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INVITED REVIEW

Dysregulation of neurogenesis by neuroinflammation: key differences in neurodevelopmental and neurological disorders

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Abstract

Embryonic neurogenesis is the process of generating neurons, the functional units of the brain. Because of its sensitivity to adverse intrauterine environment such as infection, dysregulation of this process has emerged as a key mechanism underlying many neurodevelopmental disorders such as autism spectrum disorders (ASD). Adult neurogenesis, although is restricted to a few neurogenic niches, plays pivotal roles in brain plasticity and repair. Increasing evidence suggests that impairments in adult neurogenesis are involved in major neurodegenerative disorders such as Alzheimer's disease. A hallmark feature of these brain disorders is neuroinflammation, which can either promote or inhibit neurogenesis depending upon the context of brain microenvironment. In this review paper, we present evidence from both experimental and human studies to show a complex picture of relationship between these two events, and discussed potential factors contributing to different or even opposing actions of neuroinflammation on neurogenesis in neurodevelopmental and neurological disorders.

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Introduction

Neurogenesis is the process of generating neurons by neural stem cells (NSC) and/or neural progenitor cells (NPC). Embryonic neurogenesis in humans starts at approximately 5 to 6 gestational weeks (GW), when neuroblasts proliferate and expand rapidly within the ventricular zone (VZ) lining the cerebral ventricles. At GW8, these neuroblasts begin transformation into radial glia, which divide asymmetrically into either daughter radial glia or NPCs. Post-mitotic immature neurons derived from NPCs then exit the VZ and migrate extensively to reach their destination, where they further develop into mature neurons and become integrated into local circuits. The embryonic neurogenesis peaks at late embryonic and early fetal periods, and by early postnatal stage it declines significantly. Before 1990s, it had long been believed that the adult brain lacks neurogenic potentials. This view has since been changed and today it is well-recognized that the adult brain can generate new neurons in both physiological and pathological circumstances, though the rate of neurogenesis is much lower than its embryonic counterpart. In addition, the neurogenic regions in the adult brain are largely limited to the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus (DG), known as neurogenic niche. The SVZ and SGZ harbor large numbers of NSCs and radial glia, which self-maintain the progenitor pool through the adult life, and generate new neurons upon physiological as well as pathological stimuli.

Neurogenesis during Development and Adulthood: Similarities and Differences

Embryonic neurogenesis is an evolving, dynamic, and spatiotemporally regulated developmental event orchestrated by genetic, epigenetic, and environmental factors. The ultimate goal of embryonic neurogenesis is to establish future brain structures with dedicated cytoarchitecture and chemicoarchitecture, which lies at the foundation of high brain functions. Taking corticogenesis as an example, it starts with migration of post-mitotic immature neurons out of the VZ dorsally to form the first recognizable structure named preplate. Within the preplate, early born pioneer neurons act as stepping stones to establish primitive connections from the developing thalamus and brainstem by serving as synaptic targets. The preplate later splits into the marginal zone and the subplate layer, the latter is yet another evolving layer that plays a pivotal role in establishing and refining intracortical, extracortical, and thalamocortical circuitries. Around GW 7–8, the cortical plate, which eventually develops into layers II–VI of the cerebral cortex, emerges between the subplate

(which dissolves later) and the marginal zone (which gives rise to layer I). Through such a successive migration, expansion, and maturation of neurons, the cortical laminae are formed in an "inside-out" fashion (Tau and Peterson, 2010). In order to reach the outermost layer of the cortex, post-mitotic neurons need to migrate extensively along processes of radial glia, which serve as scaffolds at this stage but also generate neurons and macroglia (astrocytes and oligodendrocytes) around birth. There are major differences in the development of projection and inhibitory neurons. The majority of cortical projection neurons migrate radially from VZ, whereas GABAergic interneurons are generated from the medial ganglionic eminence (MGE) and migrate tangentially to populate the cerebral cortex. As a critical component of neurogenesis, neuronal migration is guided by a diverse range of neurochemical cues such as neural cell adhesion molecule (NCAM), reelin, contactin-associated protein-like 2 (CNTNAP2), disrupted-in schizophrenia 1 (DISC1), *etc*. Emerging evidence suggests that dysregulation of many of those molecules plays an important pathogenic role in major neurodevelopmental disorders including autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), and schizophrenia (SZ) (Ernst, 2016).

The dogma that the adult brain lacks neurogenic potential was challenged in the 1990s. When examining post-mortem brains from cancer patients who had undergone chemotherapy, several studies found $BrdU^+$ neuroblasts in the adult brain. Shortly after these reports, the presence of proliferating neuroblasts in the adult brain was confirmed in various animal species including primates. Furthermore, it was demonstrated that adult neurogenesis takes place not only under physiological conditions but also upon brain injury, and the newly generated neurons could migrate towards injured sites, suggesting that adult neurogenesis functions as an endogenous repair mechanism (Apple et al., 2017). These pioneering studies spurred intensive interest in exploring the cellular and molecular mechanisms as well as the function of adult neurogenesis, and significant progress has been made in the past 20 years. Today, the basic neurobiology of SVZ and SGZ neurogenesis is well-elucidated. The SVZ-generated neurons migrate to the striatum and differentiate into striatal interneurons (in rodents they migrate to the olfactory bulb *via* the rostral migratory stream, RMS), whereas the SGZ generated neurons migrate to the granule cell layer, where they differentiate into mature granule neurons and integrate into local circuits. Since the hippocampus plays a central role in learning and memory, the functional contribution of SGZ neurogenesis is of particular interest. Utilizing a variety of *in vivo* approaches including neuroimaging, electrophysiology, and behavioral tests, it has been well demonstrated that SGZ neurogenesis plays a pivotal role in learning, memory, and mood regulation (Song et al., 2012). Notwithstanding that the SVZ and SGZ are considered to be the principle neurogenic regions in the adult mammalian brain, recently it has been shown that many other regions including the amygdala, neocortex, substantia nigra, tegmentum, brainstem, and spinal cord, also maintain neurogenic potentials. The functional roles of neurogenesis in these regions, however, remain largely unexplored.

A plethora of studies suggest that the molecular machineries regulating embryonic and adult neurogenesis are rather similar (Urban and Guillemot, 2014; Gotz et al., 2016). For example, both are regulated by similar neurogenic transcription factors (TFs), including the homeodomain proteins (*e.g.*, Pax6, Gsx2 and Dlx), the basic helix-loop-helix (bHLH) proneural TFs (*e.g.*, Ascl1, Neurog2, and Neurod1), and extrinsic signaling molecules (*e.g.*, Wnt, BMP, and certain growth factors). In addition, embryonic radial glia and adult NSCs share common molecular markers, such as GFAP, Nestin, and Sox2. Despite these similarities, there are several significant differences. The foremost is the distinctive behaviors between the embryonic and adult NSCs. The embryonic NSCs proliferate rapidly and their progeny, the post-mitotic immature neurons, migrate a great distance to populate the entire brain. In contrast, the adult NSCs within the neurogenic niches acquire quiescent states and remain for a long period of time out of the cell cycle, while their progeny migrate either along restricted routes or in short distances (*e.g.*, the SVZ neurons migrate to the olfactory bulb *via* RMS, while the granule cells in the DG migrate within the granule cell layer). Secondly, embryonic NSCs have greater differentiation potentials, that is, they can generate a vast diversity of neuronal and glial types, which is in contrast to rather limited neuronal types (either periglomerular or granule cells) generated from adult NSCs. The major factor underlying these differences is the distinct extracellular microenvironment in which the embryonic and adult NSCs are exposed. The extracellular milieu of the embryonic brain, which changes rapidly, favors neurogenesis, while in the adult brain it remains in a stable homeostasis and generally favors gliogenesis. Lastly, in terms of function, the adult SGZ neurogenesis is unique and clearly sets apart from embryonic neurogenesis. It becomes clear in recent years that adult-born neurons of the hippocampus is required for experience-dependent memory formation, especially spatial and contextual learning and memory (Petsophonsakul et al., 2017).

Upon pathological insults such as neuroinflammation, a large array of inflammatory cytokines are secreted into the extracellular space. The biological actions and profiles of these secreted inflammatory cytokines can vary in a context-dependent manner (*e.g.*, acute *vs*. chronic inflammation, developing *vs*. mature brain, *etc*.), and neuroinflammation as a whole can affect neurogenesis either positively or negatively. Because microglia, the primary sources of brain inflammatory cytokines upon activation, are also critically involved in normal embryonic neurogenesis (see below), the effect of neuroinflammation on neurogenesis is more complicated in neurodevelopmental disorders than

adult neurological disorders.

Dysregulation of Neurogenesis in Neurodevelopmental and Neurological Disorders

Embryonic neurogenesis consists of multiple steps of cell development, including NPC proliferation, differentiation, migration, and maturation. These events are principally controlled by genetic programs, but could also be influenced by epigenetic and extracellular factors, which are prone to adverse prenatal environmental challenges. Emerging data indicate that many neurodevelopmental and/or neuropsychiatric disorders, including ASD, ADHD, SZ, and bipolar disorders, *etc*., may stem from aberrant neurogenesis during prenatal development (Ernst, 2016). A common characteristic of these disorders is their complex etiological origins, which involve multiple genetic and environmental risk factors linked to neurogenesis. On the genetic side, for example, many risk genes for ASD and SZ are involved in neural induction, neurogenesis, synaptogenesis, and immune system (Casanova and Casanova, 2014). Among many environmental risk factors, maternal infection and/or immune challenge (which are perhaps the most pervasive adverse events during pregnancy) are increasingly realized to play a major etiological role in both ASD and SZ. While ASD and SZ seem to be two very different disorders in terms of phenotypes, they may share similar etiology and pathophysiology at critical early developmental periods. For example, several lines of evidence suggest that imbalance between excitatory and inhibitory neurotransmission, which is proposed to underline high incidences of seizure in ASD and SZ patients, is rooted at aberrant synaptic pruning and/or interneuron development. Due to ethical issue, it is not possible to study neurogenesis in human fetal tissue; however, a growing body of postmortem studies suggest that there might be an accelerated neurogenesis in ASD. For instance, neuronal density in the frontal cortex was found to be significantly higher in ASD individuals as compared to the controls (Courchesne et al., 2011), this is consistent with large body of neuroimaging data showing accelerated brain growth in ASD infants around 1-year of age (Sacco et al., 2015). In addition, it was found that genes involved in proliferation, cell cycle, and apoptosis, were differentially expressed in the prefrontal cortex of young ASD subjects (Chow et al., 2012), suggesting a dysregulated cell growth and cell number control. Strikingly, a recent study demonstrated that neural organoids developed from induced pluripotent stem cells (iPSCs) of ASD patients, exhibited accelerated cell cycles (Mariani et al., 2015). These postmortem data, although are invaluable, are not without controversy. Nevertheless, when analyzed closely with data from animal studies, together they provide great insight into early neurobiology of ASD. One of the widely used animal models for ASD and SZ is maternal immune activation (MIA, commonly induced by exposing pregnant animals to bacterial endotoxin LPS, or viral mimics such as the double-stranded RNA poly I:C). Interestingly, altered neuronal proliferation, migration, and differentiation, have been well-replicated in the MIA model (Estes and McAllister, 2016).

Adult neurogenesis is known to be highly plastic, *i.e*., it can be influenced by various physiological stimuli such as physical exercise and behavioral experience. Notably, non-physiological stimuli such as certain medications including antidepressant drugs, also affect adult neurogenesis (Samuels et al., 2014). With regard to pathological conditions, either an increase or decrease in neurogenesis has been reported. Increased neurogenesis was reported at early stages of certain neurological disorders, including traumatic brain injury and stroke (Kernie and Parent, 2009). Although direct evidence from human studies is limited, available data converge on the idea that in many chronic neurodegenerative disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), *etc*., neurogenesis is impaired (Winner and Winkler, 2015). In the case of increased neurogenesis, however, the contribution of new neurons to functional recovery is limited due to the fact that the majority of newborn neurons (~80%) die by apoptosis (Kuhn, 2015). The exact mechanisms underlying poor survival of newborn neurons are not fully understood, but may be principally attributed to challenging extracellular environments of the adult brain, both intrinsically and extrinsically. As mentioned above, the extracellular milieu of the adult brain, which is unfavorable for neurogenesis, could be further modified towards anti-neurogenic during neurological diseases.

Neuroinflammation and Neurogenesis: the Role of Microglia

Neuroinflammation is a complex cellular and molecular response of brain cells to pathological stimuli that aims at maintaining homeostasis and repairing tissue. Since both neuroinflammation and altered neurogenesis are commonly found across CNS disorders, studying a causative role of neuroinflammation in dysregulated neurogenesis has gained increasing attention. In certain disorders such as MS, stroke, and traumatic brain injury, the blood-brain barrier (BBB) is often compromised enabling systemic inflammatory mediators and/or immune cells to gain access to the brain parenchyma, where they interact with microglia to contribute to overall neuroinflammation. In most cases without clear evidence of BBB damage, neuroinflammation may be largely attributed to activate microglia and astrocytes, although systemically generated cytokines can communicate with the brain through multiple pathways including vagus nerve and circumventricular organs (McCusker and Kelley, 2012). At present, the effect of neuroinflammation on neurogenesis remains controversial; however, based on studies in neurodegenerative disorders, it appears that in general, chronic neuroinflammation negatively regulates neurogenesis. Much of the work has been focused on the roles of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6, on neurogenesis

in neurodegenerative disorders, and their effects appear to vary in different disorders (discussed below). In addition to inflammatory cytokines, toll-like receptor 4 (TLR4), which is chiefly responsible for innate immune response and is highly expressed by neuroglia including microglia, is also involved in modulating adult neurogenesis. However, the mode of actions remains inconclusive due to inconsistent or even contradictory reports. For example, it was reported that TLR4 deficiency resulted in enhanced DG NSC proliferation and differentiation in mice, while LPS treatment led to reduced NPC proliferation in wild-type mice (Rolls et al., 2007). In contrast, several *in vivo* (Su et al., 2005) and *in vitro* (Go et al., 2009) studies showed that LPS treatment led to enhanced NPC proliferation. Such discrepancies might arise from, at least partially, effects of cytokines released upon TLR4 activation. Although LPS is the most potent ligand, TLR4 can also be activated by other endogenous ligands such as ATP, fibronectin, *etc*., which could be released from damaged neural cells under pathological challenges. In stroke models, it was shown that TLR4 deficient mice exhibited increased number of NPCs in the SVZ but reduced neuroblast migration following ischemia (Moraga et al., 2014). Consistently, in an intracerebral hemorrhage stroke model, Lei et al. (2015) reported that blockage of TLR4 inhibited neurogenesis and worsened functional recovery in rats. Interestingly, β-amyloid protein appears to also interact with TLR4 to affect neurogenesis. For example, in a mice model of AD, blockage of TLR4 abolished β-amyloid oligomers-induced memory impairment in mice (Balducci et al., 2016).

In the inflamed adult brain, microglia affect neurogenesis primarily through secreted inflammatory mediators. However, in the developing brain, the mechanisms may be more complex, given the fact that microglia play essential roles in normal brain development. Microglia regulate normal embryonic neurogenesis *via* a number of mechanisms, including phagocytosis, receptor-mediated bidirectional communication with neurons, and secreted molecules such as nitric oxide (NO), cytokines, chemokines, and growth factors (see below). Although it has been long recognized that microglia plays essential roles in modulating neural network maturation *via* "synaptic pruning" and controlling neuronal numbers *via* programmed neuronal death (PND), the critical involvement of microglia in neurogenesis has emerged only in recent years. In the layer V of early postnatal mice, it was demonstrated that microglia support NPCs survival by secreting trophic factors (Ueno et al., 2013). Seemly paradoxical to such a pro-survival effect, numerous studies reported a pro-death effect of microglia on neurons. In the prenatal mice hippocampus, microglia enhance PND by CD11b/DAP12 integrin signaling-dependent production of reactive oxidative species (ROS) (Wakselman et al., 2008). During corticogenesis, microglia not only phagocytize apoptotic but also intact immature neurons in the layer V cortex (Cunningham et al., 2013). These evidence underscores complex mechanisms by which microglia regulate developing neurogenesis in a highly context-dependent manner (Ueno and Yamashita, 2014; Sato, 2015). Following activation by pathological insults, not only do microglia produce a plethora of inflammatory mediators, their normal developmental functions are likely altered. In addition, microglia can be activated by not only the pathogen-associated and danger-associated molecular patterns (PAMPs and DAMPs, respectively), but also many adverse perinatal insults such as stress, environmental toxins, and certain medications, *etc*. Thus, the effect of neuroinflammation on embryonic neurogenesis is complicated by the fact that the highly orchestrated, time-sensitive, and context-dependent microglia activities pertinent to normal neurogenesis, are compromised in neurodevelopmental disorders. Based on this, it likely that neuroinflammation either enhances or suppresses embryonic neurogenesis, depending upon a variety of factors such as the timing, magnitude, and nature of insults.

Signs of microglia activation, such as increased cell density and altered morphology, upregulation of proinflammatory and/or anti-inflammatory cytokines, have been reported in postmortem ASD patients. As mentioned earlier, several lines of evidence suggests that neurogenesis may be increased, at least in a subset of ASD cases. A critical question that remains to be determined is whether neuroinflammation plays a causative role in the enhanced neurogenesis in ASD. Recently, it was reported that in the cortex of postmortem ASD subjects, a gene module regulating M2-like microglia activation was significantly upregulated, which was negatively correlated with a dysregulated gene module involved in neuronal development (Gupta et al., 2014). Interestingly, we recently reported that rat pups (on postnatal day 3) exposed to LPS developed certain ASD-like behaviors, which were associated with a M2-like microglia activation and enhanced neurogenesis in both SVZ and SGZ regions (Pang et al., 2016). This evidence hints a potential involvement of M-2 like microglial activation in aberrant neurogenesis in ASD.

Neuroinflammation and Neurogenesis: the Role of Inflammatory Cytokines

A great effort has been devoted to investigating the role of inflammatory cytokines in regulating neurogenesis. During chronic neuroinflammation, as noted in many neurodegenerative disorders, it is thought that the classically activated microglial state and/or multiple proinflammatory cytokines act as suppressors on neurogenesis, although this remains controversial due to inconsistent or even opposite reports, especially from *in vivo* studies (Fuster-Matanzo et al., 2013). *In vitro* studies tend to more consistently report inhibitory and/or detrimental effects of proinflammatory cytokines on NPC proliferation and/or survival; however, their effect on neurogenesis can be either positive or negative, depending on many factors such as species, regions of NPCs being isolated, and different experimental settings, *etc*., as discussed in a recent review (Borsini et al., 2015). Among many proin-

flammatory cytokines, TNF-α, IL-1β, and IL-6 are the most frequently studied, and their effects on neurogenesis are complex. Both TNF-α and IL-1β regulate normal embryonic and adult SGZ neurogenesis. For example, at the embryonic stage, IL-1β is expressed at relatively high levels and is required for proper hippocampal neurogenesis, as evidence by impairments in hippocampus-mediated memory formation in IL-1 receptor knockout mice (Avital et al., 2003). In the adult brain, IL-1β is greatly downregulated but remains constitutively expressed to support hippocampal neurogenesis. Overexpression of IL-1β reduced doublecortin (DCX) positive neurons and/or inhibited memory formation (Wu et al., 2012), suggesting a dose-dependent relationship between IL-1β and neurogenesis. During chronic neuroinflammation, IL-1β is markedly upregulated and its effect on neurogenesis becomes suppressive, as demonstrated by many *in vivo* and *in vitro* studies. By contrast, the effect of TNF-α on hippocampal neurogenesis appears to be dependent on its receptors, that is, activation of TNFR1 suppresses neurogenesis, whereas TNFR2 increases neurogenesis (Chen and Palmer, 2013). Finally, many *in vitro* studies demonstrated that IL-6 promotes NPCs towards gliogenesis with a concurrent reduction in neurogenesis. Overexpression of IL-6 in the astrocytes significantly reduced neurogenesis in adult mice (Vallières et al., 2002).

Neuroinflammation is associated with production of not only classical proinflammatory mediators, but also anti-inflammatory cytokines and trophic factors. The most important anti-inflammatory cytokine and trophic factors released by activated microglia include IL-4, IL-10, transforming growth factor-β (TGF-β), insulin-like growth factor 1 (IGF-1), basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF), *etc*. Those cytokines are mostly associated with pro-neurogenic effect (Belarbi and Rosi, 2013). For example, *in vitro*, IL-10 and IL-4 upregulated the surface adhesion molecule lymphocyte function-associated antigen 1 (LFA-1) and chemokine receptors CXCR4 and CCR5 on NSCs, suggesting that IL-10 and IL-4 may promote neuronal migration. IL-4 polarized microglia have been shown to encourage neurogenesis, which is mediated at least partially by IGF-1 released from microglia (Butovsky et al., 2006). Thus, pretreatment with anti-inflammatory cytokines such as IL-4 and IL-10 may provide neuroprotection by enhancing neurogenesis, or facilitate migration of NSCs (endogenous or transplanted NSCs) to the site of damage.

Chronic Neuroinflammation and Neurodegenerative Disorders

A common feature of neurodegenerative disorders, AD and PD in particular, is chronic neuroinflammation and/or microglia activation, which likely affect adult neurogenesis and contribute to disease development. Initially regarded as an epiphenomenon in neurodegenerative process, neuroinflammation is increasingly realized as an integral component of many neurodegenerative disorders. A number of reviews have devoted to this topic (Thundyil and Lim, 2014; Calsolaro and Edison, 2016) so we will only discuss briefly. There are many potential factors contributing to a chronic neuroinflammatory state in AD and PD, and the dominant hypothesis is that a vicious cycle is formed between glial activation and neuronal death, that is, DAMPs released from degenerated neurons activate glial cells *via* TLRs, whereas neuroinflammation further promote neurodegeneration. We want to emphasize that ageing may also contribute significantly to a baseline neuroinflammation. Needless to say, aging itself is a high risk factor for a number of neurodegenerative disorders including AD and PD. It becomes clear that a chronic inflammatory state, which is present in both the periphery and central nervous system (CNS), is a prominent feature of ageing. As we age, the innate immunity becomes dysregulated, resulting in persistent inflammatory state (Shaw et al., 2013). This phenomenon was coined as "inflamaging" by Franceschi and colleagues (Franceschi et al., 2007). It was argued that individuals with healthy ageing are armed with efficient anti-inflammatory network to neutralize the pro-inflammatory state, while those with pathological aging are deficient in such an anti-inflammatory mechanism.

In summary, mounting evidence suggests that neuroinflammation affects both embryonic and adult neurogenesis, contributing to the pathogenesis of numerous neurodevelopmental, neuropsychiatric, and neurological disorders. However, many questions remain unaddressed. For example, simply put, in the inflamed brain, a diverse range of inflammatory molecules co-exist and potentially interact, and the converging effect on neurogenesis may be different from that of individual cytokines. Furthermore, such effect may vary significantly between the embryonic and adult brain. When the precise mechanisms of how neuroinflammation regulates neurogenesis in the context of different diseases are better clarified, it is hopeful that modulating neurogenesis by targeting neuroinflammation may provide a novel therapeutic strategy for those brain disorders.

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