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Review article

# Functions and mechanisms of microglia/macrophages in neuroinflammation and neurogenesis after stroke

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ABSTRACT

Microglia/macrophages are the major immune cells involved in the defence against brain damage. Their morphology and functional changes are correlated with the release of danger signals induced by stroke. These cells are normally responsible for clearing away dead neural cells and restoring neuronal functions. However, when excessively activated by the damage-associated molecular patterns following stroke, they can produce a large number of proinflammatory cytokines that can disrupt neural cells and the blood-brain barrier and influence neurogenesis. These effects indicate the important roles of microglia/macrophages in the pathophysiological processes of stroke. However, the modifiable and adaptable nature of microglia/macrophages may also be beneficial for brain repair and not just result in damage. These distinct roles may be attributed to the different microglia/macrophage phenotypes because the M1 population is mainly destructive, while the M2 population is neuroprotective. Additionally, different gene expression signature changes in microglia/macrophages have been found in diverse inflammatory milieus. These biofunctional features enable dual roles for microglia/macrophages in brain damage and repair. Currently, it is thought that the proper inflammatory milieu may provide a suitable microenvironment for neurogenesis; however, detailed mechanisms underlying the inflammatory responses that initiate or inhibit neurogenesis remain unknown. This review summarizes recent progress concerning the mechanisms involved in brain damage, repair and regeneration related to microglia/macrophage activation and phenotype transition after stroke. We also argue that future translational studies should be targeting multiple key regulating molecules to improve brain repair, which should be accompanied by the concept of a "therapeutic time window" for sequential therapies.



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*Abbreviations:* Ang1, angiopoietin 1; BBB, blood–brain barrier; CAA, cerebral amyloid angiopathy; CNS, central nervous system; CO, carbon monoxide; DAMPs, danger-associated molecular patterns; DC, dendritic cell; DCX, doublecortin; EP, ethyl pyruvate; GA, glycyrrhizic acid; Gal3, galectin-3; Hb, hemoglobin; HMGB1, high-mobility group box 1 protein; HO, hemeoxygenase; ICH, intracerebral hemorrhage; IL-18, interleukin-18; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; IRF, interferon regulatory factor; I/R, ischemia and reperfusion; LCN2, lipocalin 2; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MMP-9, matrix metalloproteinase; MyD88, myeloid differentiation factor 88; NLR, nucleotide-binding domain (NOD)-like receptor; NO, nitric oxide; Nrf2, NF-E2-related factor-2; NSCs, neural stem cells; NPCs, neural progenitor cells; P2 × 7R, purinergic 2 × 7 receptor; PAMPs, pathogen-associated molecular patterns; PPARγ, peroxisome proliferator activated receptor γ; PPRs, pattern recognitionreceptors; Prx, peroxiredoxin; RAGE, receptor of advanced glycation end-products; ROS, reactive oxygenspecies; SAH, subarachnoid hemorrhage; SDF1, stromal-derived factor 1; SGZ, subgranular zone; SSL3, superantigen-like protein 3; SsnB, sparstolonin B; STAT, signal transducer and activator of transcription; SVZ, subventricular zone; TLRs, Toll-like receptors; Tregs, regulatory T lymphocytes.

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## 1. Introduction

Over the past decades, an increasing amount of research data from experimental and clinical stroke studies have helped us to understand the complex factors relating to the pathophysiological processes of stoke, including ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Once ischemia occurs, along with the cerebral blood flow reduction and energy deprivation the native microglia undergo morphological changes (Davalos et al., 2005; Dunn et al., 2001; Gyoneva et al., 2009; Masuda et al., 2011) in preparation for the forthcoming immune response. When reperfusion begins, microglia become activated in the penumbra and start to expand cellular protrusions towards the adjacent blood vessels. Subsequently, these perivascular activated microglia start to engulf endothelial cells via phagocytosis, which allows the entrance of blood serum components (Jolivel et al., 2015). The morphological and phenotypic changes in the native microglia in the brain represent an initiation of the events in response to stroke, which are accompanied by the subsequent infiltration of macrophages. Recently, these two immune cells have been found to be derived from the same origin (Ginhoux et al., 2010) and to have similar biofunctions, such as producing inflammatory mediators and clearing cellular debris. However, these two types of cells can play different roles in the injured brain, which may involve different patterns of gene expression (Butovsky et al., 2014). For example, microglia may protect the injured brain while macrophages concomitantly damage the brain under the same circumstances (Yamasaki et al., 2014).

The immune system is considered to play a significant role in determining the condition of the brain and the survival of patients following stroke (Iadecola and Anrather, 2011). Microglia/macrophages are the major cells in an organism's immune system, and they play important roles in CNS repair and regeneration (Hanisch and Kettenmann, 2007). In addition to their neuroprotective roles, microglia/macrophages are also the major producers of proinflammatory cytokines, which can greatly inhibit brain repair and neurogenesis (Ekdahl et al., 2003; Smith et al., 2012). Therefore, the dual roles of microglia and infiltrating macrophages hamper the brain's restoration after stroke. The inflamed microenvironment greatly influences the phenotypic changes in microglia/macrophages, which results in different gene expression patterns and biofunctions in the same brain tissue. This may be explained by the findings that the M1 phenotype of microglia/macrophages induced for instance by lipopolysaccharide (LPS) mainly exhibits destructive effects on the brain, while the M2 phenotype inducible by IL-4 exhibits neuroprotective effects on the brain (Hu et al., 2015). Therefore, these results suggest that, in general, promoting the M2 phenotype and inhibiting the M1 phenotype can be beneficial to brain recovery after stroke.

Furthermore, promoting effective neurogenesis is gradually becoming an important therapeutic method for the treatment of stroke because the dead and lost neurons in the cortical lesions need to be replaced by new-born neurons to replenish and reconstruct the neuronal connections. Recent studies show that microglia/macrophages are involved in each step of neurogenesis. For example, microglia/macrophages produce trophic factors to guide cell migrations (Batchelor et al., 2002), but they can also produce inflammatory cytokines to reduce the survival of newborn neurons (Liu et al., 2007). Therefore, understanding the details of the roles and mechanisms of microglia/macrophages in neurogenesis after stroke would provide help in promoting novel and exciting therapeutic approaches for brain repair.

In this review article, we discuss microglial and macrophage morphologies and phenotypic changes in response to acute brain damage and repair in the context of stroke. Given these modifiable and adaptable functions of microglia/macrophages, we argue that future translational studies should be targeting multiple key regulating molecules involved in changes in microglia/macrophage activation and polarization and that the studies should incorporate the concept of a “therapeutic time window” for sequential therapies. Finally, we also give some suggestions for further research, such as constructing new experimental stroke models, identifying new gene signatures for circulating immune cells when they enter into the CNS, and exploring the endogenous