Insights in the Role of Glia in Mediating Brain Plasticity in Health and Disease

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Abstract

Glial cells were originally known as simply the "glue" of the central nervous system but are now recognized to play a critical role in the development and function of the brain in both health and disease. Neurons and glial cells communicate with each other in a bidirectional manner at the synapses to regulate synaptic plasticity. Neuronal-glial interactions also initiate and maintain activation of membrane-bound proteins and subsequent intracellular downstream signaling events. Since glia and microglia are equal (and not silent) partners in creating neuroinflammatory milieu observed in diverse brain disorders, it is important to understand how these cells respond to internal and external cues to impact neuron functions under physiological and pathological conditions. Brain injury has a highly heterogeneous and multifactorial pathology, and the initial injury triggered by mechanical disruption often leads to the development of a secondary cascade of cellular/molecular responses. Astrocytes and microglia influence the local microenvironment of the injured tissue by their ability to secrete cytokines, chemokines, and growth factors and by undergoing profound morphological alterations to influence the extent of damage and repair following injury.

Keywords

Astrocytes · Microglia · Neuroinflammation · Plasticity · Injury

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This chapter will cover the following aspects:

- Glia, neuroinflammation, and neuronal plasticity.
- Glia and microglia in brain injury.

1 Glia, Neuroinflammation, and Neuronal Plasticity

Growing evidence suggests that glia play an indispensable role in major aspects of synapse development, function, and plasticity. The astrocytic and microglial processes are known to be associated with pre- and postsynaptic elements and affect synaptic functions, which have long been thought to be restricted to neurons. In a healthy brain, glial cells secrete soluble factors that induce synapse formation and modulate synaptic transmission and plasticity. Concurrently, synaptic signals influence glial cells by activating their cell surface receptors and modulating ion channels. It has also been established that peri-synaptic astrocytes and microglia are positioned to sense early disruptions in synaptic activity and potentially contribute to synaptic demise (Verkhratsky et al. 2015). It is well established that glia are affected in the nervous system pathologies; however, loss/dysfunction of synapses can occur long before the signs of neuropathology and cognitive impairment associated with the disease appear (Chung et al. 2015).

1.1 Role of Astrocytes in Synaptic Plasticity

Astrocytes are the most abundant cell type in the CNS, which are essential for regulating brain function. They are positioned in close physical association with synapses to sense and modulate synaptic activity. They interact with various cellular structures, including synapses and blood vessels, through their numerous processes. This close association enables them to function as first responders to various changes in synaptic activity during development and adulthood.

Astrocytes are known to participate actively in synaptic transmission and contribute to synaptic plasticity. The most important functions of astrocytes elucidated to date include uptake of the neurotransmitters, glutamate and gamma-aminobutyric acid, and potassium buffering during neuronal activity (Thrane et al. 2013). These functions are indispensable for maintaining synaptic activity. The dysregulation in these processes may lead to neuropathological conditions, including neuronal dysfunction and seizures. It has also been reported that astrocyte-secreted glutamine is critical for the sustained release of glutamate by neurons (Tani et al. 2014), which suggests that astrocytes play an active role in the production of the neurotransmitters used by the neurons. Recent research has led to the identification of several astrocytic factors that are capable of regulating synaptic plasticity. D-serine, secreted from astrocytes, has been reported to be involved in synaptic plasticity and

maintaining long-term potentiation by functioning as a co-agonist of NMDAR (Henneberger et al. 2010). ATP and glutamate have also been reported to be secreted by astrocytes through calcium-dependent vesicular exocytosis and contribute to synaptic plasticity (Halassa and Haydon 2010). A study by Han et al. (2013) suggests that human astrocytes may be better than rodent astrocytes in controlling the synaptic plasticity events underlying learning.

Further, in in vitro studies, the addition of astrocytes and astrocyte-conditioned media to purified culture of retinal ganglion cells has been shown to cause a significant increase in the number of functional excitatory synapses (Ullian et al. 2001). Chung et al. (2015) have reported that besides their role in synapse formation and function, astrocytes are also essential for synaptic maintenance. Synapses have been shown to immediately disappear when astrocytes or astrocyte-secreted signals are removed from cultured neurons (Chung et al. 2015). Thus, the formation of mature functional synapses requires multiple astrocyte-secreted signals, implicating the role of astrocytes in synapse formation and maintenance.

1.2 Role of Microglia in Synaptic Plasticity

Microglia are the resident macrophages of the CNS. The processes of microglia are known to interact with axonal boutons and dendritic spines. The direct contact between synaptic elements and microglia has been confirmed by electron microscopy (Tremblay et al. 2010). Each microglial cell can impact many synapses in response to external stimulus (Nimmerjahn et al. 2005). Microglia are also known to regulate maturation of synapses in both juvenile and mature brain. Interleukin (IL)-1β, a pro-inflammatory cytokine primarily expressed by microglia, has been implicated in the regulation of long-term potentiation in the hippocampus region (Williamson and Bilbo 2013; Zhang et al. 2014). Another pro-inflammatory cytokine, tumor necrosis factor α (TNFα), released by glia is required for synaptic scaling after a long-term reduction in activity (Stellwagen and Malenka 2006). It has been established that the expression of TNFα is highly enriched in microglia as compared to other brain cells; so, it may be inferred that microglia mediate the process of synaptic scaling. Thus, the ability of microglia to affect synapses through microglia-synapse interactions is crucial for proper CNS function.

1.3 Underlying Role of Glia in Synaptic Dysfunction in Neuropsychiatric Disorders

Dysfunction of synapses is the hallmark feature of majority of the neurological disorders. Synaptic dysfunction is often associated with the increased level of inflammation, which may further lead to cognitive impairments. Reactive gliosis and neuroinflammation are virtually prominent in every disorder of the central nervous system. Glia are regarded as passive responders to the neuronal damage, rather than the causal factor of synaptic dysfunction. Extensive research has led to

the realization of active glial signaling with neurons, which further influences synaptic transmission and plasticity through various contact-dependent and secreted mediators. Chronic neuroinflammation often leads to targeted disruption of synaptic plasticity, which further leads to compromised neuronal integrity. It is likely that astrocyte dysfunction contributes to the initiation and progression of many neurological disorders.

Microglia have been implicated as strong regulators of neurological function and cognition in physiological conditions (Singhal and Baune 2017). Although microglia can directly modulate cognition, it is noteworthy that they can also perform this role by secreting inflammatory mediators such as cytokines, whose role has been well established in influencing learning and memory functions of the brain. Disruption in the signaling pathways of pro-inflammatory cytokines, TNFα, IL-1β, and IL-6 has been shown to cause learning and memory impairments (Goshen et al. 2007; Hryniewicz et al. 2007; Baune et al. 2008; Camara et al. 2013), which suggests that these cytokines play an indispensable role in the physiological regulation of memory processes. The regulatory role of these cytokines has been reported to be dose-dependent, since the overexpression of TNFα and IL-1β has been shown to disrupt normal learning and memory functions in rodents (Fiore et al. 2000; Barrientos et al. 2002). Recent studies have shown that disruption in microglia activation may alter hippocampus-dependent neuronal plasticity affecting learning and memory performance in adulthood (Maggi et al. 2011; Rogers et al. 2011).

Cytokines and microglia may also impact cognition indirectly by modulating neurotrophic factors and the associated signaling pathways. Cytokines have been shown to modulate the activity and levels of brain-derived neurotrophic factor (BDNF) (Calabrese et al. 2014). Removal of BDNF from microglia has led to the revelation that microglia regulate memory by promoting synapse formation through BDNF signaling (Parkhurst et al. 2013). Further, it has been reported that inflammatory cytokines can influence the production of all the hormones produced along the hypothalamic-pituitary-adrenal (HPA) axis and modulate the function of glucocorticoid receptors at multiple stages from expression to translocation and associated signaling pathways (Pace and Miller 2009). Besides their effects on neurotrophic factors and HPA axis, inflammatory processes can influence activation of kynurenine pathway. Pro-inflammatory cytokines have been shown to induce hippocampal activation of the kynurenine-producing enzyme, indoleamine 2,3-dioxygenase (O'Connor et al. 2009), which participates in the regulation of memory and learning (Too et al. 2016). Thus, alterations in neurobiological processes regulating cognition are similar across various disorders. Below, we review the evidence which suggests that inflammatory processes in particular activated microglia and inflammatory cytokines play a major role in contributing to impaired cognitive performance associated with psychiatric disorders.

Major Depressive Disorder

In patients with major depressive disorder, elevated serum levels of TNFα, TNF receptor-type 1 (TNFR1), and TNF receptor-type 2 (TNFR2) have been shown to be negatively correlated with behavioral performance in learning, executive function,

attention, working, and declarative memories (Bobińska et al. 2017). Similarly, elevated levels of IL-6 and C-reactive protein (CRP) have been shown to be associated with impaired cognitive performance in the domains of verbal memory and psychomotor speed and of attention and executive functions, respectively (Chang et al. 2012; Goldsmith et al. 2016). It has also been shown that IL-6 and CRP levels can predict the symptoms of major depressive disorder at 12 years from the baseline detection. This suggests that inflammation contributes to the progression of major depressive disorder rather than to the later stages of the disease (Gimeno et al. 2009). This relationship may be unilateral since cognitive symptoms of depression at baseline were not found to be predictive of inflammatory status at 12 years' follow-up. Further, acute treatment with cyclooxygenase-2 inhibitor, celecoxib, has been shown to improve cognitive functions in an elderly depressed woman with recurrent major depressive disorder (Chen et al. 2010).

It has been suggested that kynurenine pathway may be involved in cognitive function impairment in patients with major depressive disorder. It has been implicated in influencing glutamatergic transmission in brain structures associated with cognitive processes (Fourrier et al. 2019). Alterations in glutamatergic synaptic plasticity have been linked to depression in animal models (Mahati et al. 2016). Additionally, inhibition of microglia activation has been shown to prevent impairment in both spatial memory and hippocampal long-term potentiation in a rodent model of depression. This effect has been attributed to GluR1 phosphorylation (Liu et al. 2015). BDNF, a neurotrophic factor, is also significantly associated with memory performance in rodents. The circulating levels of IL-6 are known to represent serum BDNF levels (Jehn et al. 2015); and the inhibition of TNFα has been shown to prevent stress-induced cognitive impairment and the associated reduction of hippocampal BDNF expression (Şahin et al. 2015).

Schizophrenia

Inflammation has also been extensively reported to be a potential player in the etiology and pathophysiology of schizophrenia. Cognitive impairment associated with schizophrenia has been correlated with increase in peripheral inflammation. A systemic review by Misiak et al. (2018) reported a positive association between circulating CRP levels and worse cognitive performance. Similarly, cognitive functions have been reported to be impaired in schizophrenic patients with elevated levels of circulating IL-6, TNFR1, and IL-1 receptor antagonist (Hope et al. 2015). The administration of an anti-inflammatory drug, risperidone, for 5 weeks has been shown to improve cognition in schizophrenic patients (Müller et al. 2005). Another study showed that minocycline added to a typical antipsychotic treatment has a beneficial effect on working memory and cognition. This suggests that inhibition of microglia activation in schizophrenic patients can decrease cognitive impairments (Levkovitz et al. 2010). This is in line with the microglia hypothesis of schizophrenia, which states that the neuropathology of this disease is closely associated with the increased activation of microglia (Monji et al. 2009; Laskaris et al. 2016). In animal models of schizophrenia, free radicals and inflammatory cytokines produced by activated microglia have been shown to cause decrease in neurogenesis, white matter

abnormalities, and neuronal degeneration, which may be the underlying factor in the pathophysiology of schizophrenia. It has also been suggested that increase in inflammation in schizophrenia may cause glutamatergic imbalance, leading to the dysfunction of dopaminergic system, which may in turn exacerbate glutamatergic transmission impairments, eventually leading to cognitive impairment (Müller 2008).

Bipolar Disorder

A few studies have reported association between inflammation and cognitive performance in patients with bipolar disorder. Circulating CRP levels have been shown to be negatively associated with memory and attention in patients with bipolar disorder (Dickerson et al. 2013). Similarly, elevated levels of IL-1 receptor antagonist and TNFα have been shown to be associated with worse memory performances (Hope et al. 2015). Elevated levels of soluble TNFRI have also been found to be associated with impaired declarative memory (Hoseth et al. 2016). A study evaluating the association between cerebrospinal fluid inflammatory markers and cognition in bipolar disorder patients reported a negative association between CSF concentration of the inflammatory biomarker YLK-40 and executive function in these patients (Rolstad et al. 2015). Besides increase in peripheral inflammation and cognitive impairments in bipolar disorder patients, increased microglial activation has been reported in the right hippocampus of bipolar disorder patients as compared to healthy controls (Haarman et al. 2014). Various underlying mechanisms have been suggested that participate in inflammation-associated cognitive impairments in bipolar disorder. A study suggests that pro-inflammatory cytokines such as TNFα impair white matter integrity in patients with bipolar disorder (Benedetti et al. 2016), which can be mediated by alterations in neurogenesis (Czéh and Lucassen 2007). Further, the activity of HPA axis may be influenced by cytokines, which may subsequently lead to impaired neuroplasticity. Indeed, HPA axis alterations have been associated with impaired cognition in patients with bipolar disorder. The insensitivity of glucocorticoid receptors has been reported in bipolar disorder (Fries et al. 2015), and mifepristone (glucocorticoid receptor antagonist) treatment for 1 week has been shown to improve spatial working memory performance in bipolar disorder patients (Watson et al. 2012). Additionally, it is noteworthy that peripheral BDNF level, which is regulated by inflammation, is an indicator for cognitive function in bipolar disorder patients. Moreover, the BDNF val66met polymorphism can be a risk factor for cognitive impairment in this disease (Bauer et al. 2014), which further reinforces the possible role of BDNF in mediating the effects of inflammation on cognition in bipolar disorder.

1.4 Studies from our Lab Exploring the Link Between Neuroinflammation and Synaptic Plasticity

Recently, our lab investigated the effect of pre-administration of water extract from leaves of *Withania somnifera* (ASH-WEX) and 50% ethanolic extract of *Tinospora*

cordifolia (TCE) on memory and cognitive impairment induced by acute sleep deprivation (Mishra et al. 2016; Kaur et al. 2017; Manchanda et al. 2017). In another study, the effect of administration of dry leaf powder of *W. somnifera* and stem powder of *T. cordifolia* along with high-fat diet (30% fat by weight) for the period of 12 weeks was explored (Kaur and Kaur 2017; Manchanda and Kaur 2017; Singh et al. 2021). The extracts of *W. somnifera* and *T. cordifolia*, well known for their psychotropic effects, were found to:

- Significantly improve memory impairment.
- Significantly reduce anxiety-like behavior.
- Reduce the expression of inflammatory markers such as TNFα, IL-1β, IL-6, GFAP, Iba1, OX-42, AP-1, and NF-κB.
- Reduce the stress-induced expression of PSA-NCAM and NCAM markers in the hippocampus and piriform cortex regions of the brain.

1.5 Remarks

The vulnerable cognitive impairments across many psychiatric disorders necessitate consideration since they affect not only the quality of life but also the treatment and recovery of patients. However, the underlying mechanisms for these deficits are not fully understood. These must be elucidated for better management of these disorders. The cognitive impairments across psychiatric conditions suggest shared mechanisms, potentially leading to their development. Neuroinflammation can be a shared underlying mechanism for the development of cognitive impairments in major depressive disorder, schizophrenia, and bipolar disorder. In fact, elevation in inflammatory processes, marked by the activation of microglia and increased levels of pro-inflammatory cytokines, can disrupt neurobiological mechanisms regulating cognitive processes. Though many studies have reported associations between inflammatory biomarkers, cognition-related biological mechanisms, and cognitive performance, causal evidence is still lacking.

2 Glia and Microglia in Brain Injury

Brain injury, defined as any insult to the CNS, has a multifactorial pathology. The initial injury triggered by mechanical disruption often leads to development of a secondary cascade of cellular/molecular responses. The glial cells of the CNS, astrocytes and microglia, are the key players involved in initiating the inflammatory cascade following injury. By their ability to secrete cytokines, chemokines, and growth factors and their ability to acquire new morphology, the astrocytes and microglia influence the local microenvironment of the injured tissue. Thus, they determine the extent of damage and repair following injury.

The role of glial cells in terms of damage versus repair has been considered ambiguous in the past (Pekny et al. 2014; Rust and Kaiser 2017). On one hand,

several authors have reported the pro-inflammatory and the detrimental aspects of the astrocytes and microglia toward axonal growth (Kitayama et al. 2011; Qian et al. 2019) following injury; on the other hand, studies have also shown the astrocytic and microglial response to injury to be beneficial for restricting damage and improving functional outcome (White et al. 2008; Mukaino et al. 2010). Over the years with the development in cellular and molecular techniques, it has become evident that the astrocytes and microglia are highly heterogeneous and their distinct subtypes are implicated in distinct cellular/molecular processes following injury (Anderson et al. 2014; Karve et al. 2016). However, very little is known about how and which subtypes are involved in the different functions. It is not established whether they are present in a continuum at the injury site or they have distinct topographical locations, which subtypes are involved in a particular type of injury such as spinal cord injury (SCI) or traumatic brain injury (TBI), or whether they get activated at different time points following injury. At this time, there are more questions than answers regarding the precise role of astrocytic and microglial subtypes following CNS injury. The following section has been designed to develop a comprehensive understanding of the astrocytic and microglial subtypes instrumental in the course of brain injury and the existing gaps in knowledge.

2.1 Astrocytes Following CNS Injury

Following trauma to the CNS, astrocytes undergo a series of structural, functional, cellular, molecular, as well as genetic changes collectively known as *astrogliosis* or *reactive astrocytosis* (Sofroniew and Vinters 2010). Astrogliosis occurs in all types of CNS injuries and involves complex interactions between astrocytes, neurons, other glial cells such as microglia, and the peripheral cells that enter the CNS through the bloodstream. This response is dependent on the severity of injury and is regulated specifically in different contexts via inter- and intracellular signaling molecules. Astrogliosis significantly alters astrocytic activities and plays an important role in determining the functional outcome in the long term following the insult. Three categories of astrogliosis have been reported in literature (Sofroniew and Vinters 2010) based on the severity of injury as well as the structural and molecular changes in the astrocytes: (a) mild/moderate, (b) severe diffuse, and (c) severe astrogliosis with glial scar formation (summarized in Table 22.1).

2.2 Astrocytic Subtypes in the Injury Response

Reactive astrocytosis was originally characterized by morphological changes in astrocytes such as hypertrophy and process remodeling as well as pronounced change in the expression of the intermediate filament, glial fibrillary acidic protein (GFAP) (Eng and Ghirnikar 1994). However, accumulating evidence from genetic studies over the course of years revealed that astrocytes have an ability to acquire several different types of morphologies and express several activation markers

Table 22.1 Categories of astrogliosis (adapted from Sofroniew and Vinters 2010)

	Mild/moderate astrogliosis	Severe diffuse astrogliosis	Severe astrogliosis with glial scar formation
Insult type	Mild injury, contusive injury, innate immune activation (diffuse)	Chronic neurodegeneration, diffuse injury and ischemia, infection	Inflammation following injury, stroke, infection, autoimmune diseases, neurodegenerative diseases
Astrocyte proliferation	No proliferation	Dispersed proliferation	Pronounced proliferation
Astrocyte topography	Distant to the injury site	Occur diffusely over substantial area	Astrocytic processes form compact scar borders that surround the injury site
Change in the gene expression of astrocytes	Pronounced change in gene expression	Pronounced change in gene expression	Pronounced change in gene expression
Morphological changes in astrocytes	Hypertrophy of cell body as well as the processes	Pronounced hypertrophy of cell body as well as the processes	Elongated cell bodies and processes
Change in individual astrocytic domain	No change	Some loss of the individual astrocytic domains	Astrocytic processes intertwine extensively

following the insult (Sofroniew 2014). Reactive astrocytes can upregulate GFAP to a similar extent following different stimuli and still can show different cell functions. Thus, a simple measure such as GFAP upregulation is not a good marker for astrocyte reactivity (Sofroniew 2014).

Reactive astrocytes depict heterogeneity at multiple levels (Sofroniew and Vinters 2010), and the astrocytic response to injury depends on their location with respect to the injury site, the activation state of astrocytes, and the signals they receive from their immediate environment as well as the maturation state of astrocytes (Sofroniew 2014). Several classifications of astrocytes following injury have recently been established. The following are the different types of astrocytes described in the literature that are implicated in the CNS injury response:

- **A1 versus A2 astrocytes:** Microarray profiling studies have classified reactive astrocytes into two types, namely, A1 and A2 astrocytes, depending on their mode of activation (Lin et al. 2004; Liddelow et al. 2017). According to this classification, A1 astrocytes are generated following inflammation or through the induction of inflammatory mediators such as TNFα, C1q, IL1, etc. A1 astrocytes have been demonstrated to be of pro-inflammatory nature and have been characterized to be neurotoxic to the growth of axons following injury (Liddelow et al. 2017). On the other hand, activation of astrocytes by ischemia results in A2 astrocytes (Lin et al. 2004). A2 astrocytes have been demonstrated to upregulate neurotrophic factors and thrombospondins which likely promote the survival and

growth of neurons and synapse repair, respectively. Hence, these astrocytes are considered as beneficial for axonal growth following injury (Liddelow and Barres 2017).

- **Scar forming versus hypertrophic stellate reactive astrocytes:** In another classification, reactive astrocytes are classified as scar forming and hypertrophic stellate astrocytes (Wanner et al. 2013). These astrocytes differ in their proximity to the injury site, morphology, and proliferative ability and are demonstrated to have a different source of origin. Scar forming astrocytes are proliferative astrocytes that are present in close proximity to the injury site. They mostly arise from the proliferation of the local astrocytes. These have an elongated morphology and have overlapping cell processes. These astrocytes have been demonstrated to have high expression of STAT3 (Wanner et al. 2013). Preventing astrocyte proliferation or STAT3 activation has been shown to promote tissue damage indicating that scar forming astrocytes are necessary for repair following CNS injury. Hypertrophic reactive astrocytes are stellate and non-proliferative. They are present distal to the injury site and derive directly from mature local astroglia whose processes overlap far less extensively or remain within the original territories (Wanner et al. 2013).
- **Spatial heterogeneity according to the embryonic sites or origin:** Cell-lineage fate mapping studies have shown that astrocytes are present in the mouse spinal cord in specific spatial domains or locations (Tsai et al. 2012). These localizations are in accordance with the embryonic sites of origin of the astrocytes.

2.3 Gaps in the Knowledge

In the literature, astrogliosis has been depicted to have a dual role (Sofroniew and Vinters 2010; Pekny et al. 2014; Sofroniew 2014). Reactive astrocytes have been shown to interact with both immune and inflammatory cells (Liddelow et al. 2017). Common changes that occur in astrocytes following injury include remodeling of molecular/cellular networks associated with cell morphology, growth, proliferation, and regulation of the cytokine production (Liddelow et al. 2017). Such changes are likely to derive astrocyte functions toward detrimental pro-inflammatory and beneficial trophic interactions with other cells. Whether there is a distinct spatial as well as temporal specialization among reactive astrocytes in this context is still unknown. Which astrocyte subtypes are expressed following specific CNS injuries such as SCI or TBI and where remain to be examined. It is unclear how the A1, A2, scar forming, or hypertrophic astrocytes interact with growing axons and impact their growth. This information is needed to appropriately target the astrocytic response following CNS injuries.

Further, it is still unclear if these astrocytic subtypes have clear distinctions or whether they share overlapping characteristics. Are the hypertrophic reactive astrocytes the same as A1 astrocytes, different astrocytic states, or different gradients of astrocytic activation is not known. Very little is known about the characteristics of astrocytes having different sources of origin. Not much is known about whether

reactive astrocytes derived from different precursor lineages might exhibit different characteristics or not. Such observations raise important questions about characterizing the signaling mechanisms or the gradients of cellular changes that create such heterogeneity.

2.4 Microglia Following CNS Injury

Microglia are dynamic cells that constantly survey the CNS environment for potential injury or insult (Kraft and Harry 2011). They are implicated in mounting an immune response after CNS injury. Similar to astrocytes, microglia also undergo several morphological and gene expression changes following injury which influence the damage versus repair effect (Loane and Byrnes 2010). The acute function of microglia following CNS injury is the removal of cellular/molecular debris (Kawabori and Yenari 2015). Generally, in the uninjured tissue, the resting or quiescent microglia have a ramified morphology (Glenn et al. 1992). Microglia at this stage have been shown to express receptors that recognize factors associated with tissue damage such as ATP, glutamate, growth factors, and cytokines (Jin and Yamashita 2016). Following CNS injury, the microglia acquire a hypertrophic or bushy morphology and upregulate the expression of the ionized calcium binding adaptor molecule 1 (Iba-1) and cluster of differentiation 68 (CD68) which promote active phagocytosis of the cellular debris (Jin and Yamashita 2016). This removal of damaged cells by microglia is very important for the restoration of the normal CNS functions as the factors released from the injured cells such as the Danger-associated molecular patterns (DAMPs) can promote considerable inflammation in the tissue (Roh and Sohn 2018). However, activated microglia, especially after chronic activation, have been shown to express noxious substances such as reactive oxygen species, reactive nitrogen species, excitatory neurotransmitters such as glutamate, as well as the pro-inflammatory cytokines which can lead to direct neurotoxic effects on growing axons (Kreutzberg 1996). The pro-inflammatory cytokines as well as the glutamate released by microglia also interfere with the normal functioning of the astrocytes (Takaki et al. 2012). Further, the microglial response following CNS injury has been shown to be context specific, i.e., dependent upon both the timing and the nature of the injury (Davalos et al. 2005).

2.5 Microglial Subtypes in the Injury Response

Similar to the astrocytes, microglial activation following CNS injury results in different phenotypes (Jin and Yamashita 2016). These phenotypes have been shown to correspond to both neurotoxic and neuroprotective priming states depending on the stage of the disease and the chronicity (Loane and Byrnes 2010; Kawabori and Yenari 2015; Jin and Yamashita 2016; Rust and Kaiser 2017). The following are the two types of microglia that have been shown to be implicated in the CNS injury response:

1. **Classically activated, M1 microglia:** M1 microglia are activated in situ by the pro-inflammatory cytokines such as IFN-γ, IL-1α, IL-6, and TNF-α. The M1 phenotype is implicated in secondary damage and scar formation following CNS injury (Hu et al. 2015). These microglia produce pro-inflammatory cytokines that are destructive to the growth of axons following injury. M1 microglia have been shown to be attracted more by the astrocyte enriched medium suggesting them to be more involved with the astrocytic interactions (Kirkley et al. 2017).
2. **Alternatively activated, M2 microglia:** The M2 phenotype of microglia is shown to be produced by activation with IL-4 and IL-13 (Jin and Yamashita 2016). M2 microglia are implicated in the phagocytosis after CNS injury. M2 microglia have been shown to produce scavenger receptors, growth factors such as TGF-β, and the anti-inflammatory cytokine IL-10 that are beneficial for axonal growth and repair following injury (Michelucci et al. 2009). M2 microglia are less inflammatory and more mobile than M1 microglia. These microglia have been shown to be attracted more by the neuron enriched medium (Matsui and Mori 2018).

2.6 Gaps in the Knowledge

The polarization of microglia following CNS injury is a highly dynamic process. Transcriptomic studies have revealed that microglia display a much broader transcriptional repertoire than M1 and M2 (Hickman et al. 2013; Xue et al. 2014). The polarization state can be dynamically altered depending on the severity of the insult, time following the injury, as well as the microenvironment. Many animal studies following TBI have shown a mixed expression of different markers associated with both M1 and M2 phenotypes (Kumar et al. 2016). Furthermore, several reports have suggested the microglial polarization to be a spectrum (Butovsky et al. 2005; Schwartz et al. 2006) rather than into two distinct groups (M1 or M2). Collectively, this suggests the *need to further characterize the polarization properties* of microglia specifically.

2.7 Remarks

The microenvironment following CNS injury implicates astrocytes and microglia in states that cannot be understood in the terms of typical immunological reactions. Whether astrocytes and microglia adopt a neurotoxic or neuroprotective role following injury depends on a number of factors such as the injury cause, severity and time course of injury, and the chemical signals present in the environment. The response depends on the heterogeneous subtypes involved as well as the bidirectional conversation between these subtypes. The languages of microglia and astrocytic subtypes will be the key to understand this complex system composed of cells of prodigious diversity as well as plasticity.

References

Anderson MA, Ao Y, Sofroniew MV (2014) Heterogeneity of reactive astrocytes. Neurosci Lett 565:23–29

Barrientos RM, Higgins EA, Sprunger DB, Watkins LR, Rudy JW, Maier SF (2002) Memory for context is impaired by a post context exposure injection of interleukin-1 beta into dorsal hippocampus. Behav Brain Res 134(1–2):291–298

Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC (2014) Inflammatory mediators of cognitive impairment in bipolar disorder. J Psychiatr Res 56:18–27

Baune BT, Wiede F, Braun A, Golledge J, Arolt V, Koerner H (2008) Cognitive dysfunction in mice deficient for TNF-and its receptors. Am J Med Genet B Neuropsychiatr Genet 147(7): 1056–1064

Benedetti F, Poletti S, Hoogenboezem TA, Mazza E, Ambrée O, de Wit H, Wijkhuijs AJ, Locatelli C, Bollettini I, Colombo C, Arolt V (2016) Inflammatory cytokines influence measures of white matter integrity in bipolar disorder. J Affect Disord 202:1–9

Bobińska K, Gałecka E, Szemraj J, Gałecki P, Talarowska M (2017) Is there a link between TNF gene expression and cognitive deficits in depression? Acta Biochim Pol 64(1):65–73

Butovsky O, Talpalar AE, Ben-Yaakov K, Schwartz M (2005) Activation of microglia by aggregated β-amyloid or lipopolysaccharide impairs MHC-II expression and renders them cytotoxic whereas IFN-γ and IL-4 render them protective. Mol Cell Neurosci 29(3):381–393

Calabrese F, Rossetti AC, Racagni G, Gass P, Riva MA, Molteni R (2014) Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. Front Cell Neurosci 8:430

Camara ML, Corrigan F, Jaehne EJ, Jawahar MC, Anscomb H, Koerner H, Baune BT (2013) TNF-α and its receptors modulate complex behaviours and neurotrophins in transgenic mice. Psychoneuroendocrinology 38(12):3102–3114

Chang HH, Lee IH, Gean PW, Lee SY, Chi MH, Yang YK, Lu RB, Chen PS (2012) Treatment response and cognitive impairment in major depression: association with C-reactive protein. Brain Behav Immun 26(1):90–95

Chen CY, Tzeng NS, Chen YC (2010) Maintenance therapy of celecoxib for major depression with mimicking neuropsychological dysfunction. Gen Hosp Psychiatry 32(6):647.e7–647.e9

Chung WS, Welsh CA, Barres BA, Stevens B (2015) Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci 18(11):1539–1545

Czéh B, Lucassen PJ (2007) What causes the hippocampal volume decrease in depression? Eur Arch Psychiatry Clin Neurosci 257(5):250–260

Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB (2005) ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci 8(6): 752–758

Dickerson F, Stallings C, Origoni A, Vaughan C, Khushalani S, Yolken R (2013) Elevated C-reactive protein and cognitive deficits in individuals with bipolar disorder. J Affect Disord 150(2):456–459

Eng LF, Ghirnikar RS (1994) GFAP and astrogliosis. Brain Pathol 4(3):229–237

Fiore M, Angelucci F, Alleva E, Branchi I, Probert L, Aloe L (2000) Learning performances, brain NGF distribution and NPY levels in transgenic mice expressing TNF-alpha. Behav Brain Res 112(1–2):165–175

Fourrier C, Singhal G, Baune BT (2019) Neuroinflammation and cognition across psychiatric conditions. CNS Spectr 24(1):4–15

Fries GR, Vasconcelos-Moreno MP, Gubert C, Santos BT, Sartori J, Eisele B, Ferrari P, Fijtman A, Rüegg J, Gassen NC, Kapczinski F (2015) Hypothalamic-pituitary-adrenal axis dysfunction and illness progression in bipolar disorder. Int J Neuropsychopharmacol 18(1):pyu043

Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GD, Rumley A, Marmot MG, Ferrie JE (2009) Associations of C-reactive protein and interleukin-6

with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med 39(3):413–423
Glenn JA, Ward SA, Stone CR, Booth PL, Thomas WE (1992) Characterisation of ramified microglial cells: detailed morphology, morphological plasticity and proliferative capability. J Anat 180:109–118
Goldsmith DR, Haroon E, Woolwine BJ, Jung MY, Wommack EC, Harvey PD, Treadway MT, Felger JC, Miller AH (2016) Inflammatory markers are associated with decreased psychomotor speed in patients with major depressive disorder. Brain Behav Immun 56:281–288
Goshen I, Kreisel T, Ounallah-Saad H, Renbaum P, Zalzstein Y, Ben-Hur T, Levy-Lahad E, Yirmiya R (2007) A dual role for interleukin-1 in hippocampal-dependent memory processes. Psychoneuroendocrinology 32(8–10):1106–1115
Haarman BC, Riemersma-Van der Lek RF, de Groot JC, Ruhé HG, Klein HC, Zandstra TE, Burger H, Schoevers RA, de Vries EF, Drexhage HA, Nolen WA (2014) Neuroinflammation in bipolar disorder–a [11C]-(R)-PK11195 positron emission tomography study. Brain Behav Immun 40:219–225
Halassa MM, Haydon PG (2010) Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. Annu Rev Physiol 72:335–355
Han X, Chen M, Wang F, Windrem M, Wang S, Shanz S, Xu Q, Oberheim NA, Bekar L, Betstadt S, Silva AJ (2013) Forebrain engraftment by human glial progenitor cells enhances synaptic plasticity and learning in adult mice. Cell Stem Cell 12(3):342–353
Henneberger C, Papouin T, Oliet SH, Rusakov DA (2010) Long-term potentiation depends on release of D-serine from astrocytes. Nature 463(7278):232–236
Hickman SE, Kingery ND, Ohsumi TK, Borowsky ML, Wang LC, Means TK, El Khoury J (2013) The microglial sensome revealed by direct RNA sequencing. Nat Neurosci 16(12):1896–1905
Hope S, Hoseth E, Dieset I, Mørch RH, Aas M, Aukrust P, Djurovic S, Melle I, Ueland T, Agartz I, Ueland T (2015) Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. Schizophr Res 165(2–3): 188–194
Hoseth EZ, Westlye LT, Hope S, Dieset I, Aukrust P, Melle I, Haukvik UK, Agartz I, Ueland T, Ueland T, Andreassen OA (2016) Association between cytokine levels, verbal memory and hippocampus volume in psychotic disorders and healthy controls. Acta Psychiatr Scand 133(1): 53–62
Hryniewicz A, Bialuk I, Kamiński KA, Winnicka MM (2007) Impairment of recognition memory in interleukin-6 knock-out mice. Eur J Pharmacol 577(1–3):219–220
Hu X, Leak RK, Shi Y, Suenaga J, Gao Y, Zheng P, Chen J (2015) Microglial and macrophage polarization—new prospects for brain repair. Nat Rev Neurol 11(1):56–64
Jehn CF, Becker B, Flath B, Nogai H, Vuong L, Schmid P, Lüftner D (2015) Neurocognitive function, brain-derived neurotrophic factor (BDNF) and IL-6 levels in cancer patients with depression. J Neuroimmunol 287:88–92
Jin X, Yamashita T (2016) Microglia in central nervous system repair after injury. J Biochem 159(5):491–496
Karve IP, Taylor JM, Crack PJ (2016) The contribution of astrocytes and microglia to traumatic brain injury. Br J Pharmacol 173(4):692–702
Kaur T, Kaur G (2017) *Withania somnifera* as a potential candidate to ameliorate high fat diet-induced anxiety and neuroinflammation. J Neuroinflammation 14(1):201
Kaur T, Singh H, Mishra R, Manchanda S, Gupta M, Saini V, Sharma A, Kaur G (2017) *Withania somnifera* as a potential anxiolytic and immunomodulatory agent in acute sleep deprived female Wistar rats. Mol Cell Biochem 427(1–2):91–101
Kawabori M, Yenari MA (2015) The role of the microglia in acute CNS injury. Metab Brain Dis 30(2):381–392
Kirkley KS, Popichak KA, Afzali MF, Legare ME, Tjalkens RB (2017) Microglia amplify inflammatory activation of astrocytes in manganese neurotoxicity. J Neuroinflammation 14(1):99

Kitayama M, Ueno M, Itakura T, Yamashita T (2011) Activated microglia inhibit axonal growth through RGMa. PLoS One 6(9):e25234

Kraft AD, Harry GJ (2011) Features of microglia and neuroinflammation relevant to environmental exposure and neurotoxicity. Int J Environ Res Public Health 8(7):2980–3018

Kreutzberg GW (1996) Microglia: a sensor for pathological events in the CNS. Trends Neurosci 19(8):312–318

Kumar A, Alvarez-Croda DM, Stoica BA, Faden AI, Loane DJ (2016) Microglial/macrophage polarization dynamics following traumatic brain injury. J Neurotrauma 33(19):1732–1750

Laskaris LE, Di Biase MA, Everall I, Chana G, Christopoulos A, Skafidas E, Cropley VL, Pantelis C (2016) Microglial activation and progressive brain changes in schizophrenia. Br J Pharmacol 173(4):666–680

Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, Fennig S, Treves I, Kron S (2010) A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 71(2):138–149

Liddelow SA, Barres BA (2017) Reactive astrocytes: production, function, and therapeutic potential. Immunity 46(6):957–967

Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541(7638):481–487

Lin TN, Wang Q, Simonyi A, Chen JJ, Cheung WM, He Y, Xu J, Sun AY, Hsu CY, Sun GY (2004) Induction of secretory phospholipase A2 in reactive astrocytes in response to transient focal cerebral ischemia in the rat brain. J Neurochem 90(3):637–645

Liu M, Li J, Dai P, Zhao F, Zheng G, Jing J, Wang J, Luo W, Chen J (2015) Microglia activation regulates GluR1 phosphorylation in chronic unpredictable stress-induced cognitive dysfunction. Stress 18(1):96–106

Loane DJ, Byrnes KR (2010) Role of microglia in neurotrauma. Neurotherapeutics 7(4):366–377

Maggi L, Scianni M, Branchi I, D'Andrea I, Lauro C, Limatola C (2011) CX3CR1 deficiency alters hippocampal-dependent plasticity phenomena blunting the effects of enriched environment. Front Cell Neurosci 5:22

Mahati K, Bhagya V, Christofer T, Sneha A, Rao BSS (2016) Enriched environment ameliorates depression-induced cognitive deficits and restores abnormal hippocampal synaptic plasticity. Neurobiol Learn Mem 134:379–391

Manchanda S, Kaur G (2017) *Withania somnifera* leaf alleviates cognitive dysfunction by enhancing hippocampal plasticity in high fat diet induced obesity model. BMC Complement Altern Med 17(1):136

Manchanda S, Mishra R, Singh R, Kaur T, Kaur G (2017) Aqueous leaf extract of *Withania somnifera* as a potential neuroprotective agent in sleep-deprived rats: a mechanistic study. Mol Neurobiol 54(4):3050–3061

Matsui TK, Mori E (2018) Microglia support neural stem cell maintenance and growth. Biochem Biophys Res Commun 503(3):1880–1884

Michelucci A, Heurtaux T, Grandbarbe L, Morga E, Heuschling P (2009) Characterization of the microglial phenotype under specific pro-inflammatory and anti-inflammatory conditions: effects of oligomeric and fibrillar amyloid-β. J Neuroimmunol 210(1–2):3–12

Mishra R, Manchanda S, Gupta M, Kaur T, Saini V, Sharma A, Kaur G (2016) *Tinospora cordifolia* ameliorates anxiety-like behavior and improves cognitive functions in acute sleep deprived rats. Sci Rep 6:25,564

Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D (2018) Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: a systematic review. Schizophr Res 192:16–29

Monji A, Kato T, Kanba S (2009) Cytokines and schizophrenia: microglia hypothesis of schizophrenia. Psychiatry Clin Neurosci 63(3):257–265

Mukaino M, Nakamura M, Yamada O, Okada S, Morikawa S, Renault-Mihara F, Iwanami A, Ikegami T, Ohsugi Y, Tsuji O, Katoh H (2010) Anti-IL-6-receptor antibody promotes repair of spinal cord injury by inducing microglia-dominant inflammation. Exp Neurol 224(2):403–414

Müller N (2008) Inflammation and the glutamate system in schizophrenia: implications for therapeutic targets and drug development. Expert Opin Ther Targets 12(12):1497–1507

Müller N, Riedel M, Schwarz MJ, Engel RR (2005) Clinical effects of COX–2 inhibitors on cognition in schizophrenia. Eur Arch Psychiatry Clin Neurosci 255(2):149–151

Nimmerjahn A, Kirchhoff F, Helmchen F (2005) Resting microglial cells are highly dynamic surveillants of brain parenchyma in vivo. Science 308(5726):1314–1318

O'Connor JC, André C, Wang Y, Lawson MA, Szegedi SS, Lestage J, Castanon N, Kelley KW, Dantzer R (2009) Interferon-γ and tumor necrosis factor-α mediate the upregulation of indoleamine 2, 3-dioxygenase and the induction of depressive-like behavior in mice in response to bacillus Calmette-Guérin. J Neurosci 29(13):4200–4209

Pace TW, Miller AH (2009) Cytokines and glucocorticoid receptor signaling: relevance to major depression. Ann N Y Acad Sci 1179:86–105

Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR III, Lafaille JJ, Hempstead BL, Littman DR, Gan WB (2013) Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155(7):1596–1609

Pekny M, Wilhelmsson U, Pekna M (2014) The dual role of astrocyte activation and reactive gliosis. Neurosci Lett 565:30–38

Qian D, Li L, Rong Y, Liu W, Wang Q, Zhou Z, Gu C, Huang Y, Zhao X, Chen J, Fan J (2019) Blocking notch signal pathway suppresses the activation of neurotoxic A1 astrocytes after spinal cord injury. Cell Cycle 18(21):3010–3029

Rogers JT, Morganti JM, Bachstetter AD, Hudson CE, Peters MM, Grimmig BA, Weeber EJ, Bickford PC, Gemma C (2011) CX3CR1 deficiency leads to impairment of hippocampal cognitive function and synaptic plasticity. J Neurosci 31(45):16241–16250

Roh JS, Sohn DH (2018) Damage-associated molecular patterns in inflammatory diseases. Immune Netw 18(4):e27

Rolstad S, Jakobsson J, Sellgren C, Isgren A, Ekman CJ, Bjerke M, Blennow K, Zetterberg H, Pålsson E, Landén M (2015) CSF neuroinflammatory biomarkers in bipolar disorder are associated with cognitive impairment. Eur Neuropsychopharmacol 25(8):1091–1098

Rust R, Kaiser J (2017) Insights into the dual role of inflammation after spinal cord injury. J Neurosci 37(18):4658–4660

Şahin TD, Karson A, Balcı F, Yazır Y, Bayramgürler D, Utkan T (2015) TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression. Behav Brain Res 292:233–240

Schwartz M, Butovsky O, Brück W, Hanisch UK (2006) Microglial phenotype: is the commitment reversible? Trends Neurosci 29(2):68–74

Singh H, Bajaj P, Kalotra S, Bhandari A, Kaur T, Singh AP, Kaur G (2021) *Tinospora cordifolia* ameliorates brain functions impairments associated with high fat diet induced obesity. Neurochem Int 143:104937

Singhal G, Baune BT (2017) Microglia: an interface between the loss of neuroplasticity and depression. Front Cell Neurosci 11:270

Sofroniew MV (2014) Astrogliosis. Cold Spring Harb Perspect Biol 7(2):a020420

Sofroniew MV, Vinters HV (2010) Astrocytes: biology and pathology. Acta Neuropathol 119(1): 7–35

Stellwagen D, Malenka RC (2006) Synaptic scaling mediated by glial TNF-α. Nature 440(7087): 1054–1059

Takaki J, Fujimori K, Miura M, Suzuki T, Sekino Y, Sato K (2012) L-glutamate released from activated microglia downregulates astrocytic L-glutamate transporter expression in neuroinflammation: the 'collusion'hypothesis for increased extracellular L-glutamate concentration in neuroinflammation. J Neuroinflammation 9:275

Tani H, Dulla CG, Farzampour Z, Taylor-Weiner A, Huguenard JR, Reimer RJ (2014) A local glutamate-glutamine cycle sustains synaptic excitatory transmitter release. Neuron 81(4): 888–900

Thrane VR, Thrane AS, Wang F, Cotrina ML, Smith NA, Chen M, Xu Q, Kang N, Fujita T, Nagelhus EA, Nedergaard M (2013) Ammonia triggers neuronal disinhibition and seizures by impairing astrocyte potassium buffering. Nat Med 19(12):1643–1648

Too LK, Li KM, Suarna C, Maghzal GJ, Stocker R, McGregor IS, Hunt NH (2016) Deletion of TDO2, IDO-1 and IDO-2 differentially affects mouse behavior and cognitive function. Behav Brain Res 312:102–117

Tremblay MÈ, Lowery RL, Majewska AK (2010) Microglial interactions with synapses are modulated by visual experience. PLoS Biol 8(11):e1000527

Tsai HH, Li H, Fuentealba LC, Molofsky AV, Taveira-Marques R, Zhuang H, Tenney A, Murnen AT, Fancy SP, Merkle F, Kessaris N (2012) Regional astrocyte allocation regulates CNS synaptogenesis and repair. Science 337(6092):358–362

Ullian EM, Sapperstein SK, Christopherson KS, Barres BA (2001) Control of synapse number by glia. Science 291(5504):657–661

Verkhratsky A, Nedergaard M, Hertz L (2015) Why are astrocytes important? Neurochem Res 40(2):389–401

Wanner IB, Anderson MA, Song B, Levine J, Fernandez A, Gray-Thompson Z, Ao Y, Sofroniew MV (2013) Glial scar borders are formed by newly proliferated, elongated astrocytes that interact to corral inflammatory and fibrotic cells via STAT3-dependent mechanisms after spinal cord injury. J Neurosci 33(31):12870–12886

Watson S, Gallagher P, Porter RJ, Smith MS, Herron LJ, Bulmer S, Young AH, Ferrier IN, North-East Mood Disorders Clinical Research Group (2012) A randomized trial to examine the effect of mifepristone on neuropsychological performance and mood in patients with bipolar depression. Biol Psychiatry 72(11):943–949

White RE, Yin FQ, Jakeman LB (2008) TGF-α increases astrocyte invasion and promotes axonal growth into the lesion following spinal cord injury in mice. Exp Neurol 214(1):10–24

Williamson LL, Bilbo SD (2013) Chemokines and the hippocampus: a new perspective on hippocampal plasticity and vulnerability. Brain Behav Immun 30:186–194

Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H (2014) Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. Immunity 40(2):274–288

Zhang Y, Chen K, Sloan SA, Bennett ML, Scholze AR, O'Keeffe S, Phatnani HP, Guarnieri P, Caneda C, Ruderisch N, Deng S (2014) An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J Neurosci 34(36): 11929–11947