into proximity with the surface of the human cell and initiates cross talk and cellular activation
- a subsequent, different ligand/receptor interaction results in uptake of the bacteria into a vacuole; for many of the major pathogens this involves PAF receptor
- β-arrestin mediated cytoskeletal mechanics transit the pathogen-containing vacuole to the basolateral cell surface ending with exocytosis

A summary of suggested prokaryotic–eukaryotic interactions that mediate the first step of adherence is shown in Table 1. Although the details differ for each pathogen, recognition of carbohydrates on endothelial cells is a common theme for early tropism. For invasion, however, meningeal pathogens use the same ligand/receptor interaction: phosphorylcholine binding to platelet activating factor receptor. Meningococci (Weiser et al., 1998; Serino and Virji, 2000) and the previously important meningeal pathogen, *H. influenzae* (Weiser et al., 1997), and pneumococci (Tomasz, 1967) all covalently add phosphorylcholine to their surfaces. Phosphorylcholine is the bioactive determinant of the chemokine platelet activating factor (PAF) and thus bacteria mimic this host inflammatory component and bind PAF receptor. Absence of the PAF receptor virtually eliminates the development of meningitis

Table 1
Ligand-receptor adherence interactions between bacteria and BBB cells

	Bacterial ligand	BMEC receptor
S. pneumoniae	CbpA (Orihuela et al., 2004)	Glycoconjugate receptors
N. meningitidis	PilC1 adhesin (Kallstrom et al., 1997)	CD46 Vitronectin, alpha v β3 integrin
	Outer membrane protein (Opc) (Unkmeir et al., 2002)	
Group B streptococci	LTA (Doran et al., 2005)	?
	PilA, PilB (Maisey et al., 2006)	
E. coli	SfaS protein (Prasadarao et al., 1997)	NeuAc-a2-3-galactose epitope
	SfaA adhesin (Prasadarao et al., 1993)	
	OmpA, Ibe10 (Huang et al., 1995)	Sulfated glycolipids
		GlcNAcß1-4GlcNAc