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COMMENTARY

# Microglia and neurogenesis in the epileptic dentate gyrus

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**ABSTRACT**

Microglia are recognized as major immune cells in the brain. They have been traditionally studied in various contexts of disease, where their activation has been assumed to induce mostly detrimental effects. Recent studies, however, have challenged the current view of microglia, clarifying their essential contribution to the development of neural circuits and brain function. In this review, we particularly discuss the role of microglia as the major orchestrators that regulate adult neurogenesis in the hippocampus. We also review the roles of microglia in seizure-induced adult neurogenesis in the epileptic dentate gyrus. Specifically, we introduce our recent study, in which we identified a novel mechanism by which viable newborn cells in the adult dentate gyrus are phagocytosed and eliminated by microglia after status epilepticus, maintaining homeostasis of the dentate circuitry. This review aims to reconsider the microglial function in adult neurogenesis, especially when they are activated during epileptogenesis, challenging the dogma that microglia are harmful neurotoxic cells.

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## Introduction

Microglia are recognized as resident immune cells in the brain that exhibit a phagocytic capacity and originate from erythromyeloid progenitors in the early embryonic yolk sac.[1] Recent studies have revealed that microglia engulf and remove less active synapses[2,3] in the healthy brain as well as dead cells and cell debris during inflammation, indicating their role in regulating homeostasis of the central nervous system (CNS). However, compared to neurons and astrocytes, the discovery and introduction of microglia into the neuroscience arena has been delayed half a century, which leaves microglia as one of the least-understood cell types in the brain. In particular, the specific molecular and cellular mechanisms through which microglia communicate and interact with other cell types are only beginning to be explored. Here, we summarize and discuss the data concerning the involvement of microglia in adult neurogenesis, a process of generating and functionally incorporating neurons into pre-existing neuronal circuits. Specifically, we focus on adult neurogenesis in the subgranular zone (SGZ) of the hippocampal dentate gyrus and discuss the role of microglia in both physiological and pathological conditions, which is related to our recently published paper entitled 'Microglia engulf viable newborn cells in the epileptic dentate gyrus' published in the journal *Glia*.[4]

## In physiological conditions

Accumulating research has promoted our understanding of the origin of newborn neurons and their survival, maturation and integration into pre-existing neuronal circuits in the adult hippocampus (Fig. 1). Genetic fate-mapping studies have demonstrated that the radial glia-like neural stem cells in the SGZ, an intermittent zone between the granular cell layer and the hilus, are the source of newborn neurons in the dentate gyrus.[5] These neural stem cells give rise to intermediate neural progenitor cells (NPCs), which in turn give rise to neuroblasts and immature neurons.[6,7] Immature neurons migrate into the inner granule cell layer and differentiate into mature dentate granule cells.[8] At each stage of neurogenesis, surveillant microglia are suggested to regulate the fate and development of adult-born neurons.

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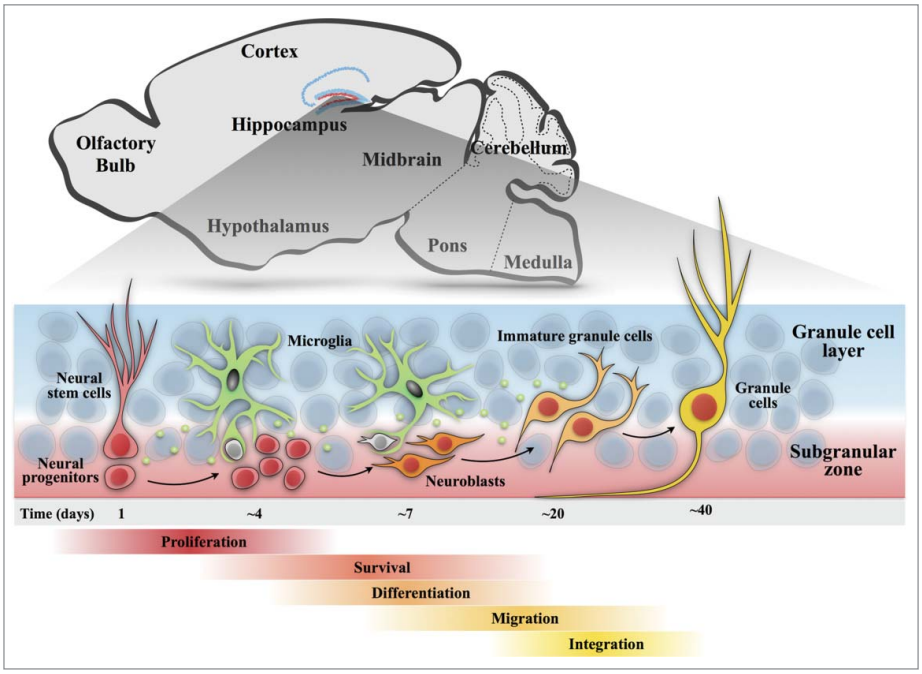


**Figure 1.** Schematic diagram of the process of adult neurogenesis in the hippocampus. A sagittal view of an adult rodent brain highlighting the dentate neurogenic niche. In the adult dentate gyrus, neurogenesis undergoes 5 continuous stages. Stage 1, proliferation: amplifying neural progenitors are generated from the neural stem cells with their cell bodies located within the subgranular zone and radial processes projecting through the granular cell layer. Stage 2, survival: a large proportion of progenitors undergoes apoptotic death (gray) in the early period of their life. Stage 3, differentiation: progenitors differentiate into immature neurons (orange). Stage 4, migration: immature neurons migrate a short distance into the granule cell layer. Stage 5, integration: new granule cells (yellow) receive inputs from the entorhinal cortex and send axons to synapse CA3 and hilar neurons. In each stage of neurogenesis, surveillant microglia regulate the fate and development of newborn neurons via the engulfment of apoptotic cells (Sierra et al., 2012) and secreting inflammatory and growth factors, such as IL-1$\beta$,[19] TGF, PDGF, EGF and BDNF[26,57].

### *Proliferation*

In normal physiological conditions, newborn cells are constantly generated in the adult SGZ, but this proliferating rate is altered by changes in the surrounding milieu, which are induced by environmental enrichment, voluntary exercise, and aging. Rodents with a free access to a running-wheel exhibit significantly enhanced cell proliferation, as well as improved performance in spatial memory and learning tasks.[9] The effects of exercise are not restricted to the proliferation of NPCs. For example, running also increases the activation of both cortical and hippocampal microglia.[10,11] Thus, it is possible that the exercise-induced activation of microglia contributes to enhanced NPCs.

Vukovic et al. found that microglia were able to activate latent NPCs through the C-X3-C chemokine receptor 1 (CX3CR1) pathway in the hippocampus of mice that underwent exercise (wheel-running).[12] The C-X3-C motif chemokine 1 (CX3CL1)-CX3CR1 signaling is important in regulating the neurotoxic effects of microglia, such as releasing cytokines and abnormal engulfment. Although it is debatable which cell type expresses CX3CL1 and CX3CR1, CX3CL1 is principally expressed in neurons, while CX3CR1 is expressed in microglia.[13-15] Previous reports have determined that interactions between CX3CL1 and CX3CR1 contribute to maintaining microglia in a resting phase, partially controlling their neurotoxicity.[16,17] In addition to the exercise-related neurogenesis, the CX3CL1-CX3CR1 axis is suggested to be involved in the aging-related reduction of neurogenesis. Both the proliferation rate of NPCs and the expression levels of CX3CL1 decrease with aging, and Bachstetter et al. investigated the relationship between CX3CL1-CX3CR1 signaling and aging-induced effects on neurogenesis.[18] They found that the disruption in CX3CL1-CX3CR1 signaling in young adult rodents decreased the proliferation of NPCs by activating interleukin-1$\beta$ (IL-1$\beta$) signaling. The activation of the IL-1 receptor (IL-1R) in NPCs decreases the level of cyclin D1, a regulator of the G1 cell cycle expressed in NPCs, which suppresses NPC proliferation without affecting apoptosis.[19]

### Survival

Ninety percent of newborn cells undergo apoptotic death in the first 1 to 4 d of their life, during the transition from amplifying NPCs to neuroblasts. Thus, the survival rate of newborn cells critically affects the number of neurons incorporated into the hippocampal circuitry. It has been shown that these apoptotic NPCs during the early stage of neurogenesis are effectively and rapidly cleared through phagocytosis by non-activated microglia.[20] However, the consequences of microglial phagocytosis on adult hippocampal neurogenesis remain elusive. Treatment of mice with annexin V, which binds to the phosphatidylserine (PS) receptor and prevents the recognition of PS on the surface of apoptotic cells, presumably blocking phagocytosis, increases the number of apoptotic cells and reduces neurogenesis in the SGZ.[21] This indicates that blocking microglial-mediated phagocytosis alone is not able to increase the survival rate of NPCs. Indeed, annexin V reduced neurogenesis by decreasing the survival of neuroblasts without affecting the proliferation of NPCs.[22] These findings suggest that the clearance of apoptotic newborn cells by microglia promotes the survival rate of NPCs.

Apoptosis of newborn cells may be directly induced by microglia-released cytokines, such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$). TNF-$\alpha$ triggers the apoptosis of hippocampal neurons via NF-$\kappa$B translocation.[23] The TNF-$\alpha$ receptor tumor necrosis factor receptor 1 (TNF-R1) is expressed in proliferating NPCs, and the survival rate of these cells in SGZ was increased in TNF-R1 knockout mice.[24] Another study showed that TNF-$\alpha$ released by microglia induces the apoptosis of NPCs, a process mediated by Bcl-2-associated X (bax) protein, which functions as an apoptotic activator.[25] In contrast, microglia-released growth factors not only enhance neuronal proliferation but also neuronal survival. The immunodepletion of transforming growth factor (TGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), or brain-derived neurotrophic factor (BDNF) from microglial conditioned medium resulted in a significant reduction in neuronal survival.[26] Furthermore, in the context of the enriched environment, the expression level of insulin-like growth factor-1 (IGF-1) was elevated in microglia in the dentate gyrus,[27] which suggested that the effects of an enriched environment on neurogenesis are partially mediated by microglia.

### Maturation

In addition to proliferation and survival, microglia have the capacity to guide the differentiation of precursor cells isolated from the embryonic brain and adult mouse NPCs toward a neuronal phenotype. An in vitro study showed that NPC cultures grown in conditioned media from microglia contain a higher proportion of neurons. Furthermore, microglia-released soluble factors, which have not yet been molecularly identified, direct the migration of NPCs.[28]

When newborn granule cells are synaptically integrated into pre-existing neural circuits, they need to compete with mature granule cells to invade and replace pre-existing synapses[29,30] probably in an activity-dependent manner.[31,32] Because adult-born immature granule cells are more excitable than mature granule cells,[33,34] they are more efficient in generating action potentials, even with weak glutamatergic inputs,[35] and probably have a greater chance to win the synaptic sites. Recent studies have demonstrated that microglia preferentially engulf weak or less active synapses, contributing to the development of refined functional neural circuits with strong or more active synapses.[2,3] Thus, the microglial-mediated engulfment of pre-existing synapses may be involved in the efficient formation of synapses by newborn granule cells.

Together, in the hippocampal neurogenic niche, microglia are versatile modulators of neurogenesis. Importantly, microglia can either enhance or suppress neurogenesis in response to the environmental milieu.

## In epileptic conditions

In the healthy CNS, microglia are in a "surveillance state," in which they exhibit a highly ramified morphology with thin processes that dynamically move in the brain parenchyma.[36] In contrast, upon a pathological insult, such as infection or brain injury, microglia rapidly retract their processes, proliferate and start releasing neurotoxic factors, such as proinflammatory cytokines.[37-39]

It has been shown that epileptic seizures induce microglial activation in the hippocampus, partly mediated by the activation of Toll-like receptor 9, an innate immune sensor known to recognize microbial DNA.[40] In animal models of temporal lobe epilepsy, status epilepticus (SE) acutely enhances adult neurogenesis, which results in an increased number of newborn

granule cells.[41,42] However, the functional properties of these extra granule cells after SE remain to be clarified. Accumulating evidence suggests that many newborn granule cells exhibit abnormal differentiation after SE and display hilar basal dendrites and aberrant axonal sprouting as well as ectopic settling in the dentate hilus.[43-46] Furthermore, the elimination of newborn granule cells after SE decreased both the abnormal sprouting of the granule cell axons and the ectopic positioning of granule cells,[46] attenuating spontaneous recurrent seizures.[47] In contrast, Jakubs et al. suggested that SE-induced newborn granule cells are normally incorporated into the dentate circuits, possibly serving a compensatory role to restore inhibition.[48] Thus, the selective elimination of SE-induced newborn granule cells is likely critical to homeostasis of the activity level of the dentate gyrus.

In our recent study published in Glia,[4] we found that microglia selectively engulf extensively proliferating cells after SE to suppress the number of newborn cells to control levels to ensure homeostasis of the dentate circuitry. However, it should be noted that newborn cells were labeled only at 4 d after SE and traced until 11 d after SE. In addition, we found that microglial activation gradually increased after SE, peaking at 6 d after SE and lasting for 2 weeks. Thus, we do not exclude the possibility that seizure-induced newborn cells that were born other than 4 d post-SE survived microglial engulfment more efficiently. These survived newborn cells may account for increased cell numbers after SE in most of long-term tracing studies, in which newborn cells were labeled several times after SE.

It has previously been assumed that microglia engulf dead or dying cells but not living cells[49] and that microglia engulf dead newborn neural progenitor cells and their cell debris in the SGZ;[20] however, recent studies have indicated that microglia can also engulf living cells during development,[50] inflammation,[51] and under neuropathological conditions.[52,53] This type of phagocytosis is referred to as "primary phagocytosis" because phagocytosis itself is the primary cause of cell death. In contrast, "secondary phagocytosis" refers to the phagocytosis of dying and dead cells (both apoptotic and necrotic) as well as cell debris.

In our study,[4] we immunohistochemically analyzed the expression of the apoptosis marker cleaved (active) caspase-3 in the DG and found that microglia are rapidly activated and engulf caspase-3 negative post-SE-born viable cells via primary phagocytosis (Fig. 2). In

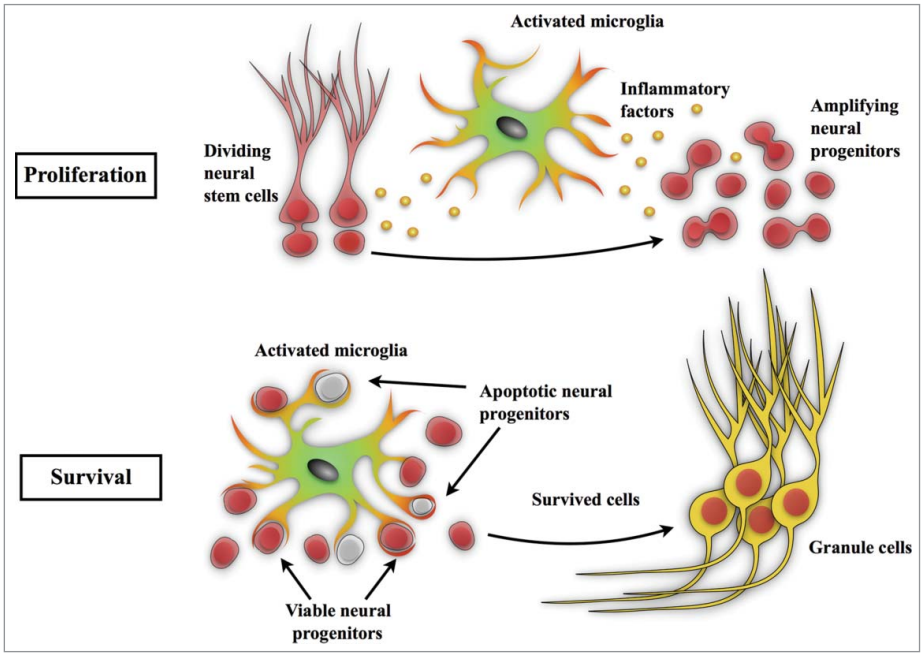


**Figure 2.** Microglia in seizure-induced neurogenesis. Epileptic seizures increase neurogenesis as well as microglial activation in the dentate gyrus. In the stage of proliferation, activated microglia produce inflammatory cytokines, such as TNF$\alpha$,[40] which suppress the aberrant proliferation of neural stem/progenitor cells. In the survival stage, our recent study[4] revealed that both apoptotic and viable newborn cells in the dentate gyrus are phagocytosed and eliminated by microglia after status epilepticus. These studies demonstrate that microglia play a pivotal role in neurogenesis and in maintaining homeostasis of the dentate circuitry after epileptic seizures.

addition, we showed that the suppression of microglial activation by minocycline resulted in an increase of ectopic newborn cells in the dentate hilus. Although activation of caspase-3 occurs at the beginning of apoptotic processes, leaving the possibility that the caspase-3 negative cells were also undergoing apoptotic processes, we confirmed that caspase-3 negative cells being engulfed by microglia exhibited normal nucleus morphologies. Consistent with our study, a recent study by Abiega et al. showed that microglia engulf viable neurons after SE in the hippocampus.[54] Thus, the activation of microglia might be a promising strategy to eliminate ectopic newborn cells, which could provide aberrant excitatory networks in the dentate gyrus after SE, to prevent the resultant epileptogenic processes.

In addition to their phagocytic capacity, microglia contribute to homeostasis of neural circuits through the release of both neurotoxic and neuroprotective factors. Recently, Matsuda et al. reported that after SE, activated microglia secrete TNF-$\alpha$ to attenuate the proliferation of neural progenitor cells in the SGZ.[40] Thus, microglia perform a stepwise regulatory mechanism to maintain the number of newly incorporated cells in the dentate circuitry. However, whether microglia regulate the other processes of neurogenesis, including the migration and integration of NPCs in the dentate gyrus, remains to be clarified.

Future studies are necessary to examine whether and how microglia choose which cells to kill and which to keep alive. Several 'don't-eat-me' and 'eat-me' signals, such as PS and complement molecules, have been suggested to modulate the phagocytic capacity of microglia.[2,55,56] Whether these molecules are involved in triggering the primary phagocytosis of progenitor cells during the process of neurogenesis remains to be investigated.

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