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Neuroinflammation: good, bad, or indifferent?

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Under non-diseased conditions, CNS homeostasis is maintained by an intricate crosstalk between glia and neurons. For example, astrocytes play a key role in neurogenesis, metabolism, and regulating neuronal activity at the tripartite synapse (Parpura *et al.* 2012). Microglia are continuously surveying their microenvironments for foreign antigens and are important phagocytes of the CNS parenchyma, playing roles in synaptic pruning and clearance of apoptotic debris. However, in response to CNS infection or injury, these glial cells become activated and contribute to ensuing inflammatory processes, in either a beneficial or detrimental manner, depending on the nature, intensity, and duration of the insult. Yet, another wrinkle to this paradigm is the fact that many immune-related molecules can possess secondary functions in the CNS, which expands their portfolio of action. One such example is the ability of certain chemokines to act as neurotransmitters (Rostene *et al.* 2011). This Virtual Issue brings together prior publications in the *Journal of Neurochemistry* that highlights the diverse insults and outcomes of neuroinflammatory responses in the CNS. This group of articles is not intended as a comprehensive review of the discipline, since clearly numerous important diseases are not touched upon, but rather serves to provide insights into the important role that neuroinflammation plays across a diverse set of CNS diseases/disorders.

Further complicating the neuroinflammatory landscape is the fact that numerous CNS diseases are accompanied by a peripheral immune cell infiltrate. This brings into play issues regarding the involvement of CNS intrinsic versus invading immune cells in the inflammatory response. Some well-recognized examples include multiple sclerosis (MS) and various infectious insults of bacterial and viral origin. However, an emerging concept is that peripheral immunity may also influence neurodegenerative diseases and certain neuropsychiatric disorders. One example is post-traumatic stress disorder, where animal models have demonstrated that peripheral blood mononuclear cells can elicit post-traumatic stress disorder-like symptoms, which is accompanied by loss of hippocampal volume (Andrews and Neises 2012). The signals responsible for triggering systemic inflammation in these diseases and how they target the CNS remain areas of active investigation.

Numerous studies have shown that proinflammatory cytokines, such as IL-1β and tumor necrosis factor-a (TNF-α) induce neuron cell death. Since both cytokines are produced by

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activated microglia, they have been implicated as major contributors to neuronal loss. However, IL-1β and TNF-α also augment glutaminase expression in neurons, which may represent an autocrine mechanism to exacerbate neuronal excitotoxicity via NMDA receptor activation (Ye *et al.* 2013). Besides secretion of neurotoxic molecules, the retention of activated microglia at sites of CNS injury/neurodegeneration could also exacerbate neuron loss. One such example is Nogo-66, an extracellular peptide stretch of the myelin-associated glycoprotein Nogo-A, which was found to activate microglia and inhibit their migratory capacity (Yan *et al.* 2012). Neuroinflammation can also lead to homeostatic disturbances within CNS cells, such as iron accumulation. Iron accumulation has been demonstrated in numerous CNS disorders, including MS, Alzheimer's disease, and Parkinson's disease, where it has been postulated to promote disease by augmenting microglial proinflammatory activity, altering mitochondrial function, and inducing reactive oxygen species production (Williams *et al.* 2012). Both IL-1β and TNF-α have been shown to induce iron accumulation in neurons and microglia that was associated with changes in iron transporter expression (Urrutia *et al.* 2013). Therefore, one has to consider not only the direct toxic role of proinflammatory mediators but also secondary consequences emanating from cytokine action. This is a particular concern when attempting to identify potential therapeutic pathways to target for the treatment of CNS neuroinflammatory diseases.

Aging has been associated with a progressive increase in inflammatory marker expression, although the mechanisms responsible for this altered baseline have yet to be fully understood. Proinflammatory cytokine expression was elevated in the aging frontal cortex concomitant with reduced neurotrophin expression that correlated with promoter hyper-methylation (Keleshian *et al.* 2013), suggesting that an imbalance between pro- versus anti-inflammatory pathways may be a contributor toward changes associated with the normal aging brain. Neuroinflammation also plays a key role in numerous neurodegenerative diseases of both adult and pediatric onset. With regard to the latter, microglia in juvenile neuronal ceroid lipofuscinosis, a fatal pediatric-onset lysosomal storage disease, are primed toward a proinflammatory phenotype (Xiong and Kielian 2013). Specifically, diseased microglia over-produce a wide array of proinflammatory mediators in response to endogenous “danger signals” released from dying neurons, whereas normal microglia are relatively non-responsive to these stimuli. This suggests an intrinsic altered baseline of microglia, which may play a key role in neuron loss in this neurodegenerative disease. A similar intrinsic dysfunction in microglia has been reported in the context of presenilin 2 mutation, which has been associated with Alzheimer's disease. Specifically, miR146, a negative regulator of proinflammatory responses in monocytes, was significantly reduced in presenilin 2-deficient microglia concomitant with elevated nuclear factor-κB pathways that are associated with proinflammatory activity (Jayadev *et al.* 2013). In general, the majority of evidence to date ascribes a deleterious role for inflammatory responses in the context of neurodegenerative disorders and represents an area of intense focus for the development of therapeutics to halt disease progression.

Finally, although much attention has been paid to identifying mechanisms whereby neuroinflammation leads to neuronal loss, it is equally important to understand how these processes are halted. In terms of endogenous antiinflammatory mechanisms, the major brain

n-3 polyunsaturated fatty acid, docosahexaenoic acid, has been shown to attenuate glial activation, proinflammatory mediator production, and neuron loss (Orr *et al.* 2013). These types of endogenous resolvin-like molecules are likely key mediators in dampening inflammation in numerous CNS diseases. The triggering of adenosine A_2A receptors (A_2AR) has also been shown to be neuroprotective by attenuating inflammation and subsequent demyelination in experimental autoimmune encephalomyelitis an animal model for MS (Yao *et al.* 2012). Besides discrete biochemical molecules, neuroprotective effects can also be afforded by specific cell types. One such example is myeloid-derived suppressor cells (MDSCs), which are best characterized for their anti-inflammatory effects in tumors. In terms of CNS disease, MDSCs have been shown to play a critical role in attenuating inflammation following SCI and facilitating the repair process (Saiwai *et al.* 2013). Intraspinal transplantation of exogenous MDSCs at the injury site promoted tissue regeneration and functional recovery, which was attributed by their intrinsic ability to dampen deleterious inflammation. In addition, mechanisms exist to limit glial activation and associated CNS pathology. For example, the anti-inflammatory cytokine transforming growth factor-β (TGF-β) was shown to block IFN-γ-induced glial reactive oxygen species and nitric oxide production by interfering with key signaling pathways, namely, signal transducer and activator of transcription 1 and extracellular signal-regulated kinase (Herrera-Molina *et al.* 2012). This could have important implications in limiting the intensity of the initial inflammatory response, since the normal CNS has high basal levels of TGF-β, or alternatively, TGF-β could be instrumental in resolving inflammation in an attempt to return the CNS to homeostasis. The cellular prion protein (PrP^c) has been shown to regulate classical versus alternative activation of microglia in response to polarizing cytokines (i.e., IFN-γ and IL-4, respectively) (Shi *et al.* 2013), which represents another means to influence the pro- vs. anti-inflammatory decision point in the context of a neuroinflammatory insult.

Another repair mechanism is afforded by neurogenic niches in the adult brain that reside in the subventricular zone and dentate gyrus, which orchestrate neuronal replacement in response to aberrant conditions. However, our understanding of the role that neuroinflammation plays in regulating these adult neurogenic niches is limited. This is because studies have reported both beneficial and detrimental effects of inflammation on neurogenesis, which are likely attributed to the intensity, duration, and context of the inflammatory insult (Russo *et al.* 2011). A better understanding of which inflammatory mediators exert pro- versus anti-neurogenic effects may allow us to harness their activity to tailor neurogenic niches to facilitate neuron replacement or halt cellular loss during neurodegenerative processes.

In summary, it is now evident that many diseases affecting the CNS have some inflammatory component, either as a primary cause or secondary outcome of tissue damage. Much work remains to be done to identify the critical mediators and cell types involved; however, this will prove to be a challenging task given the complexities already uncovered with regard to the timing, context, and crosstalk between individual inflammatory molecules. Nonetheless, harnessing inflammation to promote CNS healing/regeneration remains an area of active investigation.

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Abbreviations used

MDSCs myeloid-derived suppressor cells

MS	multiple sclerosis
TGF-β	transforming growth factor-β