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ABSTRACT

Before the 1990s it was widely believed that the adult brain was incapable of regenerating neurons. However, it is now established that new neurons are continuously produced in the dentate gyrus of the hippocampus and olfactory bulb throughout life. The functional significance of adult neurogenesis is still unclear, but it is widely believed that the new neurons contribute to learning and memory and/or maintenance of brain regions by replacing dead or dying cells. Many different factors are known to regulate adult neurogenesis including immune responses and signaling molecules released by immune cells in the brain. While immune activation (i.e., enlargement of microglia, release of cytokines) within the brain is commonly viewed as a harmful event, the impact of immune activation on neural function is highly dependent on the form of the immune response as microglia and other immune-reactive cells in the brain can support or disrupt neural processes depending on the phenotype and behavior of the cells. For instance, microglia that express an inflammatory phenotype generally reduce cell proliferation, survival and function of new neurons whereas microglia displaying an alternative protective phenotype support adult neurogenesis. The present review summarizes current understanding of the role of new neurons in cognition and behavior, with an emphasis on the immune system's ability to influence adult hippocampal neurogenesis during both an inflammatory episode and in the healthy uninjured brain. It has been proposed that some of the cognitive deficits associated with inflammation may in part be related to inflammation-induced reductions in adult hippocampal neurogenesis. Elucidating how the immune system contributes to the regulation of adult neurogenesis will help in predicting the impact of immune activation on neural plasticity and potentially facilitate the discovery of treatments to preserve neurogenesis in conditions characterized by chronic inflammation.

1. Introduction to adult neurogenesis

Before the 1990s, it was widely thought that neurons in the adult human brain did not regenerate. Consequently, it was thought that if neurons died during your adult life for any reason (e.g., oxidative stress, stroke, neurodegenerative disease, head trauma, normal aging), they would never be replaced. However, in the 1960s, Altman and colleagues challenged this idea, reporting that new neurons are continuously and spontaneously born in at least two regions of the adult rat brain: the subgranular zone of the hippocampus with cells migrating to the granule layer of the dentate gyrus (Altman and Das, 1965) and the subventricular zone with cells migrating to the olfactory bulb (Altman, 1969). Due to the longstanding dogma that postnatal neurogenesis is non-existent in mammals, it took more than three decades before the Altman and Das (1965) discovery was broadly accepted.

Multi-potent stem cells reside in the subgranular zone of the dentate gyrus and the subventricular zone. These stem cells divide asymmetrically producing one daughter progenitor cell and one stem cell. The progenitor cell can then divide asymmetrically producing daughter cells that differentiate into either astrocytes or neurons and one progenitor cell retaining the capacity to divide multiple times. Studying the growth, survival and differentiation of these new cells often involves exogenous administration of the thymidine analog, bromodeoxyuridine (BrdU) that labels dividing cells. The presence of new cells (i.e., BrdU positive cells) is then detected by an antibody conjugated to a fluorescent label, often in conjunction with other markers to distinguish the fate of the new cells. For instance, a BrdU positive cell that co-labels with neuronal nuclear protein (NeuN) would indicate a mature neuronal phenotype (see Fig. 1). Whereas, a BrdU positive cell that co-labeled with S100β would indicate an astrocyte phenotype. One advantage of the double label technique as opposed to using gross morphology to identify whether new cells differentiated into neurons (Altman, 1969; Altman and Das, 1965) is that it does not rely on subjective assessment of the cellular phenotype. Additional modern immunohistochemical techniques (e.g., detection of the mitotic marker Ki67, and the marker of immature neurons, doublecortin [DCX]) in combination with double-labeling techniques have assisted in establishing that new neurons are continuously

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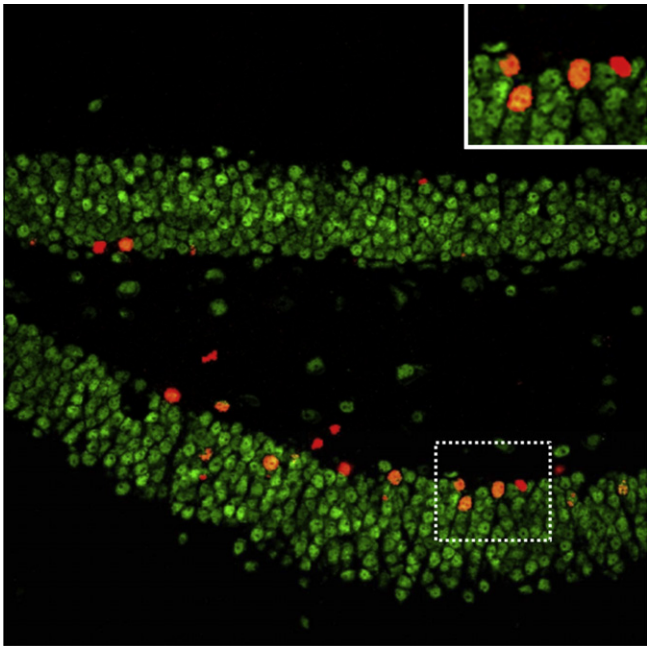

Fig. 1. Image of a mouse dentate gyrus double-labeled with fluorescent antibodies against BrdU (new cells in red) and NeuN (mature neuronal marker in green). New cells that have differentiated into neurons are co-labeled with both BrdU and NeuN (new neurons in orange). The area within the dashed lines contains 3 new neurons and one new cell of unknown phenotype and is shown zoomed in at the top right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

incorporated into the dentate gyrus and olfactory bulb throughout adulthood in most mammals (but perhaps not bats, Amerein et al., 2007).

Adult neurogenesis is thought to be an activity-dependent process (Deisseroth et al., 2004; Stone et al., 2011). Activation of the granule neurons generally leads to increases in neurogenesis, and inactivation leads to decreases. Whether neurogenesis can be regulated in an activity-independent manner is not known. The granule layer of the dentate gyrus can increase or decrease in volume by a relatively large magnitude, on order of 5–20% at a given age, depending on rates of neurogenesis that are largely determined by environmental factors such as stress, diet, environmental enrichment, and exercise (Clark et al., 2009; Coe et al., 2003; Mustroph et al., 2011; Pham et al., 2003; Rutten et al., 2010). Moreover, the increase and decrease in volume of the granule layer is attributed mostly to a change in the total numbers of new granule neurons as opposed to enlarged or shrinking neurons, or greater or lesser space between neurons (Rhodes et al., 2003).

A highly active area of research focuses on the extent to which adult neurogenesis contributes to learning and memory (Gould et al., 1999b; Kempermann, 2008) or whether it merely reflects development and maintenance of the brain regions where it occurs (Amrein et al., 2011). The learning and memory theory is in part based on the idea that new neurons which are not yet fully integrated into the circuitry could mold their connections to experiences more extensively as compared to older neurons that are already incorporated into the circuitry. Clearly old neurons can modify their synapses in response to experiences, but younger neurons may display a greater degree of malleability or plasticity. Electrophysiological evidence is consistent with the idea that young neurons are highly plastic units. For example, new neurons in the hippocampus and olfactory bulb display a lower threshold for long term potentiation (Nissant et al., 2009; Schmidt-Hieber et al., 2004; van Praag et al., 1999), and GABA acts as an excitatory neurotransmitter in young immature granule neurons of the dentate gyrus (Deisseroth and Malenka, 2005; Ge et al., 2006). New dentate gyrus granule neurons approximately 6–8 weeks old are also more likely than older neurons to display immediate early genes (IEG, e.g., c-Fos, Zif268, Arc) in response to a behavioral stimulus (Clark et al., 2012, 2011; Kee et al., 2007).

The assumption that new neurons are highly plastic units implies that there is a critical period in the development of new neurons where they display heightened plasticity, which is lost as they mature. However, the exact duration for this hypothetical critical period is not known, and may greatly vary between species. For example, in mice, it takes several days to weeks for a newborn cell in the granule layer of the dentate gyrus to display mature neuronal markers, and functionally integrate into hippocampal circuitry (Kempermann et al., 2003; van Praag et al., 2002) whereas in macaque monkeys it takes 6 months (Kohler et al., 2011). Similar analyses are not possible in humans for ethical reasons, but the macaque data suggest that if a critical period exists, it may be much longer in humans than in mice.

Many papers have reported positive correlations between levels of adult hippocampal neurogenesis and behavioral performance on hippocampus-dependent tasks (e.g., Gould et al., 1999a; van Praag et al., 1999; Thuret et al., 2009), but correlation does not imply causation. Moreover, several articles have reported no correlation (Jaholkowski et al., 2009) or a negative correlation between levels of neurogenesis and learning (Ambrogini et al., 2004; Kerr et al., 2010; Rhodes et al., 2003). Many studies have attempted to test whether neurogenesis causally contributes to changes in behavioral performance by directly manipulating neurogenesis. Techniques to reduce neurogenesis that have been used include anti-mitotic chemical agents (Shors et al., 2001), focal irradiation (Clark et al., 2008; Meshi et al., 2006), and transgenic animals (e.g., Deng et al., 2009; Dupret et al., 2008; Saxe et al., 2006; Zhang et al., 2010), but most of these have various side effects that make interpretation difficult. Moreover, results often conflict. One example is determining the contribution of adult neurogenesis to pro-cognitive effects of exercise. Many studies have shown that exercise both increases adult hippocampal neurogenesis and enhances learning and memory (Mustroph et al., 2011; Trejo et al., 2008; van Praag et al., 1999). However, exercise produces many changes throughout the brain including modifying synapses (Dietrich et al., 2008; Eadie et al., 2005), increasing blood vessel density (Clark et al., 2009), increasing release of trophic factors (Neeper et al., 1995), growth factors (Ding et al., 2006), and neurotransmitter levels (Meeusen and De Meirleir, 1995). In one study, irradiation was used to ablate neurogenesis in runners and it was found that without the increase in neurogenesis from running, the behavioral enhancement on the water maze test of spatial learning was lost (Clark et al., 2008). However, an earlier study using a similar method in a different strain of mice found that neurogenesis was not required for environmental enrichment (that included running wheels) to improve water maze performance (Meshi et al., 2006). Hence, the extent to which new neurons generated from running contribute to pro-cognitive effects of exercise remains unclear.

Recent studies have suggested that new neurons in the adult hippocampus play a role in pattern separation, that is, the ability to form distinct representations of similar inputs (Clelland et al., 2009; Creer et al., 2010; Sahay et al., 2011). New neurons have also been suggested to play a role in cognitive flexibility (Burghardt et al., 2012). Others have proposed that new neurons play a specific role in the behavior that led to their survival and integration (Kee et al., 2007; Tashiro et al., 2007). In our opinion, new neurons in the granule layer of the dentate gyrus probably contribute to any and all the functions of the dentate gyrus, not in any one specific cognitive function such as pattern separation, or in one behavior that was coincident with their survival. New neurons may have some

unique characteristics as compared to older neurons as discussed above but they eventually integrate into pre-existing hippocampal circuitry and therefore likely contribute to the general maintenance and function of the dentate gyrus. Evidence for the non-specificity of new neurons comes from a study showing that new neurons generated from running function in different behavioral tasks that do not involve running (Clark et al., 2012). In our opinion, the question of the functional significance of new neurons in the hippocampus is the same as the question of the functional significance of the granule layer of the dentate gyrus.

The microenvironment conducive for increasing net neurogenesis, i.e., proliferation, survival, differentiation, and network incorporation, is extremely complex and involves increases in vasculature (Palmer et al., 2000), growth factors (Anderson et al., 2002), trophic factors (Lee et al., 2002), changes in the chemical and electrical environment (Deisseroth et al., 2004), and glial support cells (Barkho et al., 2006; Morrens et al., 2012). The immune system contributes to the microenvironment through the cellular activity of immune cells in the brain (e.g., microglia) and from inflammatory signaling molecules entering from the periphery (Yirmiya and Goshen, 2011). Therefore activation of the immune system has the potential to influence the proliferation and survival of new neurons. In addition, many of the lifestyle factors that are known to regulate the proliferation, survival, differentiation and incorporation of new neurons into the circuitry, including, stress, diet and exercise, may exert some of their effects via interacting with the immune system and immune cells in the brain (Kohman et al., 2011; Kubera et al., 2011; Morgan et al., 2007; Wong et al., 2005; Wu et al., 2008). To the extent that adult neurogenesis is related to cognitive performance and behavior, immune-related changes in neurogenesis may have functional implications for cognition. Below we define neuroinflammation as it relates to neurogenesis, followed by a section focused on the impact of immune activation on neurogenesis, the contribution of age-related changes in immune function to neural plasticity, and the potential relevance of immune-induced alterations in hippocampal neurogenesis to cognitive function.

2. Neuroinflammation

The immune system can be divided into the innate and adaptive immune systems. While these divisions work together to orchestrate the immune response each serves distinct roles that facilitate recovery from an injury or infection. The innate immune system serves as the initial defensive to combat an infection. This response is rapid, but non-specific and is primarily mediated by cells of a myeloid origin (i.e., macrophages, neutrophils, and dendritic cells). In contrast the adaptive branch of the immune system is driven mainly by lymphocytes (i.e., T- and B-cells) which create an antigen specific immune response that takes time to develop, but provides lasting immunity. The combined efforts of the innate and adaptive branches of the immune system protect and facilitate recovery following infection or injury within the peripheral nervous system.

While the brain is no longer considered to be an immune privileged site, as we now know that immune cells within the periphery communicate with the brain and immune cells actually reside within the brain differences exist between immune activation within the periphery and CNS. These immunological differences are likely related to the presence of the blood brain barrier (BBB) that separates the central and peripheral nervous systems. The BBB protects the brain by limiting what enters and leaves the brain creating distinct environments within the body. This boundary between the brain and periphery has direct effects on immune activity. While parallels between the type of cells that reside in and the activity they perform within the periphery and brain are evident, key differences exist. For instance, following a systemic infection cells of the innate immune system become activated and participate in initiating the adaptive immune response to aid in clearing the infection. Whereas cells in the brain that mediate the innate response cannot efficiently activate the adaptive branch of the immune system (Ransohoff and Brown, 2012). While cells from the periphery may be able to infiltrate the CNS and assist with clearing an infection, particularly when the BBB is compromised, majority of the burden of protecting the CNS from injury or infection falls on a select group of cells, namely, microglial cells, astrocytes, and mast cells. Mast cells reside within the brain and are important for attracting and potentially activating other immune cells within the brain via the secretion of proinflammatory cytokines and chemoattractants (Skaper et al., 2012). Astrocytes also contribute to the local immune response within the brain through the production of both pro- and anti-inflammatory cytokines, complement components, and chemokines (Ransohoff and Brown, 2012). Though a variety of cells contribute to the development of inflammation within the brain researchers have focused on microglial cells as the primary mediators of the neuroinflammatory response.

Microglia are myeloid cells derived from the embryonic yolk sac that migrate into the brain during early development and sustain a resident population through proliferation (Ajami et al., 2007; Alliot et al., 1999). Microglia are similar to peripheral macrophages as they can take on several phenotypes of activation that allows them to survey the environment, remove cellular debris or pathogens, and support regenerative processes. The induction of these varied phenotypes occurs in response to the signals from the surrounding environment. In response to an infection or injury microglia acquire a reactive inflammatory phenotype, also referred to as the classic phenotype. The classic inflammatory phenotype is characterized by increased microglia proliferation, morphological changes (e.g., swelling of the cell body and retraction of the processes), and the release of several inflammatory molecules including cytokines, chemokines, reactive oxygen species, and nitric oxide (Kettenmann et al., 2011). The induction of this classic inflammatory phenotype is at the heart of the neuroinflammatory response. For the sake of brevity we will use the term neuroinflammation interchangeably with activation of microglia towards the classic inflammatory phenotype, as the increased expression of pro-inflammatory cytokines and a host of inflammatory-related molecules associated with the classic phenotype defines the neuroinflammatory response for the purposes of this review.

3. Phenotype-specific effects of microglia on hippocampal neurogenesis

Microglia can have both supportive and harmful effects on adulthood neurogenesis depending on their state of activation. Microglia that express a proinflammatory phenotype generally impair neurogenesis whereas as microglia that express a neuroprotective phenotype can facilitate new cell survival. The present section will cover the differential phenotypes microglia express and the distinct effects each phenotype has on influencing hippocampal neurogenesis.

3.1. Resting microglia

In the healthy uninjured brain microglia typically reside in what's been termed a resting state. Resting microglia display a ramified morphology, with many fine processes and a small cell body (Kettenmann et al., 2011). They use their fine cellular processes to vigilantly survey the surrounding area checking for evidence of damage or infection. In the hippocampus, resting

microglia actively participate in adult neurogenesis through their phagocytic capacities (Sierra et al., 2010). Though thousands of new cells are born in the subgranular zone of the dentate gyrus every day, not all of these cells will survive and differentiate into neurons. At least half of these new cells will die, likely through apoptosis, within the first few days to weeks after they are born (Biebl et al., 2000; Cameron and McKay, 2001; Dayer et al., 2003; Kempermann et al., 2003). Sierra et al. (2010) demonstrate that unchallenged microglia play a crucial role in neurogenesis by removing the apoptotic new cells through phagocytosis. Additionally, they report that phagocytosis of new cells does not activate microglia, indicating that phagocytosis is possible without complete activation of microglia. These findings show a novel role for microglia in supporting basal hippocampal neurogenesis in the absence of an activated phenotype.

Further evidence that microglia in the unchallenged state may influence hippocampal neurogenesis comes from the work of Walton et al. (2006) who found in culture that microglia release factors that rescue neuroblasts and instruct neuronal cell differentiation. Neural stem cells (NSCs) isolated from subventricular tissue of 8-day-old C57BL/6 mice were cultured and, as expected, the proportion of neuroblasts decreased the longer the cultured was maintained. This reduction in neuroblasts is reported not to result from depletion of NSCs, but rather appears to reflect a reduction in proliferation of non-neuronal cells, particularly microglia, as microglial cell loss was found to be correlated with the neurogenic potential of the culture. Additionally, the data indicate that microglia secrete unknown factors that prolong the culture's neurogenic potential as conditioned medium from a microglia rich brain area enhanced the neurogenic capacity of cultured NSC. Interestingly, conditioned media derived from older mice was less effective than media derived from young mice in stimulating neurogenesis, indicating that age-related changes in microglia activity may contribute to the age-associated decline in neurogenesis (Walton et al., 2006). Collectively, the data indicate a role for microglia in supporting basal neurogenesis in the absence of microglia activation, broadening our understanding of the microglial cell's role within the brain. Further work is needed to fully characterize the precise role microglia play in supporting neurogenesis within the hippocampus.

3.2. Classically activated microglia

Overwhelming evidence indicates that activation of microglia towards the classic inflammatory phenotype has negative effects on hippocampal neurogenesis. A common experimental method to simulate an inflammatory response within the brain and induce classic microglia activation is through administration, either centrally or systemically, of the bacterial endotoxin lipopolysaccharide (LPS). LPS activates microglia through binding to toll-like receptor-4 (TLR4) molecules and induces the release of several proinflammatory cytokines including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) among other inflammatory molecules.

The initial work demonstrating that classically activated microglia impair hippocampal neurogenesis was reported by Monje et al. (2003) and Ekdahl et al. (2003) following LPS administration. Ekdahl et al. (2003) report that 4 weeks of intracortical infusion of LPS drastically decreased new neuron survival, whereas LPS had no effect on proliferation of new cells. Similar findings were observed by the independent report published by Monje et al. (2003) who found that an intraperitoneal injection of LPS significantly decreased new cell survival, but had no effect on proliferation. Additionally, LPS administration decreased the differentiation of new cells into neurons as evidenced by a reduction in expression of the early neuron marker doublecortin (DCX) in LPS treated rats. In both reports, the survival of new neurons was negatively correlated with the number of activated microglia. Further, administration of the microglia inhibitor, minocycline, blocked the LPS-induced decrease in new neuron survival, indicating microglia activation mediated the impaired neuron survival (Ekdahl et al., 2003). Collectively, these reports provided the foundational evidence, later replicated by others (Bastos et al., 2008), that neuroinflammation suppresses hippocampal neurogenesis through decreasing new neuron survival.

Though new cell survival is clearly impaired by neuroinflammation, additional papers have reported that inflammation also affects the proliferation component of hippocampal neurogenesis. For instance, Fujioka and Akema (2010) report that 5 h after a single intraperitoneal (ip) injection of LPS, expression of the proliferation marker pHH3 (serine10 phosphorylated histone H3) was decreased in the granule layer. Further, they report the number of new cells was reduced in LPS-treated animals 24 h after labeling cells with BrdU (Fujioka and Akema, 2010). Additionally, a transgenic mouse model that overexpresses the proinflammatory cytokine IL-6 from astrocytes shows reduced progenitor cell proliferation when samples were collected one day after BrdU administration (Vallieres et al., 2002). The reason for the discrepancy in the effect of LPS administration on proliferation is unclear as similar doses and routes of LPS were used as well as the species (i.e., rats), though differences in strain and the sex of the rats may alter the response to LPS in these studies (Fujioka and Akema, 2010; Monje et al., 2003).

The impact of inflammation on neurogenesis is not simply via effects on proliferation, survival and cell death, but also can affect the integration of new neurons into pre-existing neural networks and the cellular properties of the new cells that survive. For example, Jakubs et al. (2008) report that inflammation increases inhibitory signaling to new neurons. Specifically, Jakubs et al. (2008) examined changes in morphology and electrophysiological properties of new granule cells that were born in an environment characterized by chronic inflammation that was induced by an intrahippocampal infusion of LPS and produced persistent microglia activation. Cells born one week after LPS infusion showed no changes in dendritic tree morphology, location within the granule layer, intrinsic membrane potential, or axon projection. However, the LPS-induced chronic neuroinflammation altered the synaptic input to both pre-existing and new neurons. Both new and pre-existing neurons showed an overall increase in the frequency of spontaneous excitatory postsynaptic current (EPSC) compared to granule cells in control animals, indicating that cells residing in an inflammatory environment receive an increase in excitatory activation. Though both new and pre-existing cells showed the increased excitatory input only the new cells born one week after LPS administration showed an enhanced inhibitory input. The time between spontaneous inhibitory postsynaptic current (IPSC) was shorter in new neurons compared to pre-existing neurons. Additionally, new cells had a higher density of inhibitory synapses on their distal dendrites compared to pre-existing neurons. Collectively, these data indicate that neurons that mature in an inflammatory environment have increased inhibitory input from synapses that may potentially alter new neuron function.

Additional evidence of altered integration comes from the work of Belarbi et al. (2012) who demonstrated that chronic inflammation reduces new neuron participation in hippocampal processing of contextual information. In this study, rats received intracerebroventricular infusions of LPS or cerebral spinal fluid (CSF) for 28 days, rats then received five BrdU injections to label dividing cells. Two months after LPS or CSF treatment rats were placed in a novel environment and allowed to explore for 5 min and sacrificed 30 min later to assess differential expression of the plasticity-related immediate early gene Arc (activity regulated

cytoskeleton-associated protein) in pre-existing and new neurons in the granule layer. As expected, the authors observed persistent microglia activation following chronic LPS administration, as evidenced by increased MHC II expression two months after treatment. Though microglia showed prolonged activation, the authors report no difference in the number of BrdU positive new cells in the granule layer. This lack of an effect on new cell survival may result from using a lower dose of LPS than prior studies. In agreement with past reports, 30 min after exploring a novel environment a greater proportion of new neurons expressed Arc compared to pre-existing neurons in the CSF-treated rats, indicating increased recruitment of new neurons. However, in the LPS-treated rats there was no difference in Arc expression between new and existing neurons, indicating that chronic inflammation attenuated the recruitment of new neurons into hippocampal networks (Belarbi et al., 2012). These findings in conjunction with the work of Jakubs et al. (2008) demonstrate that inflammation may alter the unique cellular processes that new neurons display during development potentially making them less able to fully integrate and function in pre-existing hippocampal networks.

The mechanisms through which inflammation reduces hippocampal neurogenesis is still not fully understood, but evidence indicates that activation of microglia and the subsequent release of inflammatory molecules creates an environment that does not support survival of new cells. Evidence suggests that the classic proinflammatory cytokines, IL-1β, IL-6, and TNF-α contribute to the inflammation-related decrease in neurogenesis (see Table 1). In vitro findings indicate that IL-6 is a key factor released by microglia that reduces neuron survival (Monje et al., 2003). Further overexpression of IL-6 within the brain reduces proliferation, survival, and neural differentiation of new cells (Vallieres et al., 2002).

Similar anti-neurogenic effects of TNF-α have also been reported. For instance, systemic administration of TNF-α was found to reduce cell proliferation within the granule layer (Seguin et al., 2009). Further, addition of TNF-α to an in vitro model of hippocampal neural differentiation led to increased apoptosis of hippocampal stem/progenitor cells (Hofer et al., 2011). Cultured hippocampal cells that undergo differentiation in the presence of TNF-α show a significant reduction in the proportion of cells that become neurons and an increase in the proportion of newly developed astrocytes (Keohane et al., 2010). Exposing differentiating cells to TNF-α was found to increase expression of the anti-neurogenic gene hairy-enhancer-of-split 1 (Hes1) that decreases neuronal differentiation by suppressing expression of pro-neural genes (Keohane et al., 2010). These finding are in agreement with prior work that showed exposing new cell in culture to TNF-α increases the proportion of cells that differentiate into astrocytes (Johansson et al., 2008). Further, mice lacking the TNF-α type 1 receptor show increased basal levels of proliferation in the subgranular zone, indicating TNF-α acting through the type 1 receptor negatively regulates cell proliferation (Iosif et al., 2006). Collectively, the data indicate that elevated levels of TNF-α can reduce cell proliferation and impact differentiation of new cells by increasing the likelihood that these new cells will develop into astrocytes.

Elevated levels of IL-1β are implicated in altering neurogenesis by affecting cell proliferation and differentiation. NPCs have been shown to express the type 1 IL-1 receptor (IL-1R1), indicating that IL-1β may act directly on NPCs (Green et al., 2012). Culturing embryonic rat hippocampal NPCs in the presence of IL-1β significantly reduces NPC proliferation and the growth of neurospheres. Additionally, in a differentiation assay the presence of IL-1β increased the proportion of cells that became astrocytes and reduced the percentage of new neurons (Green et al., 2012). To investigate the effects of chronic neuroinflammation on neurogenesis, IL-1β was overexpressed in the adult hippocampus using a Cre-lox conditional transgenic mouse model. Chronic IL-1β expression decreased the number of DCX + cells in the granular layer of the hippocampus at both 1 and 3 months after IL-1β over-expression (Wu et al., 2012). The reduction in new neurons (i.e., DCX + cells) is mediated through activation of the IL-1R1, as overexpression of IL-1β in the hippocampus of IL-1R1 knockout mice had no effect on DCX + cells. Further, chronic expression of IL-1β reduced the proportion of new cells that differentiated into new neurons and increased the proportion of cells that became astrocytes, indicating that IL-1β shifts the fate of new cells towards astrocytes (Wu et al., 2012). IL-1β has also been implicated in mediating stress-induced reductions in hippocampal neurogenesis. Koo and Duman (2008) showed that acute or chronic stress decreases cell proliferation and that the reduction could be blocked by administration of the IL-1 receptor antagonist (IL-1Ra) as well as mice that lacked the IL-R1 showed no effect on cell proliferation following stress exposure. Additionally, they report that chronic stress decreased the number of new neurons, as measured by DCX expression in BrdU positive cells, and that this reduction could be prevented by central infusion of IL-1Ra (Koo and Duman, 2008). To identify the mechanism through which IL-1β reduced proliferation, adult neural progenitor cells were cultured in the presence or absence of IL-1β. Results showed that the addition of IL-1β did not increase cell death, but rather levels of cyclin D1, a protein involved in regulating mitotic events, was reduced in the presence of IL-1β and again

Table 1
Summary of the effects of select immune signaling molecules on proliferation, survival and neuronal differentiation of new cells in the hippocampus.

	Proliferation	Survival	Neuronal differentiation	Astrocyte differentiation	References
IL-6	↓	↓	↓		Monje et al. (2003) Vallieres et al. (2002)
IL-lbeta	↓		↓	↑	Green et al. (2012) Koo and Duman (2008)
TNF-alpha	↓		↓	↑	Keohane et al. (2010) Iosif et al. (2006) Johansson et al. (2008) Seguin et al. (2009)
Prostaglandins		↓			Bastos et al. (2008) Keene et al. (2009) Monje et al. (2003)
TGF-beta		↑	↑		Battista et al. (2006) Mathieu et al. (2010)
IL-4			↑		Butovsky et al. (2006)
IL-10	↑				Cacci et al. (2008) Kiyota et al. (2011)

Note: ↓ indicates a reduction and ↑ indicates and increase. Cells that are left blank indicate that the effects are currently unknown.

this effect could be blocked by IL-1Ra (Koo and Duman, 2008). Taken together, the data indicate that IL-1β can suppress progenitor cell proliferation by slowing the cell cycle and that IL-1β alters rates of differentiation by increasing the probability that a new cell will differentiate into an astrocyte rather than a neuron.

In addition to proinflammatory cytokines, prostaglandins are released in response to an immune challenge which may mediate aspects of the inflammation-induce reduction in hippocampal neurogenesis (Table 1). Monje et al. (2003) report that administration of indomethacin, a non-selective inhibitor of cyclooxygenase (COX), an enzyme that allows conversion of arachidonic acid to prostaglandins, attenuates microglia activation and prevented the LPS-induced decrease in new cell survival. Later work demonstrated that the ability of indomethacin to prevent the reduced neuron survival following LPS administration is likely mediated by COX-2, as a selective inhibitor of COX-2 blocked the LPS-induced decrease in new neuron survival, whereas a selective COX-1 inhibitor did not rescues cell survival (Bastos et al., 2008). Further work indicates that signaling through prostaglandin E_2 receptor subtypes EP1 and EP2 are required for LPS-induced suppression of hippocampal neurogenesis (Keene et al., 2009). Collectively, these data indicate that the decreased survival associated with an immune challenge is mediated in part by the production of prostaglandins.

Another major component of the immune response that can alter neurogenesis is activation of the hypothalamic–pituitary–adrenal (HPA) axis. Evidence suggests that increases in glucocorticoid levels resulting from activation of the HPA axis contribute to the inflammation-induced decreases in hippocampal neurogenesis (Wolf et al., 2009). Immune stimulants, such as LPS, that induce a large increase in corticosterone levels in the brain of rodents are associated with reduced neurogenesis whereas administration of a T-cell specific stimulant, staphylococcus enterotoxin B (SEB), which produces a smaller increase in corticosterone levels in the brain compared to LPS actually enhances hippocampal neurogenesis (Wolf et al., 2009). These data indicate that moderate increases in corticosterone support hippocampal neurogenesis whereas substantial increases may inhibit neurogenesis, potentially indicating that elevated corticosterone levels induced by activation of the immune system may contribute to the reduction in neurogenesis.

Activation of the immune system induces a broad response that leads to release of a host of immune molecules, including cytokines, prostaglandins, and chemokines, and activation of the HPA neuroendocrine system among others. Generally, the transient activation of the immune system is beneficial and aids the body in recovering from an infection, but the induction of a neuroinflammatory response has detrimental effects on neurogenesis which may be of particular importance when the immune response becomes chronic or is exaggerated. Together, the evidence indicates that a variety of immune molecules can negatively affect neurogenesis and often have overlapping effects. Proinflammatory cytokines generally decrease cell survival and shift the balance away from neurogenesis and towards astrogliogenesis. Further, elevated levels of prostaglandins and glucocorticoids are implicated in inflammation-associated reductions in new cells survival. Cooperatively, the secretion of inflammatory molecules within the brain likely modifies the neurogenic niche, creating an environment in which new neurons cannot prosper. Interestingly, astrocyte production is favored during times of inflammation. Whether the enhancement of astrocyte differentiation has any functional significance in facilitating the neuroinflammatory response or subsequent recovery from it has not been determined.

3.3. Alternatively activated microglia

In contrast to the classic inflammatory phenotype, microglia can acquire what's been termed the alternative neuroprotective or M2 phenotype that plays a central role in regenerative processes (for review see Colton, 2009). The alternative phenotype is characterized by expression of MHC II, arginase 1 (AG1), mannose receptor (MRC1), peroxisome proliferation activation receptor gamma (PPAR-γ), Ym1 (Chitinase 3-like 3), and found in inflammatory zone 1 (FIZZ1) (Colton, 2009). Further, the alternatively activated microglia often show increased expression of the anti-inflammatory cytokines interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and growth factors such as insulin-like growth factor (IGF), neural growth factor (NGF), and brain derived neural growth factor (BDNF). The expression of the alternative phenotype often follows an inflammatory response, potentially making the alternative phenotype a compensatory response to aid in healing (Cacci et al., 2008; Thored et al., 2009). Anti-inflammatory cytokines, such as IL-4 and IL-13 can induce expression of the alternative phenotype (Butovsky et al., 2006; Colton, 2009). Given the protective properties associated with the alternative phenotype it has been suggested that microglia expressing the alternative phenotype contribute to the maintenance of neurogenesis.

Evidence suggests that anti-inflammatory cytokines may support neurogenesis (see Table 1). For example, Mathieu et al. (2010) report that chronic expression of the anti-inflammatory cytokine TGF-β, induced by administration of an adenoviral vector expressing TGF-β into the SVZ increased survival of BrdU positive cells. Further, Battista et al. (2006) found that TGF-β plays a role in the increase in hippocampal neurogenesis following adrenalectomy (ADX). ADX has been reported to increase proliferation of new cells as well as increase neuronal differentiation. They found that inhibiting TGF-β with a blocking antibody had no effect on the ADX-induced increase in proliferation, but reduced neuronal differentiation, indicating the TGF-β may encourage new cells to differentiate into neurons (Battista et al., 2006).

The notion that microglia have differential effects on neurogenesis depending on the phenotype they express is supported by work by Butovsky et al. (2006). They found that neural progenitor cells (NPCs) cultured with microglia that were stimulated with LPS showed low levels of neuronal differentiation, whereas NPCs cultures with IL-4 stimulated microglia showed an increased the proportion of new neurons. In agreement, more cells were found to be DCX + when co-cultured with microglia stimulated with IL-4 compared to control cells that were cultured with un-stimulated microglia (Butovsky et al., 2006). Additionally, stimulating microglial cells with IL-4 increased microglia expression of IGF-1 that is known to support neurogenesis (Annenkov, 2009). In agreement, a more recent paper reported that co-culturing NPCs with IL-4 stimulated microglia enhanced neuronal differentiation. Additionally, it was observed that IL-10 stimulated microglia enhance NPC proliferation, but have no effect on differentiation in culture (Kiyota et al., 2011). Further, Cacci et al. (2008) reported that in culture microglia releasing IL-10 were supportive of neuronal differentiation and new cell survival. Collectively these data indicate that expression of the alternative phenotype in microglia supports different aspects of neurogenesis and that depending on the activating stimulus can enhance proliferation or the production of new neurons.

The pro-neurogenic effects of microglia have also been reported in an ischemic injury model. Initially, following injury, microglia express the inflammatory phenotype. However, with time a portion of the cells begin to express the alternative phenotype. Thored et al. (2009) showed that following an ischemia-induced injury in the striatum microglia acquired the alternative phenotype which persisted for 16 weeks post-injury. Additionally the injury increased new cell production within the SVZ and many of these new cells migrated to the injury site within the striatum. Alterations in microglial cell activation have been suggested to support the production and migration of new cells to the site of injury by

acquiring the alternative neuroprotective phenotype. Microglia within the SVZ showed increased expression of IGF-1 after stroke that corresponded to the increases in neurogenesis (Thored et al., 2009). Collectively these data indicate that alternatively activated microglia facilitate neuronal differentiation, migration and integration into neuronal networks following an injury.

Research on an animal model of Alzheimer's disease has shown that neuroinflammation may contribute to the depression of neurogenesis and that converting microglia to the alternative phenotype may alleviate the decrease in neurogenesis. The transgenic mouse APP + PS1 model of Alzheimer's disease that expresses both the human amyloid precursor protein (APP) and human presenilin-1 (PS1) show a reduced number of new neurons compared to non-transgenic mice (Biscaro et al., 2012; Kiyota et al., 2011). Chronic administration of minocycline has been reported to increase new neuron survival in APP + PS1 mice, indicating that microglia activation contributes to the decrease in hippocampal neurogenesis (Biscaro et al., 2012). Additionally, work by Kiyota et al. (2011) showed that overexpression of the anti-inflammatory cytokine IL-10 attenuates the reduction in neurogenesis in the Alzheimer mouse model. They report that overexpression of IL-10 in the hippocampus of APP + PS1 mice increased the number of new cells and the number DCX + cells and BrdU + NeuN + co-labeled cells. Increased IL-10 expression did not reduce the total amyloid beta load within the hippocampus, indicating that reductions in Aβ cannot explain the enhancement of hippocampal neurogenesis. One possibility, though not directly assessed in the study, is that elevated IL-10 levels within the hippocampus reduced microglia expression of the inflammatory phenotype, which is known to reduce neurogenesis, and/or increased expression of the alternative phenotype in microglia, which is associated with enhanced neurogenesis. Collectively, the data potentially indicate that balancing the pro- and anti-inflammatory activity within the brain may have beneficial effects on measures of neural plasticity in the diseased brain.

4. Role of microglia in activity-induced increases in neurogenesis

As discussed, neurogenesis is regulated by a variety of factors. Exercise has been consistently shown to enhance hippocampal neurogenesis by increasing neuronal differentiation and new cell survival. Though the data are limited, there is reason to speculate that immune cells may participate in the enhancement of neurogenesis following exercise and environmental enrichment. For example, Ziv et al. (2006) report that interactions between T-cells and microglia participate in the environmental enrichment-induced increase in neurogenesis. They found that SCID mice, which lack functional B- and T-cells, fail to show the enrichment-induced increase in neurogenesis. However, the enhancement of neurogenesis can be recovered if T-cells that are specific to a neural antigen are replaced. The authors suggest that following environmental enrichment T-cells may shift microglia towards the alternative M2 phenotype, as microglia showed an increase in MHC II expression and many of them appeared to co-label with the neuroprotective molecule, IGF-1 (Ziv et al., 2006). Additionally, the beneficial effects of environmental enrichment in T-cell replaced SCID mice were blocked if minocycline was administered, indicating that microglia are involved in this response.

The involvement of T-cells and microglia was called into question by the work of Olah et al. (2009) who found that 10 days of wheel running increases neurogenesis, but found no evidence that microglial cells were activated from exercise, as measured by MHC II expression. Additionally, they found no evidence of T-cell infiltration within the brain. However, the authors did observe an increase in microglia proliferation from exercise that occurred in several areas and therefore was not specific to neurogenic regions. The differences between these reports may result from methodological differences as Ziv et al. (2006) employed environmental enrichment that included running wheels, whereas Olah et al. (2009) used only running wheels. Though discrepancies exist, both studies provide evidence that microglial cells are responsive to the environment and/or physical activity. Further support, comes from work by Kohman et al. (2011) who found that voluntary wheel running significantly increases the proportion of microglia that co-label with IGF-1 in both adult and aged mice. These data are in agreement with the findings of Ziv et al. (2006). Olah et al. (2009) failed to observe an increase in IGF-1 expression following exercise, but this difference likely reflects the shorter running periods (i.e., 10 days versus 8 weeks) and possibly a difference in assessment of gene expression versus protein levels. Collectively, these data indicate that microglia are responsive to environmental factors, such as engaging in exercise, and that these differences are correlated with levels of neurogenesis. However, future work is needed to establish whether the relationship is causal, i.e. that microglia directly contribute to changes in neurogenesis.

A recent study by Vukovic et al. (2012) supports a role for microglia in exercise-induced increases in neurogenesis. In agreement with prior findings, two weeks of wheel running was found to increase the proportion of DCX + cells, BrdU + cells and increase the percentage of neurospheres observed. The authors created single cell suspensions of neural precursor cells (NPCs) isolated from the hippocampus of exercising or sedentary mice and then either added microglial cells or left them without microglia and assessed the proportion of neurospheres 14 days later. The absence of microglia had no effect on neurosphere formation in sedentary animals. However, the absence of microglia significantly reduced the proportion of neurospheres in runners. Further, if microglia from exercising mice were added to a NPC culture from a sedentary mouse there was a significant increase in the percent of neurospheres compared to NPCs that received microglia from a sedentary animal, indicating that exercise-induced changes in microglia may facilitate the increase in neurogenesis. The authors propose a role for the chemokine CX3CL1 for mediating the exercise-induced changes in microglia that contribute to increased NPC activity (Vukovic et al., 2012). Exercise significantly increased CX3CL1 levels in the hippocampus and two weeks of central administration of a CX3CL1 blocking anti-body prevented the beneficial effects of exercise on neurosphere formation. Additionally, when recombinant CX3CL1 was added to NPC culture there was a significant increase in the proportion of neurospheres, but this effect was attenuated if microglia were absent from the culture, indicating that microglia are required to observe the beneficial effects of CX3CL1 (Vukovic et al., 2012). Collectively, the data indicate that microglia activity is altered by lifestyle factors, such as exercise and environmental enrichment, and that these changes may support the pro-neurogenic response, potentially through altering the environment in which new cells are born.

5. Role of microglia in age-related decline in neurogenesis

Hippocampal neurogenesis persists throughout an individual's life, as centurions show evidence of neurogenesis (Knoth et al., 2010). However, there is a substantial decline in neurogenesis with normal aging. Aging is associated with a decrease in both proliferation and survival of new cells (Blackmore et al., 2009; Kohman et al., 2011; van Praag et al., 2005). Several factors likely contribute to the age-related decrease in neurogenesis. For instance, neural progenitor cells have been reported to proliferate at a slower rate in middle-aged rats compared to adults (Walter et al., 2011) and there is evidence that the number of viable stem cells is reduced

in aged animals (Rao et al., 2005; Seki and Arai, 1995). An additional contributing factor may be age-related changes in the neuroendocrine system, as prolonged reductions in corticosterone levels have been reported to attenuate the age-associated reduction in hippocampal neurogenesis (Montaron et al., 2006). Age-related changes in microglial cell activity and elevated basal levels of neuroinflammatory molecules may further contribute to suppression of neurogenesis.

Normal aging, in the absence of an infection or injury, is associated with increased microglia activity and development of low-grade chronic inflammation (for review see Dilger and Johnson, 2008). Microglia in the aged brain are primed towards the classic inflammatory phenotype, as microglia in aged animals show increased expression of MHC II, CD86 and moderately elevated levels of IL-1β and IL-6 (Frank et al., 2006; Godbout et al., 2005; Griffin et al., 2006; Perry et al., 1993; Sierra et al., 2007; Tarr et al., 2011; Ye and Johnson, 1999). Additionally, in vivo and in vitro models have shown an age-related increase in the proportion of dividing microglia and that aged female, but not male, mice show an increase in the total number of microglia in the hippocampus compared to adults (Kohman et al., 2011; Mouton et al., 2002; Rozovsky et al., 1998). Presently, the factors or events that induce these age-related changes microglia have yet to be fully elucidated. However, an age-related decrease in neuroimmune regulatory molecules (e.g., CD200 and fractalkine), an increase in irregular protein folding, and microglia senescence have been proposed to contribute to the development of primed microglia within the aged brain (Dilger and Johnson, 2008; Frank et al., 2006; Streit and Xue, 2009).

The age-related decrease in hippocampal neurogenesis is correlated with microglia activation and levels of proinflammatory cytokines within the brain (Gemma et al., 2007; Kuzumaki et al., 2010). As noted, conditioned medium from microglial cells from aged mice was less effective in stimulating neurogenesis in culture compared to medium from adult mice, potentially indicating that microglia from aged animals may release factors that are detrimental to neurogenesis or have decreased expression of factors that support neurogenesis (Walton et al., 2006). Additionally, Gemma et al. (2007) report that administration of the capase-1 inhibitor, which blocks the conversion of IL-1β to the mature form, significantly increases the number of new cells in the granular cell layer in aged rats. Similar increases in neurogenesis were obtained when aged rats were treated with fractalkine (Bachstetter et al., 2011). The chemokine, fractalkine, is a neuroimmune regulatory molecule released by neurons that acts on CX3CL1 receptors (CX3CR1) localized on microglial cells and maintains microglia in their resting phenotype (Cardona et al., 2006; Harrison et al., 1998). Aged rats show reduced protein levels of fractalkine within the hippocampus relative to adults (Bachstetter et al., 2011). Restoring fractalkine levels in aged rats by administrating fractalkine for seven days was found to increases the number of new cells within the granule cell layer. The ability of fractalkine to increase neurogenesis in aged rats is proposed to results from a reduction in IL-1β levels. Chronically blocking the CX3CR1 receptor in adults is reported to increase IL-1β levels and decrease proliferation. Further, the anti-proliferative effects of inhibiting the CX3CL1 receptor can be blocked if an IL-1 receptor antagonist is administered (Bachstetter et al., 2011). These findings indicate that decreased levels of fractalkine reduces regulatory control over microglia and subsequently results in an increase in IL-1β that has been shown to inhibit neurogenesis. Collectively, the data indicate that age-related changes in neuroinflammatory molecules contribute to the decline in hippocampal neurogenesis with aging. However, neuroinflammation is clearly not the only factor regulating neurogenesis during aging. Decreases in neurogenesis occur much sooner in life than neuroinflammatory changes. Moreover, while attenuating inflammation within the aged brain increases neurogenesis, the recovery is not complete. Hence, attenuation of neuroinflammation can only modify the naturally occurring downward trajectory of adult neurogenesis, it cannot reverse it. Inflammation can further suppress neurogenesis during aging, but others factors such as loss of stem cells, elevated corticosterone level, or senescence of cells produce the major decline in hippocampal neurogenesis with aging.

6. Potential role of neurogenesis in inflammation-induced cognitive deficits

Activation of the immune system leads to a host of well characterized behavioral changes, some of which are adaptive responses that facilitate recovery and others less so. Sickness behavior is a constellation of behavioral alterations that include a decrease in locomotion, social and sexual behavior, development of anorexia and a fever response (Dantzer, 2004). These behavioral changes are thought to reflect an altered motivation state rather than a physical disability and expedite recovery through energy conservation among other mechanisms. In addition to the expression of sickness behaviors, activation of the immune system has been shown to impair aspect of cognitive function. These inflammation-induced cognitive deficits may simply reflect unwelcomed side effects of immune activation that can persist beyond the expression of sickness behaviors (Kohman et al., 2007). While it is beyond the scope of the present review to discuss all of the research that demonstrates inflammation can impair cognitive function we intend to highlight central findings and the potential connections between the alterations in behavior and hippocampal neurogenesis.

Though exceptions can be found, the cognitive deficits induced by inflammation are typically observed in hippocampus-dependent tasks, such as contextual fear conditioning, the Morris water maze, or tasks that have a hippocampal component such as two-way active avoidance (Hein et al., 2010; Kohman et al., 2007; Kranjac et al., 2012; Pugh et al., 1998; Sparkman et al., 2005; Yirmiya and Goshen, 2011) whereas tasks such as auditory fear conditioning that are independent of hippocampal activity are unaffected (Pugh et al., 1998). Inflammation has been shown to affect various stages of memory formation from impairing acquisition to disrupting consolidation and reconsolidation broadening the potential scope of processes that may be affected by inflammation (Kohman et al., 2007; Kranjac et al., 2012; Pugh et al., 1998; Yirmiya and Goshen, 2011). Generally, immune activation is a transient response and with it the deficits in cognition recede as the immune response terminates. However, certain factors such as normal aging or the presence of a chronic inflammatory disease may make individuals more susceptible to persistent inflammation-induced cognitive deficits. Therefore identifying the mechanisms through which inflammation impairs cognitive processes may have particular benefit for individuals suffering from conditions characterized by chronic inflammation.

Currently, the mechanisms through which inflammation impairs cognitive function remain unknown. However, several processes known to play a role in learning and memory are impaired following immune activation. For instance, evidence indicates that inflammation may impair cognitive processes through disrupting aspects of long-term potentiation (LTP), one of the most widely recognized cellular mechanisms for learning and memory (Cunningham et al., 1996; Murray and Lynch, 1998). An additional mechanism through which inflammation could disrupt cognitive function is through altering levels of neurotrophic factors in the brain such as brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor (IGF), which

are known to be critically involved in supporting memory formation, neurogenesis and LTP (Fan et al., 1995; Guan and Fang, 2006; Kranjac et al., 2012; Park et al., 2011). Inflammation is also associated with reduced basal and event-induced neural activation as measured by expression of the immediate early gene Arc (Frank et al., 2010; Hein et al., 2010), indicating that neuroinflammation blunts the brain's response to a learning experience as compared with a healthy brain. As described, inflammation decreases neurogenesis which has been correlated with performance in several of the behavioral tasks that show deficits following an immune challenge. These data potentially indicate that the inflammation-induced deficits in cognitive performance may be related to the reductions in neurogenesis, particularly when the inflammatory response persists for extended periods of time. However, presently there is no direct evidence to indicate that inflammation-induced suppression of hippocampal neurogenesis mediates the cognitive deficits associated with immune activity. Future work is needed to address the extent to which reductions in hippocampal neurogenesis directly contribute to the cognitive deficits following immune activation.

7. Conclusion

The evidence clearly indicates that neuroinflammation can suppress hippocampal neurogenesis. However, we are just beginning to understand the role microglia play in regulating neurogenesis under basal conditions in the absence of an infection or injury. Clearly, microglia are not simply waiting around in the brain for an infection to occur, but rather are participating in basal neural processes, such as neurogenesis. Progress in research has created a broader view of microglia's role within the brain. Potentially through understanding the phenotypes microglial cells can acquire, and the factors and circumstances that induce the varied states of activation, we can identify means of regulating microglia in ways that promote brain health and cognitive function. Further, a more complete understanding of the immune system's interaction with new cells born in the adult brain and how immune activation contributes to or modifies the neurogenic niche has vast potential to aid in development of novel therapies to facilitate regenerative processes within the brain. New strategies that target microglial cells and/or neuroinflammatory signaling in the brain could potentially improve the success of neural replacement therapy, and help to preserve the rate of neurogenesis throughout life.

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