

# Role of neuroinflammation in ischemic stroke

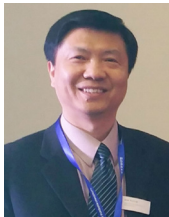
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## ABSTRACT

Ischemic stroke causes the depletion of energy and induce excitotoxicity and neuroinflammation in the brain that results from thrombotic blockage. Neuroinflammation occurs initially depending on activated resident microglia that has the same function as the macrophage. Activated microglia participates in the neuroinflammatory process by phagocytosing the injured brain cells and producing the pro- and anti-inflammatory mediators. In this review, the authors present an overview of the role of microglia in mediating neuroinflammation in ischemic stroke.

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## INTRODUCTION

Stroke is an acute episode of focal dysfunction of the brain, retina or spinal cord lasting longer than 24 h, or for any duration if imaging (computed tomography or magnetic resonance imaging) or autopsy show focal infarction or hemorrhage relevant to the symptoms. Stroke is comprised of ischemic stroke (most

common at approximately 85%) causing cerebral, retinal, and spinal infarction and hemorrhagic stroke (15%) that may result from intracerebral hemorrhage and subarachnoid hemorrhage [Figure 1]. Almost 90% of strokes are attributable to risk factors such as hypertension, regular physical inactivity, high apolipoprotein, insufficient diet quality, psychosocial factors, current smoking, cardiac causes, high alcohol



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consumption, and/or diabetes mellitus.<sup>[1]</sup>

Ischemic stroke is caused by arterial embolism and *in situ* small vessel diseases. Embolism in brain results in oxygen and glucose deprivation, leading to brain damage and neurologic deficit. The cellular and molecular mechanisms underlying ischemic stroke-induced brain damage have been extensively investigated. Excitotoxicity, oxidative stress, and inflammation have been considered as major contributors to ischemic neuronal injury.<sup>[2]</sup> Cerebral ischemia induces large release of glutamate that causes over-activation of NMDA receptors and large inflow of  $\text{Ca}^{2+}$ , leading to excitotoxicity-induced cell death.<sup>[3-7]</sup> The process of ischemia-reperfusion induces the production of superoxide and nitric oxide from damaged neurons and astrocytes and depletes glutathione, a primary antioxidant to protect against reactive oxygen species-mediated DNA damage.<sup>[8-10]</sup> Inflammation occurs after ischemia-reperfusion injury, which is caused by the dying cells and debris in the absence of microbes.<sup>[11,12]</sup>

There is an increasing evidence to showing complex role of the immune system in the pathophysiological changes that occur following ischemic stroke.<sup>[13]</sup> For example, brain injury activates neutrophils and macrophage/microglia,<sup>[14]</sup> as well as the lectin pathway of complement activation and the toll-like receptors (TLRs) that are the sensors in the innate immune system,<sup>[15,16]</sup> which leads to amplification of the inflammatory cascades. The immune system is closely involved in all the stages of ischemic stroke-induced brain damage and tissue repair by the parenchymal processes.<sup>[17,18]</sup> When activated, the adaptive immune system is intervened by lymphocyte populations that include T - B cells and regulatory T

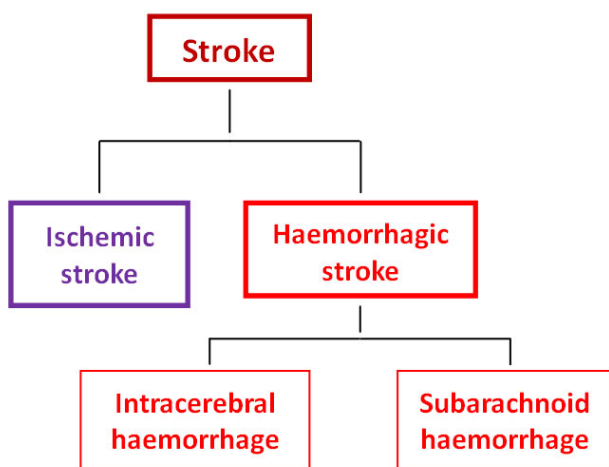
cells.<sup>[19]</sup> Additionally, stroke induces the deleterious antigen-specific autoreactive responses, but it also has beneficial effects.<sup>[20]</sup> The ischemic brain can act through the autonomic nervous system to have suppressive effect that can induce intercurrent infections and contribute to the morbidity and mortality after stroke.<sup>[21-23]</sup> Therefore, immune system-mediated inflammation is critically involved in determining the fate of the brain following ischemic stroke.<sup>[24-26]</sup> Understanding the mechanisms underlying role of neuroinflammation in ischemic stroke would provide important targets for the development of therapy in ischemic stroke.

The aim of this review is to offer an overview of the current knowledge about the immune system and the neuroinflammatory processes in ischemic stroke. We focus on how the neuroinflammatory processes are triggered by ischemic stroke, and how microglia cells play a role in neuroinflammation after ischemic stroke.

## NEUROINFLAMMATION

Neuroinflammation, an inflammatory response in the brain, occurs in a variety of acute brain diseases.<sup>[27,28]</sup> The non-diseased brain is separated by the blood brain barrier (BBB) from periphery.<sup>[29]</sup> The BBB prevents immune cells that are in the blood from entering brain tissue.<sup>[30]</sup> Brain is an independent immune-privileged organ with the innate. Neuroinflammation is regulated by the production of reactive oxygen species (ROS), cytokines and chemokines.<sup>[31]</sup> Once neuroinflammation happens, it enhances the release of several cytokines in the brain.<sup>[32,33]</sup> It also involves the reaction of innate immune cells (i.e. the microglia) in the parenchyma, the infiltration of myeloid cells and the adaptive immune cells (i.e. lymphocytes).<sup>[34]</sup> But the own innate immune system of brain operates mainly dependent on microglia, astrocyte and the expression of TLRs on these glia as well as the release of interleukins.<sup>[35,36]</sup>

Microglia is an innate immune cell that is well-characterized as the resident macrophage of the brain.<sup>[37]</sup> Astrocyte is important mediator of homeostasis in the brain.<sup>[38]</sup> These two cells are key players in the multicellular response to central nervous system (CNS) trauma and disease, including the immune reactions.<sup>[39,40]</sup> TLRs, the well-defined pattern recognition receptors of the immune system,<sup>[41]</sup> can initiate an immune response upon exposure to harmful microorganisms<sup>[42]</sup> and play a key role in macrophage activation. Neuronal TLR's play a central role in connecting the interactions between the immune system and the nervous system.<sup>[42]</sup> Interleukin's act as



**Figure 1:** Stroke is comprised of ischemic stroke (85%) and hemorrhagic stroke (15%) (intracerebral hemorrhage and subarachnoid hemorrhage)

essential innate immune modulators and conduct an array of biological processes.<sup>[43]</sup>

The neuroinflammation process is decided by the scene, duration and course of the neurological insult.<sup>[44]</sup> Neuroinflammation can perform function that are either supportive or destructive by which is determined by the immune signals relayed to the CNS. The nature of neuroinflammatory function can depend on the conditions and the intensity and duration of inflammation.<sup>[45]</sup> The positive role associated with neuroinflammation is only present for a brief, controlled inflammatory situations and responses and this can be considered as performing a protective function to the host organism.<sup>[46-48]</sup> For example, during low transient inflammation that may occur during infections, the immune cell signals to the brain by increasing the expression of interleukin (IL)-1 cytokine, this then increasing the 'surveillance' role of glia cells in the brain if infected.<sup>[49,50]</sup> The transient inflammation of traumatic CNS injury, following the expression of IL-4, has been shown to promote injury recovery and axonal regrowth.<sup>[51,52]</sup> On the contrary, the negative aspects of neuroinflammation mainly represent maladaptive inflammatory responses.<sup>[53,54]</sup> The common characteristics of this aspect is increasing, supraphysiological production of cytokines [IL-1 and tumor necrosis factor (TNF)], ROS, and other inflammatory mediators including inducible nitric oxide synthase.<sup>[55]</sup> These markers are highly evident in the high traumatic CNS, giving rise to collateral damage.<sup>[56]</sup> Following the acute phase of CNS trauma, the IL-1 and IL-6 drive a low-level and chronic inflammatory response, leading to cognitive impairments and reduced neuronal plasticity.<sup>[57]</sup>

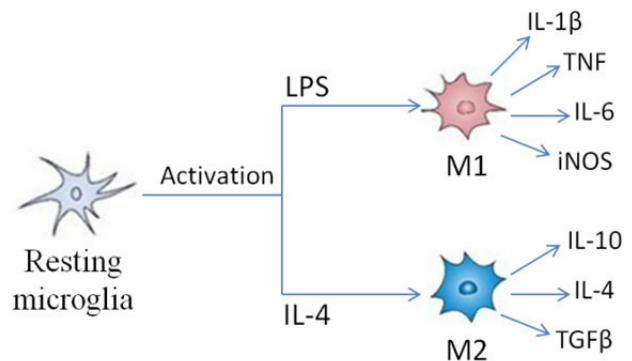
## MICROGLIA AND NEUROINFLAMMATION

Microglia are the innate immune cells of the CNS, and are key modulators of the immune response in the brain.<sup>[37]</sup> Microglia is considered as the resident macrophage in the brain and the initial responders to tissue damage.<sup>[58]</sup> Microglia express receptors that respond to various stimuli that may as a consequence result in their activation.<sup>[59]</sup> A large number of studies indicate that microglia expresses different proteins and cytokines that display different role to express different function.<sup>[60]</sup> Activated microglia have two phenotypes: classically activated (M1) and alternatively activated (M2).<sup>[61]</sup> The M1 microglia are pro-inflammatory and thus secrete cytokines and oxidative metabolites such as IL-1 $\beta$ , TNF, IL-6 and nitric oxide,<sup>[62]</sup> whereas M2 microglia contributes to recovery after brain injury. M2 microglia expresses anti-inflammatory mediators, such as IL-10, IL-4 and give out various neurotrophic

factors, which prevent inflammation and improve injury [Figure 2].<sup>[63]</sup> M1 microglia tends to induce neuronal cell death. Recent research has demonstrated that the M1 phenotype microglia can be switched to the M2 phenotype.<sup>[64]</sup> One study has shown that HIV-associated dementia initiates and maintains M1 phenotype microglia in the CD40 ligation by CD40L and TNF $\alpha$ . These microglia may later switch microglia to the M2 phenotype via up-regulation of CD45.<sup>[65]</sup> In a pathological condition, the corresponding stimuli may active microglia and cause them to change their shape and function and initiate phagocytosis.<sup>[66]</sup> Microglia works in close association with astrocytes to release cytokines that lead to a cascade of events which can modulate the neuroinflammatory respond. Meanwhile, the microglia cells produce and release excitotoxic metabolites that can damage surrounding tissue. Sometimes a short-term neuroinflammatory response is likely good for recovering the damages or infected tissue.<sup>[67]</sup> On the contrary, a long period of time neuroinflammatory process may damage the surrounding brain tissue.<sup>[68]</sup>

## ROLE OF MICROGLIA IN NEUROINFLAMMATION AFTER STROKE

Neuroinflammation occurs in different types of brain injuries including ischemic stroke. Ischemic stroke mediated brain injury results in necrosis and apoptosis.<sup>[69-71]</sup> The damaged cells and debris induces neuroinflammation in areas in and around the ischemic injury in the brain.<sup>[72]</sup> Ischemia-induced cell debris and increased ROS lead to neuroinflammation by activating resident microglia and astrocytes as well as attracting infiltrating leukocytes from circulating blood.<sup>[73]</sup> These cells increase major



**Figure 2:** Activated microglia has two activation phenotypes: classically activated (M1) and alternatively activated (M2). M1 microglia is considered as pro-inflammatory, activated by LPS which produces pro-inflammatory cytokines and oxidative metabolites such as IL-1 $\beta$ , TNF, IL-6 and nitric oxide. M2 microglia contributes to recovery after brain injury activated by IL-4 and express anti-inflammatory mediators, such as IL-10, IL-4, TGF $\beta$ . LPS: lipopolysaccharide; IL: interleukin; TNF: tumor necrosis factor; TGF: transforming growth factor

histocompatibility complex class II molecules and cytokines.<sup>[74-76]</sup> Following activation of microglia, the release of pro-inflammatory mediators from these microglia favor the permeability of the BBB. Together with the secretion of chemokines, this promotes the successive entry of systemic leukocytes including neutrophils, macrophages and lymphocytes, which share several functional features with microglia.<sup>[77,78]</sup>

Microglia is the resident macrophage of the brain and a key modulator of immunologic responses after ischemic stroke. Under normal conditions, microglia is primarily involved in activity-dependent synaptic pruning and repair.<sup>[37]</sup> When ischemic stroke occurs, the native microglia undergoes morphological transformation from a ramified resting state in preparation for the forthcoming immune response.<sup>[79,80]</sup> Once reperfusion beginning, microglia come to be activated to an active, characterized by many branching processes in the penumbra, motile amoeboid state.<sup>[81]</sup> These activated microglia start to engulf endothelial cells via phagocytosis, which allows the entrance of blood serum components.<sup>[82]</sup> Active microglia phagocytoses foreign organisms as well as injured brain cells.<sup>[60,83]</sup> In ischemic stroke, activation of microglia is the early stages of the neuroinflammation process even within minutes.<sup>[83-85]</sup> Several reports have demonstrated that defective microglial activation increased the infarction and apoptosis after ischemic stroke.<sup>[86]</sup>

Microglial activation following ischemic stroke can promote activated microglia to migrate toward the ischemic hemisphere of the cerebral cortex.<sup>[87]</sup> It is suggested that active microglia have predominantly harmful effects in the acute stages of ischemic stroke and most beneficial effects appear in delayed stages.<sup>[62,88]</sup> Microglia morphology is changed either to M1, the typically activated phenotype, or to M2, an alternatively activated phenotype, after stroke.<sup>[61,89,90]</sup> M1 microglia activated by LPS and the pro-inflammatory cytokine interferon-gamma (IFN- $\gamma$ ) shows harmful effect after stroke.<sup>[91]</sup> In contrast, M2 phenotype microglia contribute to stroke recovery through anti-inflammatory cytokines such as IL-4.<sup>[92]</sup> In ischemic stroke, the M2 phenotype is dominant in both local microglia and newly recruited macrophages at earlier stages. The M1 phenotype increases progressively in peri-infarct regions. Thus, ischemic neuron induces changes towards the M2 phenotype in microglia and macrophages.<sup>[62]</sup> Considering the opposing roles of microglia phenotypes in ischemic stroke, it is critical to develop therapeutic strategy by restraining the morphological transformation and promoting the beneficial of microglia.

## ROLES OF CYTOKINES IN CEREBRAL ISCHEMIA

### IFN- $\gamma$

IFN is a type cytokines that plays a key role in the immune system. The IFN family cytokines are divided into two types. Type I IFNs constitute by a largest IFN class and comprise the IFN- $\alpha$ , - $\beta$ , - $\epsilon$ , - $\kappa$ , and - $\omega$ , type that share notable sequence homology and are produced by most cell types. IFN- $\gamma$  is a unique member of the type II IFN.<sup>[93,94]</sup> IFN- $\gamma$  is principally secreted by monocytes, macrophages, T cells, natural killer (NK) cells, dendritic cells and B lymphocytes. IFN- $\gamma$  is a critical regulator of immune function and provides a robust first-line of defense against invading pathogens. Additionally, IFN- $\gamma$  has plenty of biological functions including regulation of several aspects of the immune responses, stimulation of antigen presentation via upregulating class I and class II major histocompatibility complex (MHC) molecules on the surface of macrophages and T cells. IFN- $\gamma$  when bound to its cognate receptor can activate a variety of downstream signaling pathways, particularly the Janus kinase (JAK)/signal transducer and activator of transcription (STAT).<sup>[95,96]</sup> All of these characteristics potentially influence the process of atherogenesis. Numerous lines of evidence have indicated that IFN- $\gamma$  is highly expressed in atherosclerotic lesions and believed to have a critical role in the atherogenesis.<sup>[97]</sup> Stroke is the main atherosclerosis disease.<sup>[98]</sup> Under inflammatory conditions, MHC class II specific CD4+ cells will be activated. Activated CD4+ cells easily infiltrate through BBB into the CNS following cerebral I/R.<sup>[99]</sup> Therefore, microglia have the opportunity to retain and further stimulate CD4+ cells already primed to differentiate into T helper 1 (TH1) cells producing proinflammatory cytokines (IL-2, IFN- $\gamma$ , TNF- $\alpha$ ) or into T helper 2 (TH2) cells producing cytokines that support antibody-mediated responses (IL-4, IL-5, IL-10, IL-13).<sup>[100]</sup> IFN- $\gamma$  is thought to have a key role in the polarization of microglia. TH1 cells produces proinflammatory cytokines IFN- $\gamma$  that can return to activation microglia into M1 phenotype, shows pro-inflammatory response, and produces pro-inflammatory cytokines and oxidative metabolites.

### IL-1 $\beta$

IL-1 $\beta$  belongs to the family IL-1. IL-1 $\beta$  is a key immunoregulatory and proinflammatory cytokine that affects almost all cell types. IL-1 $\beta$  is produced following the formation of a inflammasome; such as monocytes and macrophage/microglia.<sup>[101]</sup> After Ischemic stroke, IL-1 $\beta$  can activate nuclear factor (NF)- $\kappa$ B via the activation of TLRs allowing NF- $\kappa$ B to transactivate genes associated with cytokines,

chemokines and other proinflammatory mediators.<sup>[102]</sup> In a pathological condition, IL-1 $\beta$  also connects with the activation and proliferation of astrocytes and microglia. After Ischemic stroke, the microglia will be activated, the M1 phenotype of microglia can express IL-1 $\beta$  which act as a proinflammatory cytokines to play neurotoxic effect.<sup>[62]</sup> In addition, IL-1 $\beta$  can prime the endothelium for increased leukocyte adherence and edema formation.<sup>[103]</sup> At suprphysiological levels IL-1 $\beta$  can be neurotoxic, however, IL-1 $\beta$  can also promote astrocytes to secrete survival promoting factors.<sup>[104]</sup> IL-1 $\beta$  when bound to its cognate receptor the IL-1 receptor (IL-1R) can also result in IL-1R-dependent increase in NF- $\kappa$ B pathways. However, if the levels of IL-1 $\beta$  are increased above a specific threshold, it can result in the increase of greater amounts of the IL-1 receptor antagonist (IL-1Ra). It is this balance between IL-1 $\beta$  and its antagonist the IL-1Ra that is more important for its global effect and role than just the IL-1 $\beta$  itself.<sup>[105]</sup> Thus, we predict that balance of IL-1 $\beta$  and IL-1Ra might be good predictor for patient outcome following ischemic stroke. However, few clinical studies have made use of their level as stroke biomarkers. IL-1 $\beta$  levels mostly were associated with poor long-term functional outcome in study,<sup>[106]</sup> while IL-1Ra levels have shown to be predictive of the development of post-stroke infections.<sup>[107]</sup>

### Transforming growth factor beta

Transforming growth factor beta (TGF- $\beta$ ) proteins are multifunctional cytokines with pleiotropic functions.<sup>[108]</sup> TGF- $\beta$  can regulate various biological processes, including hematopoiesis, angiogenesis, cell proliferation, differentiation, migration and apoptosis. TGF- $\beta$  also plays an important role in the regulation of the immune system. TGF- $\beta$  is a superfamily, including inhibins, activins, growth differentiation factors (GDFs), bone morphogenetic proteins (BMPs), TGF- $\beta$  isoforms, and glial cell derived factors.<sup>[109]</sup> The main research object is TGF- $\beta$  isoforms. TGF- $\beta$  exists in at least three isoforms: TGF- $\beta$ 1, TGF- $\beta$ 2, and TGF- $\beta$ 3.<sup>[110]</sup> In the TGF- $\beta$  superfamily, only TGF- $\beta$ 1, produced by activated microglia, and TGF- $\beta$ 2, produced by astrocytes and neurons.<sup>[111]</sup> TGF- $\beta$ 1 and TGF- $\beta$ 2 increased prominently after ischemic stroke. After Ischemic stroke, TGF- $\beta$  produced by activated M2 phenotype macrophage, plays an anti-inflammatory role and contributes to recovery after brain injury.<sup>[63]</sup> TGF- $\beta$  reduces microglial activation and thus reduces the potential harmful effects associated with activated microglia. TGF- $\beta$  decreases the expression of other poisonous cytokines and suppresses the release of oxygen and nitrogen derived products. TGF- $\beta$  can also stimulate the release of IL-1Ra and promote angiogenesis.<sup>[112]</sup> Its protective effects, however, are

limited to the peri-infarcted area, as TGF- $\beta$  can inhibit apoptosis but not necrosis.<sup>[113]</sup>

### IL-4

IL-4, its congener of IL-13, a product of select immune cells that has highly polyfunctional properties. IL-4 is known to regulate a variety of immune and inflammatory responses, including T cell differentiation and IgE class in B cells.<sup>[114]</sup> IL-4 is primary produced by TH2 cells.<sup>[115]</sup> During CD4<sup>+</sup> cellular activation, cytokines are through T cell receptor mediated signaling and co-stimulation. For instance, IL-4 mediated activation of the signal transducer and activator of transcription 6 plays an important role during TH2 cell differentiation.<sup>[116]</sup> IL-4 have a unique properties as it polarizes macrophages/microglia toward the M2 phenotype which is anti-inflammatory phenotype.<sup>[117]</sup> M2 macrophages/microglia expresses anti-inflammatory mediators and give out various neurotrophic factors that aid in the resolution of inflammation via increased trophic input and the augmentation of phagocytosis and proteolysis of dead, diseased cells/proteins, ultimately paving the way for tissue repair.<sup>[118]</sup> Consequently, IL-4 may have a neuroprotective function to promote tissue repair and may act as a therapeutic factor.

## STROKE-ASSOCIATED INFECTION AND NEUROINFLAMMATION

Infection frequently occurs in both and after stroke that can induce immune and neuroinflammatory responses.<sup>[119-122]</sup> The characteristics of post-stroke infections include immune suppression, elevation of IL-6, decreases in TNF- $\alpha$  levels and inflammation are among the factors. Along with stroke-associated infection, inflammatory responses are the defense mechanism against infection and it can also be a pathogenic mechanism that precipitates stroke and neurological sequelae.<sup>[123]</sup> It is generally recognized that stroke-associated infection may be a source of inflammation and autoimmunity as infection facilitates the maturation of APCs into potent immunostimulatory cells.<sup>[124]</sup> Stroke-associated infection is mostly induced by virus.<sup>[125-127]</sup> Virus enters the CNS through two pathways: (1) hematogenous dissemination through BBB;<sup>[125]</sup> (2) neuronal retrograde dissemination.<sup>[126]</sup> It also suggested that virus can replicate in macrophage and CCR5<sup>+</sup> T cells in the CNS.<sup>[127]</sup>

## CONCLUSION

The role of neuroinflammation in ischemic stroke has drawn increasing attention. In this review, we summarize the relevance of inflammation in the nervous system and introduce the neuroinflammatory cells

and mediators that occur following ischemic stroke. Microglia is the resident macrophages of the brain. After ischemic stroke, the M1 and M2 phenotype of microglia play different roles at different times. The M1 phenotype tends to induce neuronal cell death, but M2 microglia contributes to the recovery after brain injury. Down-regulation of M1 phenotype and up-regulation of M2 phenotype are considered to be the potential strategy to counteract ischemic brain injury. Recent research has demonstrated that the M1 phenotype can be switched to the M2 phenotype. But the underlying mechanisms remain unclear. Thus, understanding how and why the M1 phenotype is down-regulated and the M2 phenotype up-regulated are important current and next steps to improve our understanding of the differing role of microglia post-stroke. Probing the mechanisms of M1-M2 switch could provide new approach to protect against ischemic neuronal death. Properly controlling the transformation of microglia is an important task in the treatment of ischemic stroke.

## DECLARATIONS

### Authors' contributions

Concept and design: Q. Wan

Data analysis, manuscript preparation and editing: R. Liu

Literature search: M.X. Pan, J.C. Tang, Y. Zhang, H.B. Liao, Y. Zhuang, D. Zhao

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### Conflicts of interest

There are no conflicts of interest.

### Patient consent

No patients were involved.

### Ethics approval

Not applicable.

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