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Chemokines and the hippocampus: A new perspective on hippocampal plasticity and vulnerability

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ABSTRACT

The hippocampus is critical for several aspects of learning and memory and is unique among other cortical regions in structure, function and the potential for plasticity. This remarkable region recapitulates development throughout the lifespan with enduring neurogenesis and well-characterized plasticity. The structure and traits of the hippocampus that distinguish it from other brain regions, however, may be the same reasons that this important brain region is particularly vulnerable to insult and injury. The immune system within the brain responds to insult and injury, and the hippocampus and the immune system are extensively interconnected. Immune signaling molecules, cytokines and chemokines (chemotactic cytokines), are well known for their functions during insult or injury. They are also increasingly implicated in normal hippocampal neurogenesis (e.g., CXCR4 on newborn neurons), cellular plasticity (e.g., interleukin-6 in LTP maintenance), and learning and memory (e.g., interleukin-1β in fear conditioning). We provide evidence from the small but growing literature that neuroimmune interactions and immune signaling molecules, especially chemokines, may be a primary underlying mechanism for the coexistence of plasticity and vulnerability within the hippocampus. We also highlight the evidence that the hippocampus exhibits a remarkable resilience in response to diverse environmental events (e.g., enrichment, exercise), which all may converge onto common neuroimmune mechanisms.

1. Introduction

The brain and the immune system are extensively interconnected and each cannot function without the other. Molecules once thought to function exclusively within the peripheral immune system are required for many normal functions within the central nervous system (CNS). The hippocampus is critical for learning and memory, and its unusual structure and signaling properties may underlie its important role in cognition. The hippocampus is incredibly plastic, especially as one of only two robust neurogenic regions in the mature brain (Altman, 1969; Altman and Das, 1966). This region is also remarkably vulnerable to injury, insult, and CNS disorders, such as ischemia (Franklin et al., 2003; Horn and Schlote, 1992; Pulsinelli et al., 1982) and Alzheimer's disease (AD; Araujo and Lapchak, 1994; Selkoe, 2001; Small et al., 2011). This paradoxical combination led Bruce McEwen to propose years ago that the vulnerability of the hippocampus is directly related to its incredible plasticity (1994). He hypothesized that the connection between vulnerability and plasticity was via the double-edged sword of adrenal steroids and their effects on hippocampal neurogenesis and long-term potentiation (LTP) in opposition with their effects on stress pathways through the hippocampus (McEwen, 1994). We propose in this review that the basal function of immune molecules in the normally functioning hippocampus may be another mechanism that directly connects its unique plasticity and vulnerability.

There is now a well-recognized link between environmental disruption and hippocampal dysfunction due to the impact of immune processes on neural function within the brain, including the activation of microglia and astrocytes, the infiltration of peripheral leukocytes such as T cells into the brain, and soluble messengers such as cytokines, chemokines (chemotactic cytokines), prostaglandins, and reactive oxygen species, among others (Cunningham and De Souza, 1993; Yenari et al., 2010; Yirmiya and Goshen, 2011b; Yokoyama et al., 2011). This has led to the erroneous belief that immune molecules are only present or active within the brain during pathology (e.g., neuron death), or when the dysregulation of the immune system occurs (e.g., autoimmunity). However, there is increasing support for the notion that normal hippocampal function requires a basal level of neuroimmune signaling. Cytokines now have demonstrated roles in learning and memory (Avital et al., 2003; Ben Menachem-Zidon et al., 2008, 2011; Goshen et al., 2007; Williamson et al., 2011), synaptic plasticity (e.g., LTP) (Balschun et al., 2004; Jankowsky et al., 2000) and

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neurogenesis (Bhattacharyya et al., 2008): all critical functions of the hippocampus throughout life. Moreover, immune molecules are important for the developing brain, in the guidance of synaptogenesis (Tremblay and Majewska, 2011; Tremblay et al., 2011), synaptic pruning (Goddard et al., 2007; Schafer et al., 2012; Shatz, 2009; Stephan et al., 2012; Stevens et al., 2007), and neural migration (Addison et al., 2000; Dziembowska et al., 2005; Imitola et al., 2004; Tran et al., 2004, 2007), among numerous other functions (Deverman and Patterson, 2009).

Notably, the hippocampus recapitulates developmental processes, specifically neurogenesis, well into adulthood. We propose that it is for this reason – its enduring pseudo-developmental phenotype, combined with its remarkable ongoing plasticity – that the hippocampus is uniquely sensitive to perturbations in the environment, and moreover, that immune molecules are critical players in this dichotomy. The role of chemokines in these processes will be our primary focus in this review; their influence on hippocampal plasticity and vulnerability has been explored primarily at the cellular and molecular level, and only recently have the tools to properly assess these molecules during behavioral tasks become available.

Our working hypothesis is that the hippocampus lies at a crossroads between vulnerability and resilience for two reasons: (1) the hippocampus displays a high degree of cellular plasticity, and is unique among cortical structures in that it recapitulates development throughout the lifespan of the organism, and (2) immune molecules, such as cytokines and chemokines, are critical for normal brain development, including cellular differentiation, migration, and connectivity, processes that occur continuously in the hippocampus. Thus, the dysregulation of these molecules can lead to profound pathology. Given the diffuse signaling properties of immune molecules inside and outside the CNS, we propose neuroimmune crosstalk is a direct link between diverse environmental disruptions (e.g., stress, infection, and trauma) and hippocampal vulnerability on the one hand; and between interventions (e.g., exercise, nutrition, and social factors) and improved hippocampal function or resilience on the other.

2. Neuroimmune crosstalk

Immunocompetent cells are located throughout virtually every organ of the body, including the brain and other endocrine tissues, and sophisticated interactions occur among these cells, via hormones, neurotransmitters, and members of the cytokine super families, including interleukins [IL], interferons [IFN], tumor necrosis factors [TNF], chemokines, "cytokine-like" hormones (e.g., leptin, growth hormone), and many others. Though immune processes within the brain are not identical to those occurring in the periphery, microglia produce cytokines and other inflammatory molecules in response to disturbances in homeostasis in a manner similar to peripheral immune cells. Other CNS cells, including perivascular macrophages, astrocytes, endothelial cells, oligodendrocytes, and neurons also produce cytokines and chemokines and express their receptors under varying circumstances that remain to be fully defined (Mantovani et al., 1992; Sawada et al., 1993; Tyor et al., 1992; Wong and Licinio, 1994). In addition to resident immunocompetent cells, there are multiple pathways by which peripherally-derived immune factors can affect the brain, and in turn by which the brain can impact peripheral immune responses. These include the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis, which have been extensively reviewed (Bellinger et al., 2008; Costa-Pinto and Palermo-Neto, 2010; Dantzer et al., 2000; Elenkov et al., 2000; Webster Marketon and Glaser, 2008; Nance and Sanders, 2007; Rabin et al., 1990; Rivest, 2010; Schiltz and Sawchenko, 2003; Turnbull and Rivier, 1999). Cytokines are produced within the brain in response to virtually any perturbation of CNS homeostasis, including trauma, stroke, ischemia, neurodegeneration, or infection (Ban et al., 1993; Hopkins and Rothwell, 1995; Rothwell and Hopkins, 1995). Cytokines are also produced within the brain in response to peripheral cytokine production or infectious stimuli, indicating that cytokine signals are transmitted from the periphery into the brain. This transmission may occur via several routes, including: (a) neurotransmission following cytokine binding to their receptors on vagal afferents (Andersson and Tracey, 2012; Dantzer et al., 1998; Ericsson et al., 1995; Goehler et al., 2000; Johnston and Webster, 2009); (b) signaling across the blood-brain-barrier (BBB) – e.g., via endothelial cells, astrocytes, and microglia within the BBB that recapitulate the immune signal from the periphery by secreting their own cohort of cytokines into the brain (Skaper et al., 2012; Verma et al., 2006; Wiese et al., 2012); (c) crossing into the brain at circumventricular organs where the BBB is permeable or leaky (e.g., area postrema (Wuchert et al., 2008)); or (d) active transport across the BBB by specialized transporters (Banks and Erickson, 2010; Banks et al., 1995). These routes of transmission have been reviewed previously (Banks and Erickson, 2010; Banks et al., 1995; Dantzer and Kelley, 2007a; Maier and Watkins, 1998; Mignini et al., 2003; Quan and Banks, 2007; Rivest, 2003; Wrona, 2006). Important for this review is that cytokines and chemokines have critical neuromodulatory properties within the brain during normal brain function (Brenneman et al., 1992; Hanisch, 2002; Williamson et al., 2011), including homeostatic functions such as sleep and metabolism (Farrar et al., 1987; Kubota et al., 2000; Vitkovic et al., 2000; Yirmiya and Goshen, 2011a), and, notably, hippocampal development, plasticity, and function.

3. Hippocampal plasticity in the healthy brain

The hippocampus has been studied as an individual entity for decades. Its gross anatomical structure fascinated ancient scientists and its unique layout and interconnectivity continue to fascinate modern-day scientists in many fields, from psychology to molecular biology (Bliss et al., 2007a). While the attraction to this curious cortical structure arises from many different fields of study, the importance of the hippocampus stems from its distinctiveness in the cortex. The hippocampus is a critical neural substrate for many expressions of learning and memory and offers a unique, well-studied region for understanding brain function (Morris, 2007), development (Frotscher and Seress, 2007) and plasticity (Bliss et al., 2007b; Gould, 2007).

The major neuronal cells of the hippocampus – pyramidal and granule cells – are organized in clear layers and their inputs are well-characterized. The hippocampus has primarily unidirectional inputs rather than the radial connectivity (or crosstalk) that occurs in the rest of the cortex (Amaral and Lavenex, 2007). The dentate gyrus (DG) has a steady level of neurogenesis throughout the lifespan, whereas the cortex has limited, if any, generation of new neurons (Altman and Bayer, 1990; Altman and Das, 1966). The hippocampus receives an incredible number of processed sensory inputs from many neocortical regions and further processes these inputs unidirectionally through the hippocampal formation (Amaral and Lavenex, 2007). The entorhinal cortex (EC) projects to the DG, where information is sparsely encoded by a small population of granule cells (Jung and McNaughton, 1993; Leutgeb et al., 2007; O'Reilly and McClelland, 1994). The DG then projects to the CA3 (*cornu ammonis 3*), which, in turn, projects to the CA1. The CA1 region, thought to organize inputs in a linear fashion (Guzowski et al., 2004; Mizumori et al., 1989), then projects to the subiculum and onto the EC or directly to layer VI of the EC itself. This particular flow of neuronal signaling within the hippocampus with its limited redundancy may underlie in part both

its critical role in learning and memory as well as its more vulnerable attributes during insults.

4. The vulnerability of the hippocampus

Activation of peripheral signaling systems, including the immune and endocrine systems, can specifically alter and impair hippocampal function. Our laboratory has long had an interest in how interactions between the brain and immune systems might be altered by the early-life environment, alterations that can impact brain development and, thus, endure through the lifespan. In a model of neonatal *Escherichia coli* infection, rats infected early in life show exaggerated hippocampal IL-1β expression to a subsequent immune challenge (lipopolysaccharide; LPS) in adulthood. Moreover, the LPS challenge selectively impairs hippocampal-dependent memory in these rats made vulnerable by the neonatal infection; i.e., memories that do *not* depend on the hippocampus remain unperturbed (Bilbo et al., 2005a; Bilbo et al., 2005b; Williamson et al., 2011). Neonatal exposure to endotoxin (LPS) also impairs hippocampal-dependent memory and attenuates the adult neuroimmune response to similar pathogens (Kohman et al., 2008). Endotoxin exposure likewise disrupts learning and memory in previously unexposed adult mice (Kranjac et al., 2012). Similarly, postnatal infections increase hippocampal seizure susceptibility following administration of convulsants in adulthood (e.g., kainic acid), as well as hippocampal excitability *in vitro* (Galic et al., 2008; Riazi et al., 2010). Peripheral gut inflammation in adult rats increases seizure susceptibility and microglial activation in the hippocampus (Riazi et al., 2008). Other types of peripheral infection have similar effects on the hippocampus. Adult mice exposed to the influenza virus exhibit altered DG granule cell dendrite morphology, increased reactivity of microglia in the DG, increased cytokine and decreased growth factor mRNA expression within the hippocampus, and impairments in the Morris Water Maze task, a hippocampal-dependent learning and memory paradigm (Jurgens et al., 2012). These selective effects on the hippocampus are not only apparent early in life and young adulthood: peripheral infection impairs long-term hippocampal dependent memory of contextual fear conditioning and long-term memory for a platform location in the water maze in aged rats as well, whereas non-hippocampal dependent functions remain unimpaired (Barrientos et al., 2006). Peripheral infection similarly leads to exaggerated sickness behavior and neuroinflammation within the hippocampus of aged mice (Godbout et al., 2005).

Several pathologies specific to the CNS have more damaging effects in the hippocampus compared to other brain regions as well, including Alzheimer's disease, seizures, and ischemia. The effects of AD on memory processes and hippocampal function are well-characterized, and neuroinflammation and dysregulation of immune signaling within this region are often considered hallmarks of AD. In both the human and rodent literatures, AD patients and model organisms consistently show increased cytokine and chemokine levels as well as increased microglial activation and activity (IL-1β and IL-2 in humans, Araujo and Lapchak, 1994; IL-1β in humans, Griffin et al., 1995; human TNF polymorphisms, Perry et al., 2001; reactive microglia in human subjects, Sheng et al., 1998; TGFβ in mice, Wyss-Coray et al., 2001). Seizures are another disorder that dramatically affects the hippocampus and its function. Immune challenges early in life increase susceptibility to seizures (Galic et al., 2008; Riazi et al., 2008, 2010) and seizures, in turn, increase immune activation in the hippocampus, the thalamus and the neocortex (IL-1β in mice, Donnelly et al., 1999; IL-1β in rats, Jankowsky and Patterson, 1999, 2001; CCL2 in mice, Turrin and Rivest, 2004). Ischemia and the subsequent reperfusion of blood flow to the brain is particularly damaging to the CA1 region of the hippocampus for several days following the insult (Horn and Schlote, 1992; Pulsinelli et al., 1982; Sandstrom and Rowan, 2007). Ischemic events that disrupt blood flow to the CNS (including those caused by cardiac arrest and other blockages) set off a series of inflammatory events, including the activation of microglia and astrocytes that release a storm of cytokines and chemokines (Denes et al., 2010; Molina-Holgado and Molina-Holgado, 2010). Microglia and peripheral macrophages flock to the site of infarction (Franklin et al., 2003; Saganova et al., 2003; Stoll et al., 1998). Notably, ischemic insults, seizures, or other inflammatory stimuli markedly impact the proliferation, migration, differentiation, and survival of neural stem cells (NSCs) in the DG (Belmadani et al., 2006; Das and Basu, 2008), suggesting an important role for interactions between immune signaling and NSCs in pathology.

5. Chemokines and the brain

Cytokines and chemokines are small cell-signaling molecules whose functions have been primarily defined within the peripheral immune system. Chemokines are 8–12 kD proteins that mediate chemotaxis; e.g., the recruitment of leukocytes to sites of insult or injury (for review, see Mackay, 2001) (Fig. 1). The family of chemokines is large with over 40 ligands and a host of receptors that bind them. Their receptors are G-protein-coupled with 7 transmembrane domains; the similarity between receptors in this protein family results in broad promiscuous binding of the chemokine ligands and a lack of specificity between various ligands and their potential receptors (Cardona et al., 2008; Charo and Ransohoff, 2006; Graham and Nibbs, 2007; Ransohoff et al., 2007). However, this breadth of binding possibilities also suggests a high degree of flexibility, diversity, and precision in communication among multiple cell types. For instance, specific chemokine ligands draw specific cell types (e.g., CXCL8 and neutrophils; (Murdoch and Finn, 2000)) to the site of injury and modulate distinct responses to invading pathogens. These molecules are highly expressed in human disease states, including kidney disease (CX3CL1 in humans and animal models; Koziolek et al., 2009), atherosclerosis (CX3CL1 in mice; Liu and Jiang, 2011; for review, see Reape and Groot, 1999), rheumatoid arthritis, and cancer (CCR2 in mice; Boring et al., 1998; CX3CL1; Jones et al., 2010), suggesting they are valuable targets for intervention or treatment. For instance, HIV-1 infection and disease progression are directly dependent on the chemokine receptors CCR5 and CXCR4 (Berger et al., 1999; Huang et al., 1996).

In the nervous system, chemokines are secreted by multiple cell types, including neurons and glial cells (Giunti et al., 2012; Harrison et al., 1998; Murase and Hayashi, 2002; Sawada et al., 1993; Tian et al., 2009) and are important for both inflammatory cascades within the CNS as well as normal cognitive function, though the latter remains less well defined. The importance of many canonical proinflammatory cytokines (e.g., IL-1, IL-6) in CNS function has been thoroughly reviewed (Avital et al., 2003; Balschun et al., 2004; Becher et al., 2000; Dantzer and Kelley, 2007b), but the study of chemokines in the CNS, and especially the hippocampus, is in its infancy (Cardona et al., 2008; Charo and Ransohoff, 2006; Ransohoff et al., 2007). Notably, they have recently been suggested as the "third major form of neuromodulatory communication within the CNS" (Adler et al., 2005) and have effects throughout the normal developing and adult brain, which we outline in the sections that follow.

Neurogenesis. The majority of DG granule cells are born during the first few weeks of life after birth (Altman and Das, 1966; Bayer and Altman, 1974, 1975), and their generation and integration into hippocampal circuitry continues long after the brain is fully developed, albeit at a reduced level. CA3 neurons, whose generation

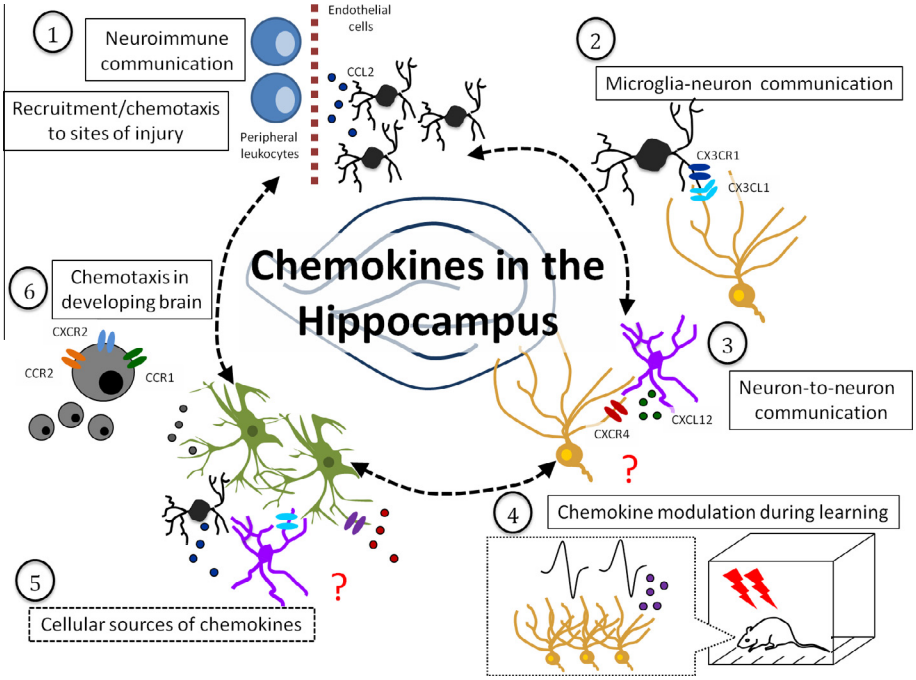

Fig. 1. Chemokines have important roles within the hippocampus and may modulate plasticity and vulnerability within this unique structure. (1) Neuroimmune signaling can occur across the blood-brain-barrier (BBB) via endothelial cells, astrocytes, and microglia within the BBB that recapitulate the immune signal from the periphery by secreting their own cohort of cytokines into the brain (Skaper et al., 2012; Verma et al., 2006; Wiese et al., 2012). Chemokines recruit cells to sites of injury as well (Mackay, 2001). (2) Microglia receive input from neurons via several membrane-bound and secreted factors, including neuronal CX3CL1 (fractalkine) and its receptor, CX3CR1, on microglia (Harrison et al., 1998), which allow direct neuroimmune interaction. (3) CXCL12 is released from vesicles concomitantly with GABA from basket cells onto immature neurons in the DG granule cell layer (Bhattacharyya et al., 2008). (4) In the healthy brain, chemokines may modulate neuronal signaling during behavior, though this phenomenon remains to be explored. (5) The spatial and temporal signaling and cellular sources of chemokines and their receptors are critical for understanding their function in the hippocampus. (6) Several chemokine receptors, including CCR1, CCR2 and CCR5, are found, *in vitro*, on hippocampal NSCs (Imitola et al., 2004; Tran et al., 2007; Tran et al., 2004).

peaks on embryonic day 17 (E17) in rats, are generated slightly earlier than CA1 cells, which peak on E18 and 19 (Altman and Bayer, 1990; Angevine, 1965; Bayer, 1980). The DG, on the other hand, begins its development at the same time as CA1 and CA3, but the generation of cells in the DG extends into the neonatal period and, beyond, into adulthood. In addition to differentiating into granule cells, the neural stem cells in the subgranular zone (SGZ), a neurogenic cell layer between the granule cell layer and the hilus, can also become astrocytes in the constant turnover of the DG (Palmer et al., 1997). The capability of the DG to produce and incorporate new cells throughout the lifespan maintains a state of pseudo-development in the hippocampus.

Chemokines are vital to the migration and development of NSCs in the DG of the hippocampus (Kolodziej et al., 2008; Tran et al., 2007) both in development and into adulthood. NSCs basally express several chemokine receptors, including CCR1, CCR2, CCR5, CXCR2, CXCR3 and CXCR4, the receptor for CXCL12 (Imitola et al., 2004; Tran et al., 2004, 2007) (Fig. 1). Neurospheres are induced to migrate *in vitro* by CCL2 (Widera et al., 2004). CXCL12 and its receptor CXCR4 are especially well-defined in hippocampal development (Lu et al., 2002; Ma et al., 1998; Zou et al., 1998), and knockout models show disrupted cerebellar and hippocampal granule cell development without these proteins. In the CA3 region of the developing hippocampus, CXCL12 inhibits GABA signaling, suggesting it may play a role in activity-dependent synapse formation by altering GABA giant depolarizing potentials (Kasiyanov et al., 2008). It selectively modulates hippocampal neuron axon outgrowth without altering branching (Pujol et al., 2005) and guides immature granule cell development in the adult DG in an agonistic relationship with its receptor CXCR4; internalization of the receptor following CXCL12 binding permits the developmental trajectory of granule cells to proceed unimpeded (Kolodziej et al., 2008). CXCL12 is also directly involved in GABA-ergic transmission within the DG. The protein is stored in vesicles of DG basket cells and co-localized with GABA vesicles that synapse onto immature neurons that are integrated in the granule cell layer (Bhattacharyya et al., 2008). Given the chemotactic roles for chemokines in the peripheral immune system, their similar effects as chemoattractant signals for NSCs highlight a potential evolutionary conservation of these molecules (Huising et al., 2003).

In early adulthood, rats produce thousands of new cells in the DG daily (Cameron and McKay, 2001). Few of the new cells survive; however, once surviving cells differentiate into neurons, they are integrated into the blades of the DG and begin to extend processes and connections to receive inputs as well as extend axonal projections to the CA3 (Hastings and Gould, 1999; Markakis and Gage, 1999). The purpose of new neurons and their importance for hippocampal function continues to be debated (Aimone et al., 2006, 2010a,b, 2011; Deng et al., 2010; Eisch et al., 2008; Kempermann, 2002; Kempermann et al., 2003, 2004, 2010; Lagace et al., 2007; Zhao et al., 2008) and will not be discussed in detail here. Regardless of their function, the consistent turnover of the granule cell population establishes a constantly changing signaling pathway in the hippocampus, especially as the flow of information often passes through the DG on its way to the rest of the structure. This state offers great potential for flexibility and plasticity in hippocampal function, but likely also contributes to the selective vulnerability of the hippocampus.

Synaptic plasticity. Chemokines are also important for several putative cellular and molecular mechanisms underlying learning and memory, including plasticity at the neural network, single neuron, and synaptic levels in the adult brain (e.g., LTP, AMPA receptor trafficking) (Alkon and Nelson, 1990; Bliss et al., 2007b; Gould, 2007; Kandel, 1997). Altering AMPA receptor number

changes the effects of glutamate on the post-synaptic neuron and is thought to underlie the strengthened connections observed during LTP (for review, see Malinow and Malenka, 2002). Dendritic spines that contain AMPA and NMDA receptors are thought to be formed *de novo* during the induction of LTP (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). Chemokines influence AMPA receptor-mediated plasticity broadly throughout the CNS. For instance, *in vitro* studies show that CXCR2 expression in human embryonic kidney (HEK) cells increases both the apparent affinity of GluR1 homomers for glutamate and the GluR1 homomer channel open probability (Lax et al., 2002). Application of CXCL2, a ligand for CXCR2, on Purkinje neurons cultured from the cerebellum increases spontaneous AMPA-type glutamatergic excitatory activity (Lax et al., 2002). CXCR4 modulates synaptic depression in the cerebellum (Ragozzino et al., 2002). CXCL12, the only known ligand for CXCR4, reduces NR2B subunit expression in NMDA receptors on cultured cortical neurons, and the reduction of this subunit decreases calcium excitotoxicity (Nicolai et al., 2010).

Thus, in various cell populations, chemokines can modulate plasticity at the cellular and molecular level, and hippocampal signaling in particular is heavily modulated by these molecules. For instance, fractalkine (CX3CL1) reduces AMPA-mediated currents in hippocampal neuron culture preparations, through interactions with its receptor, CX3CR1 (Lauro et al., 2008). Fractalkine also alters excitatory post-synaptic current (ESPC) in patch-clamped CA1 pyramidal neurons in the rat hippocampus (Ragozzino et al., 2006). The same preparation reduces AMPA current responses through a G_i-coupled dependent attenuation of intracellular cAMP. In transgenic mice that overexpress CCL2, neuronal responsiveness, as measured by extracellular field potentials in hippocampal slices, was reduced and short term potentiation was enhanced (Nelson et al., 2011). Bath application of CCL2 on hippocampal slices in another study increased EPSC occurrence and quantal content (Zhou et al., 2011). Application of CCL3 on hippocampal slices increased intracellular Ca^{2+} levels as well as NMDA-evoked Ca^{2+} signaling and increased numbers of NMDA receptors on the hippocampal neurons (Kuijpers et al., 2010). Many of these findings were discovered *in vitro* and provide a foundation for future *in vivo* characterization of many chemokines, particularly during learning and memory paradigms. For instance, fractalkine-knockout mice show reduced freezing to context after fear conditioning and less precise memory for a platform location after water maze training, and their deficits are caused by an increase in the action of IL-1β in the brain (Rogers et al., 2011). We predict that many other chemokines will be implicated in cognitive or other hippocampal-dependent behavioral dysfunctions as this field continues to assess changes in chemokines and their receptors. Hippocampal dysfunction, however, may be a cost of its increased plasticity, and chemokines may have key roles in the flexibility of the hippocampus as well.

6. The resilience of the hippocampus

As the above sections have shown, neuroimmune interactions influence the susceptibility of the hippocampus to disruptive influences as well as modulate its functioning in the normal brain. In turn, the hippocampus also has a remarkable capacity for repair and flexibility. For example, environmental enrichment (EE) is a housing manipulation that increases physical and social stimuli and has profound impacts on hippocampal plasticity and function (Baamonde et al., 2011; Diamond et al., 1976; Jones and Smith, 1980). EE in rodents increases neurogenesis and cell survival (Kempermann et al., 2002; van Praag et al., 2000) and can be neuroprotective following CNS insult or injury (e.g., ischemia (Briones et al., 2011) or seizures (Steiner et al., 2004)). In addition to changes in neuronal number and function, astrocyte outgrowth is modulated by EE (Viola et al., 2009) and MHCII-negative microglia increase neurosphere development in culture following exercise, an important aspect of some EE paradigms (Vukovic et al., 2012). However, the effects of EE on neuroimmune function are largely unknown. Following 7 weeks of EE in our laboratory, rats were treated with lipopolysaccharide (LPS) or saline. We found that EE selectively protects the hippocampus from exaggerated cytokine and chemokine responses to the immune challenge, while the neuroimmune response in the adjacent parietal cortex was not altered by EE (Williamson et al., 2012). Similarly, EE attenuated the expression of IL-1β and TNFα in the hippocampi of mice infected with influenza and improved performance in the Morris Water Maze (Jurgens and Johnson, 2012). EE increases LTP in WT mice, whereas LTP is unaffected by EE in CX3CL1-knockout mice (Maggi et al., 2011). Thus, functional alterations in hippocampal immune signaling may be a mechanism by which this region builds resilience to insult or injury, especially in response to manipulations that increase neuronal resilience and/or complexity. For instance, voluntary exercise increases expression of a pro-neurogenic phenotype in the hippocampus of aged mice (Kohman et al., 2012) and, in aged rats infected with *E. coli*, exercise attenuated exaggerated hippocampal IL-1β, hippocampal-dependent memory impairments, and microglial activation (Barrientos et al., 2011).

Environmental interventions can also improve outcomes in chronic inflammatory conditions. In a mouse model of AD, running wheel exercise increases clearance of soluble fibrillary Aβ, an especially cytotoxic form of Aβ protein, and decreases inflammatory cytokines (e.g., IL-1β, TNFα) (Nichol et al., 2008). Following whole brain irradiation, growth factor expression, DG neurogenesis, and cognitive deficits were rescued by voluntary wheel running, such that mice that ran after irradiation showed an attenuated reduction in neurogenic growth factors, new cells in the DG and cognitive impairments on the Barnes Maze compared to their sedentary counterparts (Wong-Goodrich et al., 2010). Absent any peripheral immune challenge, wheel running altered cytokine tone in the hippocampi of female mice, reducing TNFα expression and increasing IL-6 and IL-1ra expression (Pervaiz and Hoffman-Goetz, 2011). The majority of these studies did not assess chemokine expression, but the prediction is that these molecules would be altered in addition to cytokines. In fact, our own work suggests that both the constitutive and insult-induced levels of chemokines within the brain are much higher (as much as 10-fold) than the oft-measured cytokines IL-1, TNF, and IL-6, suggesting the biological impact of chemokines may be profound ((Schwarz and Bilbo, 2011; Schwarz et al., 2011; Williamson et al., 2012). Taken together, these data show that the plasticity of the hippocampus can also lend protection or repair in the face of insult, in contrast to vulnerability alone.

7. Conclusions and implications

In closing, the full scope of the relationship between the CNS and the immune system remains to be elucidated, but mounting evidence indicates that this intricate relationship is a critical part of maintaining normal function in both systems. The findings addressed here illustrate clear, mechanistic ways in which immune molecules function within the normal hippocampus, including neurogenesis and synaptic plasticity. Immune molecules such as chemokines modulate these processes in injury and in health, and hippocampal reliance on these molecules may be a key factor for its vulnerability. However, many questions remain. For instance, do chemokines alter firing thresholds in neurons *in vivo*, similar to neuromodulators such as dopamine or serotonin, which would have important implications for mental processing (and

possibly neuropsychiatric disorders), and not only recovery from injury? If so, then chemokines could act as important "coincidence detectors" during learning events, such that the release of chemokines concurrent with neural activation may modulate learning and memory formation, or other aspects of behavior.

The cellular source(s) of many chemokines have yet to be determined *in vivo*, and this lack of knowledge also raises several questions – for instance, are chemokines primarily neuromodulatory (e.g., by impacting neurotransmission) during normal brain function, but primarily chemotactic within the CNS following injury? If so, do chemokines recruit peripheral leukocytes into the brain consistent with their traditional functions outside the brain, or do they solely alter NSC behavior and/or short-range plasticity mechanisms (e.g., via the recruitment or modification of synaptic elements such as adhesion molecules)? For each of these questions, does the cellular source of the chemokines matter? In the peripheral immune system, the cellular source of many cytokines is often critical in disease resistance and resolution (e.g., T cell vs. macrophage-derived interleukins, Hedrich and Bream, 2010). In the brain, when chemokines are released from vesicles during normal neurotransmission (e.g., CXCL12 in the DG (Bhattacharyya et al., 2008)), they have a specific range of signaling. When released by microglia during injury, however, chemokines may affect several surrounding cell types, including other microglia, or they may even cross the BBB to the periphery. If their effects are more widespread, do chemokine signals modulate CNS health and connectivity via immune changes within the periphery that feed back to the brain? It is notable that the structure of the hippocampus itself may impact the effects of immune molecules on its function. The linear signaling of the hippocampus suggests that any changes in signaling (i.e., neural, immune or neuroimmune) in the DG will have downstream effects on the entire structure. Conversely, manipulations promoting growth and plasticity in the DG (e.g., EE) can provide a buffering effect throughout the hippocampus (Williamson et al., 2012), as outlined in the previous section. The hippocampus itself may be an ideal neural substrate for these initial investigations of unknown roles for chemokines, as it offers a broad range of cellular, molecular, neural network and behavioral targets for study. In summary, targeting chemokines or their receptors via pharmacological, behavioral, or environmental interventions may hold tremendous promise for human mental health and cognition.

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