

Inflammation in the pathogenesis of ischemic stroke

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1. ABSTRACT

Ischemic stroke is a common cause of permanent disability in adults worldwide. Inflammation plays a significant role in the pathogenesis of ischemic stroke and its mechanism is complex. Both pro-inflammatory and anti-inflammatory mediators are involved in the pathogenesis of ischemic stroke, an imbalance of which leads to inflammation. Inflammatory cells from both the innate and acquired immune systems are involved in ischemic stroke-related inflammation; processes that are linked by the action of interleukin-17A (IL-17A). Although most inflammatory cells promote inflammation, T regulatory cells (Tregs) may have a protective function at the early stages of an ischemic injury, but a negative role during later stages. However, the precise mechanism of inflammation in ischemic stroke remains elusive; further understanding of it may provide new ideas for the prevention and treatment of ischemic stroke. In this review, we discuss the role of pro-inflammatory and anti-inflammatory mediators and related immune cells in the pathogenesis of ischemic stroke.

2. INTRODUCTION

Stroke is the fourth leading cause of death and a leading cause of disability in the

United States (1). Ninety-five percent of patients suffering a stroke are over the age of 45 and two-thirds of patients affected by a stroke are over the age of 65 (2, 3). Ischemic stroke is due to ischemia resulting from occlusion of an artery in the brain or a hemorrhage (4). Ischemic stroke accounts for more than 80% of all strokes (5). At the start of ischemic stroke, severe focal hypoperfusion causes excitotoxicity, which leads to oxidative damage and initiates post-ischemic inflammation (6). It is also accepted that oxidative stress after ischemic stroke is involved in the inflammatory response (7).

A decreased level of the inflammatory marker C-reactive protein (CRP) in the blood serum of patients who suffered an acute ischemic stroke is associated with good rehabilitation of neurological functions within one month after the stroke (8). CRP is also a candidate biomarker for the etiology and prognosis of childhood-onset arterial ischemic stroke (9). Thus, inflammation plays a significant role in the whole process of ischemic stroke. In the current review, we provide an overview of the role of inflammation in the pathogenesis of ischemic stroke, including the role of pro-inflammatory and anti-inflammatory mediators and related immune cells.

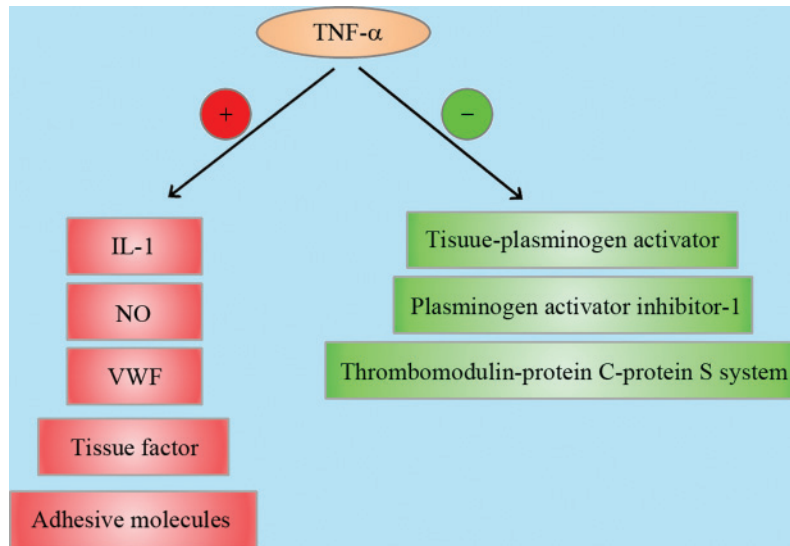


Figure 1. TNF- α in the inflammation of ischemic stroke. In the inflammation of ischemic stroke, TNF-alpha induces tissue factor, adhesive molecules for leukocytes, IL-1, nitrogen oxide (NO), clotting factor VIII (von Willebrand factor), while it suppresses the thrombomodulin-protein C-protein S system and decreases the levels of tissue-plasminogen activator and plasminogen activator inhibitor-1

3. INFLAMMATORY MEDIATORS IN THE PATHOGENESIS OF ISCHEMIC STROKE

Increased expression of pro-inflammatory mediators and lower levels of anti-inflammatory mediators are associated with larger infarctions and poorer clinical outcome. In the cerebrospinal fluid (CSF) of patients in the acute period of ischemic hemispheric stroke, pro-inflammatory cytokines are increased; whereas, protective anti-inflammatory and trophotropic factors are decreased, which may promote an inflammatory response after ischemic stroke (10). Tumor necrosis factor-alpha (TNF- α), interleukin-1 (IL-1), IL-6, IL-17 and IL-10 are cytokines involved in the inflammation of ischemic stroke. TNF- α and IL-1 are the first cytokines released before the manifestation of inflammatory symptoms and they induce the synthesis of subsequent pro-inflammatory cytokines, such as IL-6. TNF- α and IL-1 are secreted by microglia cells, intrathecal macrophages and migrating macrophages, while IL-6 is produced by microglia cells and neurons (11,12).

3.1. TNF- α

In ischemic stroke, TNF- α is crucial in terms of brain damage. The level of TNF- α in CSF is increased, both in the short-term within 24 hours after ischemic stroke, and in the long-term 3 months after the stroke (13,14). In patients with ischemic stroke,

the increased level of TNF- α in a lacunar infarction is associated with neurological severity on admission, and suggests small arterial lesions (15). In a mouse model of focal ischemic stroke, the TNF- α inhibitor 3,6'-dithiothalidomide can improve the outcome after stroke by suppressing neuroinflammation, further confirming the pro-inflammatory role of TNF- α in ischemic stroke (16). In the inflammation of ischemic stroke, TNF- α induces tissue factors, adhesive molecules for leukocytes, IL-1, nitrogen oxide (NO), and von Willebrand factor (vWF); but suppresses the thrombomodulin-protein-C-protein-S system and decreases the levels of tissue-plasminogen activator and plasminogen activator inhibitor-1 (17) (Figure 1).

3.2. IL-1

Increased expression of TNF- α , during the course of cerebral stroke, causes release of interleukin-1 (17). IL-1 plays a key role in promoting inflammation by augmenting the inflammatory response following injury. There are two forms of IL-1, IL-1 α and IL-1 β , and the IL-1 receptor antagonist (IL-1Ra) (18). IL-1 α and IL-1 β are both produced by lymphocytes or monocytes at local sites of inflammation and exert similar functions, which are mediated by IL-1Ra. Both IL-1 α and IL-1 β promote vascular damage and atherosclerosis by stimulating cell proliferation and differentiation and releasing matrix-degrading enzymes. During cerebral ischemia, both IL-1 α and

IL-1 β are secreted in the brain (19-21). Blocking IL-1 actions by administering the naturally occurring and selective IL-1Ra causes a significant reduction in neuronal loss and inflammation (22,23). IL-1 β mRNA production can be strongly induced by middle cerebral artery occlusion (MCAO) (24,25). Intraventricular injection of recombinant IL-1 β after reperfusion increases the development of brain edema, and the size and influx of neutrophils (26), whereas blockade of IL-1 β leads to a decrease in the infarct size and decreased neurological and behavioral deficits after MCAO (25). IL-1 has been identified as a novel therapeutic target for secondary prevention of ischemic stroke (27), which is demonstrative of its pro-inflammatory role in ischemic stroke. Studies investigating the mechanism of IL-1 in ischemic stroke tend to focus on the IL-1 gene and associated risk for the disease. In the Chinese population, IL-1 α -889 C/T gene polymorphism has been found to be associated with susceptibility to ischemic stroke in different studies (28,29). Two single nucleotide polymorphisms (SNPs) of IL-1 β , rs3917356 and rs1143633, are associated with an increased risk of stroke (30). The IL-1Ra gene VNTR polymorphism is associated with ischemic stroke in a Chinese population (31). In a study carried out in Sweden, the SNP rs380092 of IL-1Ra was found to be associated with an increased risk of ischemic stroke (32).

3.3. IL-6

Both IL-1 and TNF- α can induce the production of IL-6. IL-6 can act as both a pro-inflammatory cytokine, by enhancing leukocyte recruitment by up-regulating the production of chemokines and expression of adhesion molecules (33), and an anti-inflammatory cytokine, by inhibiting TNF- α expression and inducing the expression of soluble TNF- α receptors and the IL-1R antagonist (34). In ischemic stroke, IL-6 usually acts as a pro-inflammatory mediator. Patients with obstructive sleep apnea and stroke also show an increased level of IL-6 (35). An increased IL-6 level in patients, within 3-5 days after an ischemic stroke, is associated with an unfavorable clinical outcome (36). In addition to a poor outcome after ischemic stroke, the increased level of IL-6 in both acute and subacute phases is predictive of the severity of the stroke lesion (15). In the acute phase of ischemic stroke, increased IL-6 acts as a risk factor for developing comorbidities, including depressive disorders, apathy/amotivation,

somatic symptoms of depression, and neurological symptoms (37). Although IL-6 is an accepted biomarker in the prognosis of ischemic stroke, the mechanism for this role is rarely investigated. Cole and colleagues (38) observed that IL-6 gene SNPs are associated with early-onset ischemic stroke among African-American women, and that the T allele of IL6 SNP rs2069830 was found to be protective among non-smokers, suggesting this gene mutation may be involved in the mechanism of IL-6 action in inflammation after ischemic stroke.

3.4. IL-17

IL-17 is mainly produced by T-helper cells and mediates pro-inflammatory responses (39). In ischemic inflammation, IL-17A is upstream of chemokine induction (40,41). IL-17A, and Interferon (IFN)-gamma pathways are involved in the inflammation induced by ischemia/reperfusion injury. (40,42). In the acute phase of ischemic stroke, systemic IL-17 level is associated with increased T cell immunoglobulin and mucin domain 3, which may play an important role in the pathogenesis of ischemic stroke by regulation of pro-inflammatory cytokines (43). Therefore, IL-17 is a pro-inflammatory cytokine in ischemic stroke, which may be an upstream target for inflammatory pathways.

3.5. IL-10

While TNF- α , IL-1 β , IL-6 and IL-17 appear to exacerbate cerebral injury, IL-10 and TGF- β may be neuroprotective (44,45). In patients with ischemic stroke, the serum IL-10 level is decreased during the initial hours following the stroke (46,47). However, the IL-10 level in CSF increases during the early stages of a stroke, and peaks on day 2 (48). These findings suggest that the function of IL-10 may be inhibited at the early stages of ischemic stroke, when it acts as an anti-inflammatory cytokine, after the immunoprotective effect of IL-10 is activated. IL-10 can reduce the resulting brain injury following MCAO (49), suggesting that IL-10 has a protective role in ischemic stroke. In the brain, IL-10 may have a neuroprotective effect and prevent the decrease in 5-hydroxytryptamine synthesis (50). Studies on IL-10 gene mutations have provided more information about IL-10 and susceptibility to ischemic stroke. In a cross-sectional study with 1475 Chinese patients, both an increased level of IL-10 in serum and IL-10 SNPs (rs1800872, rs1554286 and rs3021094) are associated with an increased risk of ischemic stroke (51). There is a

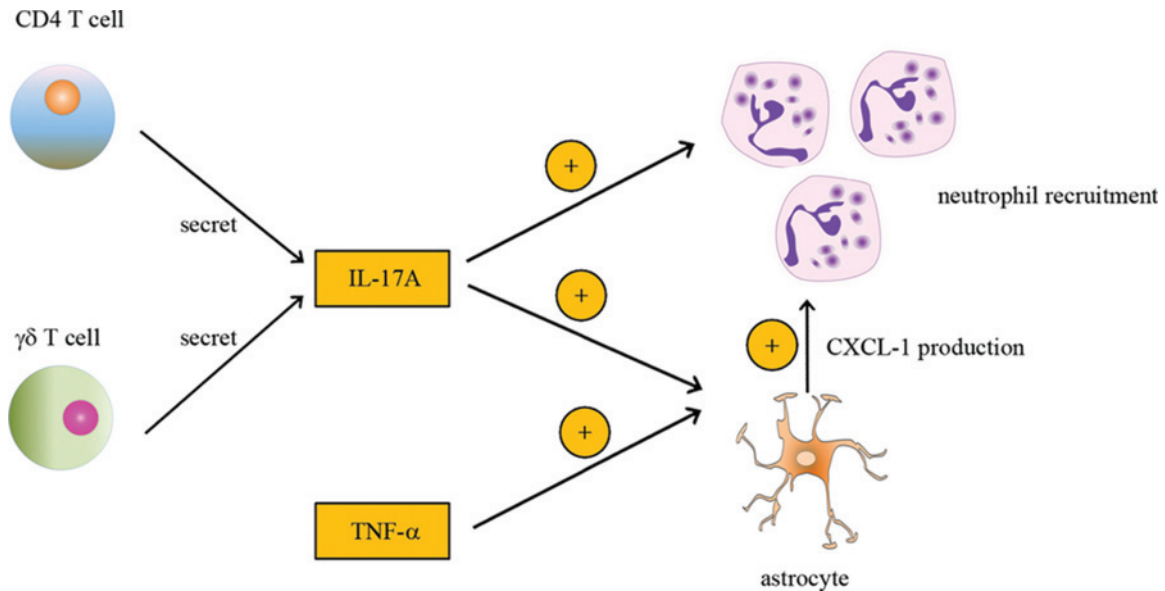


Figure 2. CD4⁺ T and CD8⁺ T cells in inflammation of ischemic stroke. In ischemic stroke, CD4⁺ T cells and gamadelta T cells produce IL-17A, resulting in neutrophil recruitment. When IL-17A is synergy with TNF-alpha on astrocytes, it increasingly secretes CXCL-1, which chemotactics neutrophil in ischemic stroke.

higher frequency of the IL-10 1082 AA genotype in adult Caucasian patients with stroke, than in controls (52). Thus, IL-10 gene mutations may be involved in the development of ischemic stroke.

4. INFLAMMATORY CELLS IN THE PATHOGENESIS OF ISCHEMIC STROKE

During ischemic stroke, microglial cells, macrophages, astrocytes, dendritic cells and T cells are involved in the inflammatory response, which has been demonstrated in a mouse model of MCAO (53). Microglial cells are resident macrophages in the brain that have immunocompetent and phagocytic functions. Ischemic stroke causes the activation of microglial cells, which induce the pro-inflammatory response by secreting pro-inflammatory mediators including TNF- α , IL-1 β , IL-6, nitric oxide, reactive nitrogen species and prostanoids (54). At the early stage after an ischemic stroke, macrophages infiltrate the local area of the ischemic lesion (55). These findings all support the pro-inflammatory role of macrophages at the acute stage of ischemic stroke. Astrocytes have a similar role to microglia in that they also produce pro-inflammatory cytokines, chemokines and NO (56).

In addition to inflammatory cells from the innate immune system, cells from the acquired

immune system participate in inflammation after ischemic stroke. In MCAO, different T-cell subpopulations are involved in the inflammatory response, despite their low level in the ischemic brain. After ischemic stroke, clonal T cell expansion is observed (57). CD4⁺ T cells, CD8⁺ T cells and gamma delta T cells promote inflammation, resulting in tissue damage (58-61). In ischemic stroke, CD4⁺ T cells and gamma delta T cells produce IL-17A, resulting in the recruitment of neutrophils. When IL-17A interacts with TNF- α on astrocytes, it increasingly secretes chemokine (C-X-C motif) ligand 1 (CXCL-1), which activates chemotactic neutrophils in ischemic stroke (62). Therefore, the innate immune response and acquired immune response are linked by IL-17A (Figure 2).

On the other hand, regulatory T cells (Tregs) and regulatory B cells may play an anti-inflammatory role in ischemic brain injury, mainly by secreting IL-10 (63,64). Although studies on regulatory B cells in ischemic stroke are rare, in recent years, research has focused on Tregs, but their role after an acute ischemic stroke remains elusive. The systemic level of Tregs is decreased 24 hours after ischemic stroke, which lasts for three days. In contrast, the number of Tregs located at the ischemic sphere is doubled on the first day after a stroke and continues to increase until day 3; and Tregs in the cerebral

parenchyma have been detected until day 5 (65). Although a previous study proposed that Tregs are cerebroprotective immunomodulators at early stages of ischemic stroke (63), a recent study found that after experimental brain ischemia/reperfusion injury, Tregs promoted acute ischemic stroke by inducing microvascular dysfunction *in vivo* through increased interaction with the ischemic brain endothelium via the leukocyte function-associated antigen-1/Intercellular Adhesion Molecule-1 (LFA-1/ICAM-1) pathway and platelets (66). These findings suggest that Tregs may have a protective function at the early stages of ischemic injury and a negative role at later stages.

5. ENDOTHELIAL DYSFUNCTION IN INFLAMMATION FOLLOWING ISCHEMIC STROKE

Vascular endothelial injury plays an important role in cerebral microbleeds, which are an indicator of cerebral vessel disease (67). The endogenous nitric oxide synthase (NOS) inhibitor, asymmetric dimethylarginine (ADMA), is a mediator of oxidative stress and endothelial dysfunction; and the structural isomer of ADMA, symmetric dimethylarginine (SDMA), is regarded as a predictor of mortality after acute ischemic stroke (68). Increased levels of ADMA and SDMA are associated with endothelial dysfunction and predict adverse outcome after ischemic stroke (68-71). After acute ischemic stroke, the plasma levels of ADMA and SDMA are associated with the levels of inflammatory mediators (72), further supporting the role of inflammation in endothelial dysfunction after ischemic stroke. On the other hand, inflammation may play a role in determining levels of vWF, which is secreted upon endothelial damage and is associated with the relative risk of ischemic stroke (73), suggesting inflammation may promote the occurrence of ischemic stroke as an upstream factor. Therefore, in the endothelial dysfunction of ischemic stroke, inflammation may be a cause as well as an effect. A further study proposed the inflammatory marker, granulocyte elastase, which is secreted by activated neutrophils and is associated with endothelial dysfunction, as a sensitive diagnostic parameter of inflammation in the initial stages of an ischemic stroke (74). Moreover, advanced endothelial dysfunction is associated with future cardiovascular events in high-risk patients (75). Inflammatory mediators, such as hs-CRP and fibrinogen, involved in the atherothrombotic process, are important predictors of future cardiovascular

mortality in patients with acute ischemic stroke (76). CRP is the most extensively studied marker of inflammation, and is a novel plasma marker of atherothrombotic disease (77). It is secreted in atherosclerotic lesions by vascular smooth muscle cells and macrophages in response to stimulation by IL-6 (78,79). CRP is associated with the risk of new cardiovascular events after ischemic stroke (80). CRP is an important marker for inflammation in the atherothrombotic pathogenesis of ischemic stroke and may be a predictor of poor patient outcome (81). The level of CRP is higher in patients with ischemic stroke than in patients with asymptomatic carotid stenosis, further demonstrating the role of CRP in predicting disease severity (82). In addition to CRP, systemic and intraplaque mediators of inflammation, including TNF- α , Chemokine (C-C motif) ligand 5 (CCL5) and intercellular adhesion molecule-1, are increased in patients symptomatic for ischemic stroke (83). Therefore, CRP plays a key role in endothelial inflammation, which is a risk factor for ischemic stroke.

6. CONCLUSIONS

Both pro-inflammatory and anti-inflammatory mediators participate in the pathogenesis of ischemic stroke. The imbalance of pro-inflammatory and anti-inflammatory mediators leads to inflammation. Inflammatory cells, including microglial cells, macrophages, astrocytes, dendritic cells and T cells, are involved in ischemic stroke-related inflammation. Among these inflammatory cells, both innate immune cells and acquired immune cells, which can be linked by IL-17A action, are involved in the inflammatory response to ischemic stroke. Whilst most of these cell types promote inflammation, Tregs may have a protective function at the early stage of an ischemic injury, and a negative role later on. Inflammation plays a significant role in the pathogenesis of both ischemic stroke and cardiovascular events, and patients with ischemic stroke often have cardiovascular complications; therefore, inflammation may be the key factor for cardiovascular events in patients with ischemic stroke. In summary, inflammation plays a crucial role in the pathogenesis of ischemic stroke; its complex mechanism involving several inflammatory mediators and inflammatory cells, remains elusive. Further understanding of it may provide new ideas in the prevention and treatment of ischemic stroke.

In the prospect, novel therapy of ischemic stroke may be promising. As far, several novel

therapeutic strategies targeting anti-inflammation have been proposed. In the acute stage of ischemic stroke, selective ablation of harmful inflammatory factors may decrease a hostile environment and promote neurogenesis (84). Kallikrein has been reported to protect against ischemic stroke by inhibiting inflammation in a rat model (85). In a mouse model of brain ischemia/reperfusion injury, the phosphodiesterase-4 inhibitor rolipram can protect from ischemic stroke by reducing inflammation through reducing the invasion of neutrophils and secretion of pro-inflammatory cytokines IL-1 β and TNF- α (86). In addition to drug therapies, long course hyperbaric oxygen can attenuate inflammation after ischemic stroke (87). These findings have led to a hope for an anti-inflammatory treatment in ischemic stroke. Future studies in patients are now needed to further investigate these possible therapies.

7. ACKNOWLEDGEMENTS

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Abbreviations: IL-17A, interleukin-17A; Tregs, T regulatory cells; CRP, C-reactive protein; CSF, cerebrospinal fluid; TNF- α , Tumor necrosis factor-alpha; IL-1, interleukin-1; Vwf, von Willebrand factor; NO, nitrogen oxide; MCAO, middle cerebral artery occlusion; SNPs, single nucleotide polymorphisms; NOS, nitric oxide synthase; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; CCL5, Chemokine (C-C motif) ligand

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