1. CYTOKINES IN THE NORMAL CENTRAL NERVOUS SYSTEM

The presence of proinflammatory cytokines in normal central nervous system (CNS) tissues remains an area of controversy (1). Several cytokines have been demonstrated in the normal CNS, and among them, tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), transforming growth factor (TGF)-β, and macrophage migration inhibitory factor (MIF) have been studied in detail. The functions of TNF-α, IL-1, and TGF-β in the context of neuroinflammation have been described in detail elsewhere in this chapter; therefore, in this section, we will discuss only the potential roles these cytokines have in CNS development and physiological functions.

There have been conflicting reports regarding whether IL-1 is present in normal CNS tissues, suggesting that its expression is very low or undetectable (1). IL-1β mRNA and protein have been detected in the CNS of mice, rats, and humans, where expression was associated with specific brain regions, including the cortex, hippocampus, cerebellum, and spinal cord (2–9). Neurons and glial cells reportedly serve as the source of IL-1β in normal CNS (1). Interestingly, the levels of IL-1β mRNA have been shown to fluctuate with diurnal rhythm (10), which could account for the failure of some investigators to detect IL-1β in normal brain. In contrast to these reports, several groups have failed to detect IL-1β in the normal CNS, even when using sensitive techniques (11–14); however, the majority of evidence indicates that IL-1β mRNA and protein are expressed in normal CNS in a region-dependent manner in both neurons and glial cells (1).

The physiological role of endogenous IL-1β in the normal CNS has been linked to the regulation of sleep and feeding patterns, temperature, and synaptic plasticity (1). These outcomes are mediated by the type I IL-1 receptor (IL-1RI) expressed on numerous CNS cell types, including neurons and glia. Regarding sleep regulation, exogenous IL-1β has been shown to increase non-rapid eye movement in rodents, and IL-1RI knockout (KO) mice have been reported to sleep less compared to wild-type (WT) animals (15). The cyclic patterns of IL-1β expression observed in rodent brains correlates with many of these physiological pathways; however, the finding that IL-1 KO mice do not exhibit any developmental or neurological abnormalities suggests that other factors are capable of substituting for IL-1β in the normal CNS.

TNF-α is another cytokine that has been detected in normal CNS; however, similar to IL-1β, its expression is controversial (1,16). TNF-α and its receptors have been detected in discrete brain regions of normal mouse, rat, and human brain, including the hypothalamus, cortex, and cerebellum (17–20). In contrast, a few groups have been unable to demonstrate any TNF-α in the normal CNS.
the growth and motility of astrocytes, neurons, and oligodendrocytes are targets for these cytokines in the CNS. The finding that TNF-α KO mice do not display any overt CNS abnormalities suggests that the functional role of TNF-α in the developing CNS is either dispensable or is substituted for by alternative factors. Other physiological functions attributed to TNF-α include regulation of feeding and ion channel permeability in neurons (1). Overall, the actions of IL-1β and TNF-α possess a large degree of overlap that may explain why single cytokine KO mice do not exhibit overt alterations in the majority of the physiological functions described above. It would be interesting to evaluate the consequences resulting from the loss of both TNF-α and IL-1β on these parameters by creating double KO mice.

TGF-β is a complex cytokine found in three isoforms: TGF-β1, TGF-β2, and TGF-β3. Each isoform is secreted from cells in a latent form that requires proteolytic processing extracellularly to become biologically active. TGF-β2 and TGF-β3, as well as their cognate receptors, are expressed in both the developing and adult CNS (23,24). The functions of TGF-β2 and TGF-β3 in the normal CNS are not known, but in vitro and in vivo studies have demonstrated that astrocytes, microglia, neurons, and oligodendrocytes are targets for these cytokines (25). TGF-β has been shown to inhibit the growth and motility of astrocytes (26–28) and influences ion channel activity, neurite outgrowth, and regeneration in neurons (29–31). TGF-β also regulates the adhesion and migration of oligodendrocytes and inhibits microglial activation (24,32,33). The functional importance of TGF-β2 and -β3 in the CNS is currently not known, since KO mice for each of these cytokines do not reveal any overt CNS abnormalities, which is likely caused by their redundant activities. The widespread expression of TGF-β during development and in the adult suggests it has a pivotal role in CNS homeostasis. It is possible that the absence of TGF-β2 and/or -β3 leads to subtle changes that are not yet understood.

We and others have detected MIF in the CNS (34–38), where both neurons and glial cells are reportedly a source of this cytokine (36,39,40). Paradoxically, MIF has been shown to have potent proinflammatory activities (41); yet, the high levels of MIF expression in the CNS argue against a role for this cytokine in promoting cerebral inflammation. Although its precise function in the normal CNS is uncertain, MIF has been shown to convert toxic products derived from catecholamine neurotransmitters into inactive derivatives (42), which suggests a protective role for MIF in neural tissues. Another potential function for MIF in normal CNS is suggested by recent studies demonstrating that MIF is a potent inhibitor of natural killer (NK) cells (43,44). NK cells are activated upon recognizing cellular targets that lack major histocompatibility complex (MHC) class I expression. Because the majority of cells in the normal CNS do not express MHC class I, they theoretically could be susceptible to natural killer (NK)-mediated cell lysis. Speculatively, MIF could safeguard against this activity (45,46).

In summary, evidence suggests that certain cytokines, including TNF-α, IL-1β, TGF-β2 and -β3, and MIF, are constitutively expressed in normal CNS. The inability to uniformly detect TNF-α and IL-1β in the brain suggest that these cytokines are present at very low and often undetectable levels. The discrepancies between reports evaluating the presence or absence of cytokines in the normal CNS may be related to the sensitivity of the assays used for detection, species differences, or the time of day at which cytokine levels are evaluated.

2. CYTOKINE EXPRESSION BY GLIA AND INFILTRATING IMMUNE CELLS IN THE CONTEXT OF CENTRAL NERVOUS SYSTEM INFLAMMATORY DISEASES

2.1. Glia

Microglia are the resident mononuclear phagocytes of the CNS parenchyma and participate in innate immune responses (47,48). They constitute approx 10 to 15% of the total cell population in...