

## STATE-OF-THE-ART CLINICAL ARTICLE

## Cytokines and Chemokines in Meningeal Inflammation: Biology and Clinical Implications

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The CNS differs from other tissues in the body by the elaboration of a tight blood-brain barrier (BBB), which drastically reduces access of leukocytes and plasma components to the subarachnoid space and brain parenchyma. During infections of the CNS, an inflammatory reaction occurs across the BBB that can affect the subarachnoid space (meningitis), the brain parenchyma (encephalitis), or both (meningoencephalitis). The composition and time course of CNS inflammation vary greatly. Acute bacterial meningitis is characterized by a rapid accumulation of granulocytes in the CSF that evolves within hours. Viral forms of meningitis are associated with moderate numbers of mononuclear WBCs. The extent of cellular inflammation in encephalitis can vary from occasional cells in the parenchyma to extensive perivascular inflammatory cuffs.

Inflammation of the CNS is of great clinical relevance for at least two reasons. First, the inflammatory reaction to the invading CNS pathogen, rather than the pathogen itself, appears to be largely responsible for the damage that results from many CNS infections. In bacterial meningitis, evidence of brain damage can progress long after the site of infection has been sterilized by antibiotic therapy. Conversely, CNS inflammation that is induced without microbial pathogens, for example by expressing a chemokine under a brain-specific promoter, can lead to brain damage similar to that seen in infectious encephalitis [1]. Second, CNS inflammation is notably ineffective in eliminating many pathogens. If bacterial meningitis and acute and chronic CNS infections caused by other pathogens (e.g., herpes simplex virus, spirochetes, rabies virus) are not treated adequately, they either progress rapidly to death or establish chronic infections.

As in other inflammatory diseases, inflammation of the CNS is dependent on the local production of soluble mediators in response to microbial stimuli. These mediators include the numerous cytokines and chemokines, which form complex regulatory networks and influence key processes such as vascular

endothelial-cell activation, leukocyte infiltration, leukocyte function, and control of the inflammatory response. Much has been learned about cytokines and chemokines, and it is the purpose of this article to summarize the role of these host-derived mediators in selected CNS infections.

### Structure and Biology of Cytokines and Chemokines

Table 1 defines the nomenclature, cellular source, and function of cytokines in meningeal inflammation and, in addition, lists five important noncytokine/chemokine agonists. The most prominent endotoxin is lipopolysaccharide (LPS), a cell-wall component of gram-negative bacteria. LPS binds to a protein called CD14 on monocytes and triggers the synthesis of a large number of cytokines, including TNF- $\alpha$ , IL-1, IL-6, IL-10, IL-12, and chemokines. LPS is also a potent stimulator of B cells. The small formyl-peptide fMLP (N-formyl-L-methionyl-L-leucyl-L-phenylalanine) is a potent chemoattractant and activator of granulocytes, and exerts its function by binding to a serpentine receptor with greatest similarity to chemokine receptors. fMLP is produced during bacterial cell lysis and may contribute to the infiltration of granulocytes to sites of bacterial infection. Platelet-activating factor also binds to a serpentine receptor and together with leukotrienes and prostaglandins forms a group of lipid derivatives that are produced by activated macrophages, neutrophils, or tissue cells during acute neutrophil-dominated inflammatory responses. These agonists are instrumental in the destruction of infectious organisms and the subsequent tissue-repair process. (See Suggested Additional Reading at the end of the article for more information about the general aspects of cytokines and chemokines.)

### Cytokines

IL-1 and TNF- $\alpha$  are the two major cytokines in innate (natural, T cell-independent) immunity and are produced by hematopoietic cells, notably activated macrophages, and by tissue cells. IFN- $\gamma$ , a cytokine characteristic of type-1 T helper (Th1) cells, is an inducer of TNF- $\alpha$  production in macrophages, linking this cytokine to specific immunity. In addition, IL-1 is a potent inducer of TNF- $\alpha$ , but not vice versa. TNF- $\alpha$  binds as a homotrimer to two different single-chain receptors (TNF-RI, TNF-RII) that are expressed widely in blood and tissue cells. IL-1 $\alpha$  and IL-1 $\beta$  are two forms of IL-1 that are encoded by

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Publication of this State-of-the-Art Clinical Article has been made possible by an educational grant from Roche Laboratories.

Received September 4, 1998.

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**Clinical Infectious Diseases** 1999;28:1–12

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1058-4838/99/2801-0001\$03.00

**Table 1.** Network of cytokines and other mediators in meningitis.

Cytokines/mediators	Production	Effects
<b>Cytokines</b>		
IL-1	Macrophages, tissue cells	Proinflammatory, chemokine/cytokine production, vascular permeability, nitric oxide production
TNF- $\alpha$	Macrophages, T and natural killer cells, mast cells	Proinflammatory, chemokine/cytokine production, high levels in CSF correlate with mortality, nitric oxide production
IFN- $\gamma$	T cells, natural killer cells	Proinflammatory, chemokine/cytokine production, phagocyte activation, T-cell differentiation, synthesis of MHC molecules
IL-4	T cells, mast cells	IgE class switch, allergic inflammation, T-cell differentiation
IL-5	T cells, mast cells, eosinophils	Eosinophil mobilization and activation, allergic inflammation
IL-6	Monocytes/macrophages, endothelial cells	B-cell differentiation, T-cell activation
IL-10	Monocytes/macrophages, T cells	Anti-inflammatory, inhibition of chemokine/cytokine production
IL-12	Monocytes/macrophages, dendritic cells	Cytotoxicity in natural killer and T cells, IFN- $\gamma$ production, T-cell differentiation
TGF- $\beta$	Leukocytes and tissue cells	Antiinflammatory, inhibition of proinflammatory cytokine function, antagonizes IFN effects, tissue repair
<b>Other mediators</b>		
Chemokines	Leukocytes and tissue cells	Leukocyte recruitment, enhanced immune cell function
Endotoxins	Cell wall component of gram-negative bacteria	Proinflammatory, chemokine/cytokine production, enhanced immune function
fMLP	Bacterial cell wall	Granulocyte recruitment and activation
Platelet-activating factor, prostaglandins, leukotrienes	Macrophages, granulocytes, tissue cells	Granulocyte activation, tissue repair

NOTE. fMLP = N-formyl-L-methionyl-L-leucyl-L-phenylalanine; MHC = major histocompatibility complex; TGF- $\beta$  = transforming growth factor beta.

two separate genes. It is notable that the formation of active IL-1 $\beta$  depends on proteolytic processing by the IL-1 converting enzyme (ICE), a cysteine proteinase with similarity to apoptosis proteins.

There are two single-chain receptors for IL-1. Type I is considered the major receptor and, similar to the TNF receptors, is expressed throughout blood cells and tissue cells. The type II IL-1 receptor is inducible and acts as a "decoy" receptor by preventing IL-1 binding to the type I IL-1 receptor. In addition, phagocytes produce an IL-1 receptor antagonist (IL-1ra) that appears similar to IL-1 and binds to both types of IL-1 receptors but does not induce cellular responses. IL-1ra and IL-1 receptors are shed from activated cells and neutralize IL-1 function and, thus, are considered important regulators of immunity to bacterial infections. IL-1 and TNF- $\alpha$  share many functions in innate immunity, including induction of synthesis of chemokines and adhesion molecules, stimulation of phagocytic functions, and tissue repair (angiogenesis and connective tissue formation). TNF- $\alpha$ , in contrast to IL-1, can cause serious

illness when present at high concentrations, including wasting of muscle and fat cells (cachexia), septic shock, and death.

IFN- $\gamma$  is produced by activated T cells, including Th1 cells and natural killer cells. The IFN- $\gamma$  receptor is composed of a high affinity  $\alpha$ -subunit and an accessory  $\beta$ -subunit; the receptor binds monomeric IFN- $\gamma$  and is present on most hematopoietic cells and some tissue cells (including epithelial and endothelial cells). IFN- $\gamma$  is a true proinflammatory cytokine with an essential role in macrophage-rich inflammatory responses. The most significant functions of IFN- $\gamma$  include activation of macrophages/granulocytes (phagocytosis, and cytokine and chemokine production), polarization of naive T cells to Th1 cells, endothelial cell activation, and induction of class I and II major histocompatibility complex (MHC) molecules in various cell types.

IL-4 and IL-5 are typical Th2 cytokines that are secreted upon T-cell activation. The IL-4 receptor consists of a specific  $\alpha$ -subunit, which for signal transduction needs to associate with either the IL-13 receptor or the so-called common  $\gamma$ -chain of

the IL-2 receptor. The IL-4 receptor is found on resting and activated T and B cells, macrophages, mast cells, hematopoietic progenitor cells, and many tissue cells. The receptor for the homodimeric IL-5 is also composed of an  $\alpha$ -subunit, which binds IL-5, and an accessory  $\beta$ -subunit that is required for signaling and, unlike IL-4, is found primarily on eosinophils and basophils. IL-4 induces the switch to IgE production in B cells, and IL-5 is a potent activator of eosinophils. Thus, both cytokines play an eminent role in Th2-dominated immune responses commonly associated with allergic inflammation and killing of intracellular pathogens. In addition, IL-4 is a differentiation factor for the generation of Th2 cells and induces the expression of adhesion molecules and some chemokines in endothelial cells.

IL-6 is often detected during gram-negative bacterial infections and is produced by monocytes/macrophages, endothelial cells, and other tissue cells upon stimulation with IL-1 and, to a lesser extent, with TNF- $\alpha$ . IL-6 is also produced by activated T cells. The IL-6 receptor is present widely on hematopoietic and tissue cells and is composed of a binding subunit and a signaling subunit, which is probably shared with other cytokine receptors. IL-6 is primarily a B-cell differentiation factor but is also known to activate T cells, to co-stimulate hematopoietic progenitor cells, and, similar to TNF- $\alpha$  and IL-1, to contribute to the acute-phase response in sepsis by induction of fibrinogen synthesis in hepatocytes. The heterodimeric IL-12 is recognized by two separate binding proteins which together may form the functional IL-12 receptor. The major sources of functional IL-12 are activated monocytes/macrophages and dendritic cells. Cellular responses to IL-12 include activation of cytotoxicity and induction of IFN- $\gamma$  synthesis in natural killer cells and T cells, and generation of Th1 cells, thus building a functional bridge between innate and specific immunity.

Due to their inflammation-inhibitory effects, IL-10 and transforming growth factor-beta (TGF- $\beta$ ) need to be discussed separately. IL-10 is produced mainly by activated monocytes/macrophages and T cells, and it binds to a single-chain receptor with prominent expression in hematopoietic cells, including macrophages and T cells. IL-10 inhibits accessory functions (down-modulation of B7-1 and B7-2) in antigen-presenting cells and, more importantly, inhibits production of proinflammatory cytokines (TNF- $\alpha$ , IL-1, and IL-12) and some chemokines in macrophages. TGF- $\beta$  is comprised of three related dimeric proteins (TGF- $\beta$  1, 2, and 3). TGF- $\beta$ 1 is produced mainly by inflammatory cells, including activated T cells and monocytes/macrophages. Two high-affinity single-chain receptors with a wide range of expression are thought to associate for signal transduction, and the third type of receptor is of low affinity and may function as a TGF- $\beta$ -presenting molecule through binding of TGF- $\beta$  to its glycosaminoglycan sites. The pleiotropic actions of TGF- $\beta$  include synthesis of extracellular matrix proteins, neovascularization, and, most importantly, inhibition of functions mediated by proinflammatory cytokines (T-cell proliferation and maturation, and macrophage activa-

**Table 2.** Chemokines found in patients with meningitis.

Chemokines	Receptors	Target cells
CXC chemokines		
IL-8	CXCR1, CXCR2	Neutrophils, monocytes
GRO- $\alpha$	CXCR2	Neutrophils, monocytes, basophils, eosinophils
IP-10	CXCR3	Activated memory/effector T cells
Mig	CXCR3	Activated memory/effector T cells
I-TAC	CXCR3	Activated memory/effector T cells
CC chemokines		
MCP-1	CCR2	Monocytes, basophils, activated memory/effector T cells
MIP-1 $\alpha$	CCR1, CCR5	Monocytes, basophils, activated memory/effector T cells
MIP-1 $\beta$	CCR5	Cultured monocytes, activated Th1-type T cells, dendritic cells
RANTES	CCR1, CCR3, CCR5	Monocytes, eosinophils, basophils, activated memory/effector T cells, dendritic cells

NOTE. GRO- $\alpha$  = growth-related protein alpha; IP-10 = IFN- $\gamma$  inducible 10 kD protein; I-TAC = IFN-inducible T cell alpha chemokine; MCP-1 = monocyte chemoattractant protein 1; Mig = monokine induced by IFN- $\gamma$ ; MIP = macrophage inflammatory protein; RANTES = regulated on activation, normal T cell expressed and secreted.

tion). TGF- $\beta$  and IL-10 can be viewed as antiinflammatory cytokines that potently inhibit both innate and T cell-dependent immune responses.

## Chemokines

Chemoattractants (which induce chemotactic migration in leukocytes) are classified as chemokines (chemotactic cytokines) and nonchemokines. Well-documented nonchemokines are few and include fMLP, leukotriene B<sub>4</sub>, platelet-activating factor, and the complement component C5a. In addition, chemoattractant activity has been reported for TGF- $\beta$ . In contrast, >40 human chemokines are presently known and, thus, constitute by far the largest family of cytokines. Chemokines contain from 68 to 127 amino acids, share a typical four-cysteine motif, and, on the basis of the arrangement of the two amino-terminal cysteines (which are either adjacent or separated by a single amino-acid residue), are further divided into two subfamilies, CC and CXC chemokines. Two additional chemokines, one that lacks two of the four conserved cysteines and one membrane-bound form with a tripeptide spacer separating the first two cysteines, may define two alternative subfamilies. The chemokines found thus far in the CSF of patients with meningitis or known to be produced by astrocytes and microglial cells are defined in table 2.

Most chemokines are inducible, i.e., they are produced and secreted by infiltrated leukocytes and tissue cells upon stimulation with proinflammatory cytokines (IL-1, TNF, IFN- $\gamma$ ), endotoxins, and phorbol esters. The rapid production of chemokines

at sites of infection leads to the generation of a chemoattractant gradient (possibly through binding to proteoglycans) that enables proper navigation and homing of effector leukocytes. As such, induction of chemotactic migration is the prototypical function of chemokines and is readily assayed for in vitro. Other leukocyte responses include enzyme release from intracellular stores, oxygen radical formation, shape change through cytoskeletal rearrangement, generation of lipid mediators, and induction of adhesion to endothelium or extracellular matrix proteins. Induction of adhesion and shape change are integral elements of the leukocyte recruitment process. Additional functions attributed to some chemokines are induction/inhibition of angiogenesis, hematopoietic precursor-cell development, and embryogenesis. Finally, several more recent chemokines were found to be constitutively produced in lymphoid organs and thought to regulate leukocyte trafficking in these organs.

Chemokines are highly diverse in their target-cell selectivity. Generally, CXC chemokines are more selective for neutrophils, T cells, or B cells, whereas CC chemokines act on more than one type of leukocyte but not on neutrophils or B cells (table 2). Chemokines with the highest selectivity are IP-10 (IFN- $\gamma$ -inducible 10 kDa protein), Mig (monokine induced by IFN- $\gamma$ ), and I-TAC (IFN-inducible T cell  $\alpha$  chemokine) for activated memory/effector T cells; B cell chemoattractant 1 (BCA-1) for B cells; and several novel chemokines for resting and/or short-term activated T cells. Chemokines interact specifically with seven transmembrane domain receptors that are present on responding leukocytes and which couple to heterotrimeric G proteins for the induction of immune functions. Signaling leads to activation of serine/threonine kinases, which prevent further signaling by the rapid phosphorylation of chemokine receptors, thus ensuring the transient nature of chemokine-mediated leukocyte responses. In addition, chemokine binding induces receptor internalization, which becomes re-expressed on cell surfaces after trafficking through endosomal compartments. Additional intracellular signaling elements that become activated include phospholipases that produce lipid metabolites, kinases that phosphorylate protein and nonprotein targets, and small guanosine triphosphate-binding proteins. The receptors are divided into two subfamilies, CXCR and CCR, according to their selectivity for either CXC or CC chemokines, and are numbered in order of their discovery. Currently, the genes for 16 individual chemokine receptors are known, and the ones that recognize those chemokines that are produced in meningitis are listed in table 2.

## Cytokines and Chemokines in CSF in Selected Infections of the CNS

### Bacterial Meningitis

A critical role of cytokines and chemokines has been carefully established in models of bacterial meningitis. Following the injection of endotoxins from gram-negative meningeal pathogens (*Neisseria meningitidis* and *Haemophilus influen-*

*zae*) or cell-wall components from pneumococci, the rapid appearance of proinflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6) can be documented in CSF, which is followed by the appearance of granulocytes and increased CSF protein concentrations [2–4]. The injection of cytokines (e.g., TNF- $\alpha$  and IL-1) directly into the CSF results in a similar inflammatory response [5]. The importance of these cytokines is further supported by the fact that antibodies to them can mitigate the extent of inflammation in experimental meningitis [3, 5]. Some chemokines (macrophage inflammatory protein [MIP] 1 and 2) are also involved in the inflammatory response in the subarachnoid space, e.g., in experimental *Listeria monocytogenes* meningitis [6]. Cytokines in CSF induce endothelial-derived adhesion molecules on the cerebral vasculature, such as P and E selectins [7]. Activation of the cerebral vasculature endothelium represents an indispensable step in the recruitment of leukocytes to the site of inflammation [8, 9].

In humans, the classic proinflammatory cytokines (TNF- $\alpha$ , IL-1, and IL-6) identified in animal models, as well as several other cytokines, are present in CSF during meningitis (table 1) [10, 11]. In addition, CXC and CC chemokines have been found in the CSF of these patients (table 2) [12, 13]. Some of the chemokines (IL-8, growth-related protein  $\alpha$  [GRO- $\alpha$ ], monocyte chemoattractant protein 1 [MCP-1], MIP-1 $\alpha$ , and MIP-1 $\beta$ ) are more prominent in bacterial meningitis than in other forms of meningitis, and the target-cell selectivity of these chemokines likely contributes to the pronounced early influx of neutrophils that is followed by monocytes and T cells.

In meningitis, as in other infections, the proinflammatory effect of cytokines is controlled by antiinflammatory cytokines (IL-10 and TGF- $\beta$ ). IL-10 reduced CSF inflammation in rabbits after injection of endotoxin or live bacteria into the subarachnoid space [14]. In the CSF of patients with bacterial meningitis the cytokine is present in high concentrations, persists longer than proinflammatory cytokines and chemokines, and may down-regulate IFN- $\gamma$  production [10, 15–17]. TGF- $\beta$  seems to play a role similar to IL-10 in down-modulating inflammation in meningitis [18]. Antiinflammatory cytokines, while potentially beneficial, may impair host defenses in certain situations. For example, IL-10 in the CSF inhibited the bactericidal activity of macrophages against *Listeria* species [19].

In addition to IL-10 and TGF- $\beta$ , soluble cytokine receptors also modulate the biological activity of cytokines within the CSF compartment. Both the IL-1 receptor antagonist (IL-1 ra) and the type II IL-1 soluble receptor down-regulate the activity of IL-1 in meningitis [20]. For the two soluble TNF receptors (p55, p75), two potentially opposing effects have been identified. On one hand, TNF receptors are capable of neutralizing TNF- $\alpha$  activity, which most likely occurs during meningitis [10]. On the other hand, soluble TNF receptors in CSF appear to stabilize the biologically active forms of TNF- $\alpha$  (i.e., oligomers), thereby prolonging the proinflammatory effect of this cytokine [21, 22]. Thus, the net biological effect of these receptors in the CSF is not fully understood.

### Viral Meningitis

Viral meningitis (a term used here to describe an aseptic meningitis syndrome of suspected or documented viral etiology) is characterized by CSF infiltrates of activated T cells and monocytes. This syndrome also involves the production of proinflammatory cytokines, in particular TNF- $\alpha$  and IL-1, which are present at much lower levels in viral meningitis than in bacterial meningitis [23, 24]. IFN- $\gamma$ , in contrast, is present at high levels in the CSF of viral but not bacterial meningitis [24]. CSF levels of IL-6 in viral meningitis are similar to those in bacterial meningitis, with the notable exception of mumps meningitis [25, 26]. The antiinflammatory cytokines IL-10 and TGF- $\beta$ , which can be present in the CSF of patients with viral meningitis for several days, may contribute to the moderate extent of inflammation in this disease [16, 27, 28].

Several chemokines are also involved in viral meningitis, where they may play a key role in the recruitment of blood mononuclear cells. These include MIP-1 $\alpha$ , regulated on activation, normal T cell expressed and secreted (RANTES), IL-8, GRO- $\alpha$ , MCP-1, and IP-10 [13, 29]. IL-8 levels correlated with CSF granulocyte counts in patients with viral meningitis, but not in patients with bacterial meningitis [30, 31]. This chemokine may thus orchestrate early granulocyte influx in patients in whom other chemotactic stimuli (e.g., TNF- $\alpha$  and bacterial products) are absent or present at only low concentrations.

### Other CNS Infections

**HIV infection.** As is true for other viral infections, proinflammatory cytokines are expressed in the CSF of HIV-infected patients with symptoms of AIDS. High CSF concentrations of IL-6 in these patients were associated with expression of other cytokines in the CSF and with evidence for intrathecal IgG synthesis [32]. Overall, there is no reliable correlation between cytokine pattern in CSF and clinical manifestations of HIV encephalopathy [33]. The chemokine MCP-1 is markedly expressed in the CSF of AIDS patients with cytomegalovirus (CMV) encephalitis, whereas levels of other chemokines are low in these patients [34].

**Tuberculosis.** In contrast to other infections, proinflammatory cytokines are present in the CSF of patients with tuberculous meningitis for weeks to months. In a study of children with tuberculous meningitis [35], persistently high IFN- $\gamma$  levels were found in the CSF that did not decline with therapy. TNF- $\alpha$  was detectable at low concentrations, and these levels also failed to decline with therapy. Only IL-1 levels showed a significant decline during 4 weeks of therapy. None of the cytokine levels correlated with the clinical stage of the disease [35]. In addition, TNF receptors are present in CSF for prolonged periods [36]. The ratio of TNF receptor to TNF- $\alpha$  in the CSF is unusually high during tuberculous meningitis [37], which is in marked contrast to bacterial meningitis and may reflect inadequate TNF- $\alpha$  production in this chronic infection.

IL-8 concentrations in tuberculous meningitis were similar to those in bacterial meningitis, but decreased only after weeks of adequate therapy, unlike the rapid disappearance (1–2 days) of IL-8 in bacterial meningitis [38].

**Fungal meningitis.** Little is known about the CSF concentrations of cytokines in fungal meningitis. In patients with coccidioidomycosis meningitis, CSF levels of TNF- $\alpha$  and IL-1 were relatively low and did not change much over time. Only the IL-1 concentration correlated with the extent of clinical symptoms and with WBC counts in CSF [39]. CSF levels of several proinflammatory cytokines (except for TNF- $\alpha$ ) in AIDS patients with cryptococcal meningitis were high, whereas levels of the antiinflammatory cytokine IL-10 were low. It is notable that the minimal CSF pleocytosis typically found in AIDS patients with cryptococcal meningitis was in contrast to consistently high levels of the chemokine IL-8 [40].

### Source of Cytokines and Chemokines in CSF During CNS Infections

The majority of cytokines are present at high concentrations in the CSF during meningitis, whereas they are undetectable in plasma, suggesting that the cytokines are produced locally [3, 21, 41]. For example, concentrations of TNF- $\alpha$ , IL-1, and their soluble receptors were elevated in the CSF but not in the plasma of patients with meningococcal meningitis, whereas the concentrations of these substances were elevated in the plasma of patients with meningococcal sepsis without meningitis [20, 42]. In addition to the predominant local production of cytokines during CNS infections, some systemically produced cytokines may enter the CNS by using specific transport systems in the blood-brain barrier (BBB) [43].

Within the brain parenchyma, microglia (the brain's resident macrophages), activated astrocytes, neurons, monocytes, and microvascular endothelial cells can produce most of the cytokines and chemokines found in CSF inflammation [44, 45]. In diseases affecting the brain parenchyma (encephalitis), production of cytokines is likely to originate from cells within the brain parenchyma, primarily from activated glial cells (i.e., microglia and astrocytes) [46]. Activated infiltrated WBCs, a rich source of cytokines and chemokines, may also contribute to the production of these substances in encephalitis. For meningitis, conflicting information is available regarding the cells that produce the cytokines detected in CSF. In rats with experimental meningitis, mRNA and proteins of multiple proinflammatory and antiinflammatory cytokines are expressed in the brain parenchyma [47].

In addition to cells in the parenchyma (likely microglia), we found TNF- $\alpha$  and IL-1 expression within ependymal cells of the ventricles in infant rats with group B streptococcal meningitis (Y. S. Kim, unpublished observation). The ependyma, with its capacity to produce cytokines in response to bacterial stimuli, is a plausible early source of proinflammatory cytokines in meningitis, since meningeal pathogens may enter the CSF

space across the choroid plexus within the ventricular system [48]. In contrast to the studies of rats, studies of rabbits with pneumococcal meningitis revealed mRNA for TNF- $\alpha$  primarily within WBCs in the area of meningeal inflammation [49, 50]. Similarly, in viral meningitis in humans, mRNA for many of the cytokines present in CSF are found in inflammatory cells within the CSF space [51]. Thus, potential sources of cytokines have been identified during meningeal inflammation, both within the brain parenchyma and in meningeal inflammatory cells. Conceivably, the stages in disease development may influence the type of cells that are actively engaged in cytokine and chemokine production.

## Effects of Cytokines on the Brain

### BBB Permeability

Enhanced BBB permeability is a hallmark of many infections of the CNS, including bacterial meningitis, and leads to the leakage of proteins and other molecules from plasma into the cerebral compartment. This may contribute to CNS inflammation and brain damage, including development of vasogenic brain edema and alterations of the neuronal microenvironment. Experimental models of meningitis have shown that the injection of TNF- $\alpha$ , and to some extent IL-1, into the CSF space leads to rapid increases in BBB permeability followed by vasogenic brain edema [52–54]. In patients with bacterial meningitis, BBB damage also correlated primarily with CSF concentrations of TNF- $\alpha$ , but not concentrations of IL-1 [55]. However, additional factors seem to be required for disruption of the BBB. These factors include blood-derived leukocytes, as evidenced in neutropenic animals that showed minimal BBB alterations after injection of proinflammatory cytokines or endotoxin into the CSF [52, 56]. Other mediators of BBB disruption that are generated in response to TNF- $\alpha$  include matrix metalloproteases and other inflammatory cell-derived proteases.

### Cerebral Blood Flow and Metabolism

Inflammation of the meninges profoundly affects cerebral blood flow and metabolism, and at least two distinct mechanisms responsible for these pathophysiologic alterations are recognized. First, the inflammatory infiltrate surrounding the cerebral vasculature in the inflamed subarachnoid space leads to vasospasms and thromboses of arteries and veins, and subsequent focal cerebral ischemia [57–61]. Second, global reduction of cerebral blood flow occurs as a consequence of reduced cerebral-perfusion pressure in the setting of impaired cerebral blood-flow autoregulation [62, 63].

Changes in the cerebral blood flow correlate with cytokine production in the CSF, as shown by a correlation between high CSF concentrations of IL-1 and IL-6 and blood-flow velocity in the middle cerebral artery in patients with bacterial meningi-

tis [64]. Conversely, injection of TNF- $\alpha$  into the CSF of rabbits resulted in reduced cerebral blood flow and increased cerebral anaerobic metabolism, the latter associated with nitric oxide production [65]. A direct correlation between TNF- $\alpha$  concentration and nitric oxide production in CSF has also been documented in patients with meningitis [66]. Although nitric oxide production is a prominent consequence of cytokines in CNS infections, the effects of nitric oxide on brain cells depend on many factors, such as the site of nitric oxide production and stage of disease progression. Nitric oxide can contribute to neuronal toxicity [67] and can alter cerebral metabolism [65], but it also may have beneficial effects such as counteracting cerebral ischemia [60].

### Cellular Effects of Cytokines

Astrocytes are critically important for the proper functioning of neurons and can be severely affected by CNS infections. Endotoxin reduces metabolism and alters morphology in astrocytes *in vitro*, possibly through the induction of cytokine production [68]. TNF- $\alpha$ , for example, was shown to induce increases in intracellular Ca<sup>2+</sup> concentrations, which resulted in changes in the electrochemical properties and functional integrity of the plasma membrane in astrocytes [69, 70]. Neurons may also be affected directly by cytokines during meningitis and other CNS infections. We have recently found that a subpopulation of neurons, the dentate granule cells of the hippocampus, undergo cell death during experimental bacterial meningitis, and that this process is mediated by TNF- $\alpha$  [71]. TNF- $\alpha$  induces the production of reactive oxygen radicals that may directly cause cell injury, as evidenced by the dramatic protective effect of an oxygen radical scavenger in experimental meningitis [59]. As a possible corollary to this form of experimental neuronal injury, MRI studies in patients who have recovered from meningitis show loss of volume in the hippocampus [72].

## Clinical Implications of CSF Cytokines and Chemokines

### Differential Diagnosis of CNS Infections

Soon after the importance of cytokines in CNS infections was established, it was recognized that some cytokines are present in higher concentrations in CSF during bacterial meningitis than in viral and other forms of meningitis [41]. This difference was particularly pronounced for TNF- $\alpha$  and IL-1 [24, 73–75]. As a result, these cytokines became useful in predicting bacterial meningitis, with a diagnostic specificity that approached 100% in patients with markedly elevated concentrations. However, the sensitivity of detection is less than optimal for the reliable prediction of bacterial meningitis (~80%) [74]. In addition, with regard to the differentiation between bacterial and tuberculous meningitis, TNF- $\alpha$  and IL-1 are also of limited value [73].

Differences in concentrations of IL-6 in CSF between bacterial and other forms of meningitis are inconsistent and are not large enough to consider this cytokine as a diagnostically useful parameter [25, 26, 76–78]. In contrast, the differences in IL-8 concentrations in the CSF are more reliable, with high concentrations in bacterial and low concentrations in viral or aseptic meningitis [30, 38, 79], and IL-8 was useful to some degree in identifying patients with bacterial meningitis (sensitivity, 81%; specificity, 92%) [80]. There are marked differences in CSF concentrations of other chemokines (e.g., MIP-1 $\alpha$  and IP-10) in bacterial and viral meningitis, but the diagnostic value of these parameters has not been ascertained [13]. Of all chemokines, IP-10, Mig, or most likely I-TAC are predicted to be characteristic of viral meningitis, since all three chemokines are unique in their selectivity for activated T lymphocytes.

In summary, at present no single cytokine allows a reliable diagnostic differentiation between bacterial and other forms of meningitis with a sensitivity and specificity of close to 100%. In contrast, several easily generated clinical and laboratory variables, such as CSF WBC and PMN counts and CSF protein and glucose concentrations are highly reliable parameters for computing the likelihood of bacterial vs. aseptic meningitis [81, 82]. Finally, determination of cytokine concentrations in CSF is costly and is not performed routinely in most laboratories and, consequently, the utility of these parameters in the differential diagnosis of meningitis is limited at present.

### Prognostic Impact of Cytokines and Chemokines

A correlation between cytokine levels and outcome of meningitis is suggested by the critical role of inflammation in CNS injury during infections. In support of this, analyses of CSF samples from children with bacterial meningitis revealed a correlation of IL-1 with several parameters of CSF inflammation, such as WBC count and glucose and protein concentrations, and with neurological outcome [83]. In infants with gram-negative enteric meningitis treated with gentamicin, CSF IL-1 plays a similarly critical role. Increased mortality among infants receiving gentamicin intraventricularly, as opposed to systemically, apparently resulted from an exacerbated release of endotoxin with subsequent stimulation of IL-1 production and inflammation [84]. High concentrations of TNF- $\alpha$  and platelet-activating factor in CSF have also been associated with severity of disease and seizures [85]. In addition, CSF concentrations of soluble TNF receptor and TGF- $\beta$ , and the ratio of TNF- $\alpha$  to TGF- $\beta$  were highest in children who died or who were left with severe neurological sequelae, suggesting that the relative concentrations of these cytokines critically influence disease progression [86, 87].

The extent to which the host responds to the invasion of pathogens, as indicated by the degree of cytokine production, immune cell recruitment, and other inflammatory mediators, is an important variable that may be determined by genetic factors. A genetically determined predisposition to produce low

levels of TNF- $\alpha$  and high levels of IL-10 in blood markedly increased the mortality rate associated with meningococcal disease [88]. It is notable that the same constellation (low concentrations of TNF- $\alpha$  and high concentrations of IL-10) in the CSF during meningitis is associated with mild CSF inflammation (see Bacterial Meningitis) and is, therefore, expected to be associated with a favorable outcome. Obviously, multiple factors including the compartment in which the inflammation occurs, the stage of the disease, and genetic factors determine variations in severity and outcome in individual patients.

### Potential of CSF Cytokines and Chemokines as Therapeutic Targets

Cytokines and chemokines represent attractive targets for the development of therapies aimed at reducing the extent of brain injury resulting from CNS infections. The topic has recently been reviewed in detail for bacterial meningitis, the CNS infection for which the most data are available [89]. At present, the most notable approach to adjunctive therapy for this disease is the use of corticosteroids, which effectively reduces the production of cytokines by mononuclear cells, including glial cells [90]. Studies of experimental meningitis have documented the effectiveness of corticosteroids in reducing CSF inflammation and associated pathophysiologic changes [3, 91–93]. It is important to note that this beneficial effect has been duplicated in clinical studies. As summarized in a recent meta-analysis of controlled studies of dexamethasone in bacterial meningitis since 1988 [94–103], there is evidence for a beneficial effect of dexamethasone on hearing loss in meningitis due to *H. influenzae*. A beneficial effect on hearing or overall neurological outcome in pneumococcal meningitis was evident only when the agent was given before or with the first antibiotic dose [104]. It is important to note that the majority of patients included in these studies were children and were infected with *H. influenzae* type b, a pathogen now largely eliminated in the United States, Western Europe, and other countries as a result of effective vaccination programs.

Alternative approaches to the use of corticosteroids for controlling the cytokine network have been explored experimentally. Pentoxifylline and thalidomide both reduce TNF- $\alpha$  production, and both agents have shown some beneficial effects on CSF inflammation in experimental meningitis [105, 106], but the overall therapeutic potential is modest and clinical trials have yet to be performed.

The use of antiinflammatory cytokines or endogenous inhibitors of cytokines represents a new approach to the treatment of meningitis. IL-1 receptor antagonist and a soluble TNF receptor produced only very minimal beneficial changes in experimental meningitis, and these changes are not likely to translate into significant clinical benefits [107]. Somewhat more promising were results with IL-10 in the same model where the antiinflammatory cytokine reduced TNF- $\alpha$  production and CSF inflammation, albeit to a lesser extent than when the cytokine

was combined with dexamethasone therapy [14]. An antibody to TNF- $\alpha$  did not influence overall inflammation or ischemic brain damage in an infant rat model of bacterial meningitis, even though it was effective in reducing injury in a subpopulation of neurons [71]. Inhibition of chemokine activity by neutralizing antibodies or chemokine receptor antagonists has not been tested for therapeutic effects in this disease. However, because the recruitment of immune cells to the site of infection forms the basis for the development of an inflammatory reaction (and eventually brain damage), interference with this process appears to be a valid novel target. Suitable reagents, especially low-molecular-weight chemokine receptor antagonists, are being developed and are expected to be of great value in the treatment of inflammation and HIV infection.

At present, effective adjunctive therapy for CNS infections based on specific inhibition of harmful cytokines has not been accomplished satisfactorily, despite the progress that has been made in understanding the role of these important biological mediators. In part, this may be related to the fact that at the time of clinical presentation, much of the inflammatory response has already developed. In addition, delivery of the therapeutic molecules in high concentrations across the BBB to the site of action in the CNS may be difficult. Chemokine antagonists may not pose this problem, since blockade of immune-cell recruitment needs to occur in the blood and not at the site of infection. Alternatively, new targets in the pathophysiologic cascade which becomes activated locally during inflammation, such as oxygen-derived radicals or excitatory amino acids, may prove valuable [59, 108]. In the mean time, dexamethasone therapy continues to be the best option to reduce neurological sequelae during bacterial meningitis in children [104], and its use is cautiously endorsed for adults with severe bacterial meningitis [109].

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