

## Review Article

# Pivotal Roles of Monocytes/Macrophages in Stroke

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Stroke is an important issue in public health due to its high rates both of morbidity and mortality, and high rate of disability. Hypertension, cardiovascular disease, arterial fibrillation, diabetes mellitus, smoking, and alcohol abuse are all risk factors for stroke. Clinical observations suggest that inflammation is also a direct risk factor for stroke. Patients with stroke have high levels of inflammatory cytokines in plasma, and immune cells, such as macrophages and T-lymphocytes, are noted within stroke lesions. These inflammatory events are considered as a result of stroke. However, recent studies show that plasma levels of inflammatory cytokines or soluble adhesion molecules are high in patients without stroke, and anti-inflammatory therapy is effective at reducing stroke incidence in not only animal models, but in humans as well. Statins have been shown to decrease the stroke incidence via anti-inflammatory effects that are both dependent and independent of their cholesterol-lowering effects. These reports suggest that inflammation might directly affect the onset of stroke. Microglial cells and blood-derived monocytes/macrophages play important roles in inflammation in both onset and aggravation of stroke lesions. We review the recent findings regarding the role of monocytes/macrophages in stroke.

## 1. Introduction

Stroke is the third leading cause of death and a major cause of disability in industrialized countries. Ischemic stroke is the most common type of stroke, occurring in approximately 80% of all strokes [1]. A less common type of stroke is hemorrhagic stroke, which occurs due to a subarachnoid hemorrhage and/or an intracerebral hemorrhage. Hypertension, cardiovascular disease, arterial fibrillation, diabetes mellitus, obesity, smoking, and alcohol abuse are risk factors for stroke [2], even if there are slight differences in the influence of these factors between ischemic stroke and hemorrhagic stroke. However, some stroke patients do not have any of these risk factors, suggesting that other risk factors exist. For many years, clinical observations showed that plasma levels of inflammatory cytokines were increased after stroke onset, and immune cells, especially monocytes/macrophages and T-lymphocytes, existed in stroke lesions and related to exaggerate brain damage. In the clinical setting, elevated plasma levels of inflammatory cytokines, C-reactive protein (CRP), and chemokines are associated with future cardiovascular

risk [3]. Plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin were observed to be increased both in large intracranial artery disease and small-artery disease [4], and plasma levels of ICAM-1 and monocyte chemoattractant protein-1 (MCP-1) were noted to be high in patients with ischemic stroke and myocardial infarction [5, 6]. Epidemiological studies have shown that elevated leukocyte count was associated with the risk for first-time myocardial infarction and ischemic stroke [7–9] and the risk of recurrent myocardial infarction and ischemic stroke in a high-risk population [10]. These observations indicate that inflammatory events occur in stroke patients and increase the risk of stroke recurrence. Recently, both clinical and animal studies revealed that these inflammatory events occurred prior to stroke onset. Plasma levels of soluble vascular cell adhesion molecule-1 (sVCAM-1), sICAM-1, sE-selectin, and MCP-1 were elevated in patients with essential hypertension in the absence of other diseases [11–13]. Anti-inflammatory strategies were shown to suppress the incidence of stroke in both human and animal models. These reports suggest that inflammation might be a risk factor for stroke. We review the recent findings regarding the

role of inflammation, especially monocytes/macrophages, in ischemic stroke which is predominant type of strokes.

## 2. Monocytes/Macrophages and Stroke

**2.1. Atherosclerosis.** Atherosclerosis is one of the major risk factors for stroke, and monocytes/macrophages affect the brain indirectly by inducing unstable plaques and plaque rupture in atherosclerotic lesions [14]. It is well recognized that atherosclerosis is an inflammatory disease and macrophages play important roles in the initiation and the progression of atherosclerotic lesion [15]. Accumulation of monocytes/macrophages in the vascular wall occurs early during atherosclerosis [15]. In addition to phagocytosis of oxidized low-density lipoproteins, macrophages secrete interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). These inflammatory cytokines and growth factors induce endothelial dysfunction, smooth muscle cell migration and proliferation, and extracellular matrix production as fibrous plaques. During later disease stages, activated macrophages secrete several classes of neutral extracellular proteases, including serine proteases, cathepsins, and matrix metalloproteinases (MMPs) [16]. Blood monocytes already express low levels of a few MMPs [17]; however, contact with matrix leads to rapid upregulation of a broad spectrum of MMPs. Cell biology experiments identify mechanisms by which excessive MMP production can cause plaque rupture, either directly by destruction of extracellular matrix [18] or indirectly through actions that promote death of macrophages [19] and vascular smooth muscle cells [20]. Rupture of unstable plaques may lead to thrombotic stroke onset.

**2.2. At the Brain.** Monocytes/macrophages directly play important roles in stroke at the brain. Microglial cells, the resident macrophages of the brain, and blood-derived monocytes/macrophages have morphologically and functionally similar roles in stroke [21, 22]. Microglial cells are activated rapidly in response to brain injury [23]. This activation occurs within minutes of ischemia onset and induces production of inflammatory cytokines, including IL-1 $\beta$  and TNF- $\alpha$ , which exacerbate tissue damage [24–26]. Following the rapid activation of resident microglial cells, blood-derived immune cells infiltrate into the brain tissue within hours to a few days [21, 22]. Most current data from mice models and humans show that blood-derived macrophages are recruited into the ischemic brain tissue, most abundantly at days 3 to 7 after stroke [27–29]. In contrast, resident microglial cells are already activated rapidly on day 1 after focal cerebral ischemia. Resident microglial cells exist in lesions even at days 4 through 7. These reports suggest that the resident microglial cell activation is induced immediately after brain injury and then blood-derived macrophage infiltration follows. On the other hand, it is reported that macrophages exist in the brain before onset of stroke in stroke-prone spontaneously hypertensive rats (SHRSP) [30, 31]. These findings suggest that the alteration of the blood-brain barrier

and macrophage activation occurs before the onset of stroke, and these changes might induce stroke onset.

**2.3. Activation of Immune Cells.** Neutrophils and lymphocytes are also observed in stroke lesions. In ischemic stroke mice model, macrophages started to appear already at 12 hours after ischemia. On the other hand, lymphocytes (B- and T-lymphocytes) and neutrophils were significantly increased at 3 days after ischemia [32]. According to this observation, it was reported that macrophages produce inflammatory cytokines and upregulate adhesion molecules in endothelial cells, thereby promoting neutrophil accumulation and migration into the brain [33]. These data suggest that macrophage infiltration occurs prior to other immune cells and macrophage activation attracts other immune cells into stroke lesions. Different subtypes of T-lymphocytes play differential roles in the stroke. CD4<sup>+</sup> TH1 cells may progress stroke through releasing proinflammatory cytokines, including IL-2, IL-12, IFN- $\gamma$ , and TNF- $\alpha$ , whereas CD4<sup>+</sup> TH2 cells may play a protective role through releasing anti-inflammatory cytokines such as IL-4, IL-5, IL-10, and IL-13 [34]. However, exact role of neutrophils in the stroke is still unclear.

## 3. Relationship between Monocytes/Macrophages and Hypertension

Hypertension is the principal risk factor for stroke and is a leading cause of cognitive decline and dementia [35]. There is a linear relationship between blood pressure and stroke mortality [36]. Hypertension might induce endothelial cell dysfunction along with macrophage activation and infiltration into the brain. There is emerging evidence that monocyte/macrophage infiltration contributes to hypertension [37].

**3.1. Endothelial Cell Dysfunction.** Endothelial cell dysfunction is the first step of monocytes/macrophages infiltration into brain. Hypertension might induce endothelial cell dysfunction [38], vascular inflammation on the vascular lumen [39], and monocyte adhesion [40]. It was reported that hypertension promoted or aggravated endothelial dysfunction, which induced the expression of ICAM-1, P-selectin, and monocyte adhesion in a rat model [40]. High intraluminal pressure activated NF $\kappa$ B in an organ culture model of mouse carotid arteries [41]. In humans, the association of chronically or acutely elevated blood pressure with markers of inflammation has also been documented. Circulating levels of sICAM-1, sVCAM-1, sE-selectin, and MCP-1 are increased in patients with essential hypertension [13, 42]. Increasing levels of adhesion molecules and chemoattractant molecules could induce monocyte adhesion on the vascular surface and migration into subendothelial lesions in both aortae and the brain.

**3.2. Monocyte/Macrophage Activation.** Hypertension might affect blood monocytes directly. The total number of blood

monocytes and activated monocytes is greater in spontaneously hypertensive rats compared with Wistar Kyoto rats, which represent the normotensive control [43, 44]. On the other hand, reducing blood pressure with angiotensin converting enzyme inhibitors suppresses endothelial dysfunction and the number of subendothelial macrophages in the aorta [45]. In humans, circulating monocytes from patients with essential hypertension are preactivated compared with those in normotensive healthy individuals. IL-1 $\beta$  secretion of peripheral blood monocytes stimulated by angiotensin II was shown to be significantly higher in patients with essential hypertension compared with normotensive healthy individuals [46].

**3.3. Renal Dysfunction.** Inflammatory cells accumulate in perivascular regions in the kidney, and in and around glomeruli in hypertensive rats [47, 48] and hypertensive subjects [49]. There is extensive perivascular infiltration of leukocytes in the kidney of double transgenic rats harboring human renin and angiotensinogen genes. In a study that emphasized the role of inflammation in blood pressure elevation, pyrrolidine dithiocarbamate, an inhibitor of NF $\kappa$ B, prevented monocyte/macrophage infiltration in animals, reduced expression of ICAM-1 and inducible nitric oxide synthase, and reduced blood pressure [48]. There is also evidence of macrophage infiltration in the glomeruli of hypertensive animals [50] and humans [49]. Monocytes/macrophages in the kidney modulate blood pressure via the production of inflammatory cytokines and modulation of renin-angiotensin-aldosterone system [51, 52]. On the other hand, drugs acting on the renin-angiotensin-aldosterone system prevent or modulate inflammation [53]. Monocytes/macrophages might play some important roles in the reciprocal influence between inflammation and hypertension.

## 4. Animal Models

**4.1. Stroke-Prone Spontaneously Hypertensive Rats.** SHRSPs are unique genetic model that mimic both microvessel and parenchymal changes in spontaneous stroke [54, 55]. The microvascular changes and brain parenchymal damage may not simply be the result of hypertension, and endothelial cell dysfunction [56] and inflammation may play a role in brain damage [55]. This animal model has been used to examine the contributions of inflammation (macrophages) to stroke. In SHRSP, fed a high-salt diet, rosuvastatin treatment significantly delayed the onset of stroke and attenuated the transcription of inflammatory biomarkers (MCP-1, TGF- $\beta$ 1, IL-1 $\beta$ , and TNF- $\alpha$ ) [57]. Pioglitazone, peroxisome proliferator-activated receptor- $\gamma$  agonist, reduced the risk of recurrent stroke in patients with type 2 diabetes [58]. In SHRSP, pioglitazone delayed the onset of stroke by improving vascular endothelial dysfunction, inhibiting brain inflammation, and reducing oxidative stress [59]. A low dose of acetylsalicylic acid (aspirin) delayed the onset of stroke in SHRSP by suppressing inflammation [60]. In addition to drug treatments, dietary restriction has been shown to delay

the onset of stroke in SHRSP via suppression of systemic and local inflammation including macrophage infiltration into the brain [31].

**4.2. Middle Cerebral Artery Occlusion.** Permanent or transient middle cerebral artery occlusion is an established method for inducing focal ischemic stroke in mice or rats. Middle cerebral artery occlusion produces highly reproducible lesions, and macrophages primarily infiltrate into the core of the ischemic lesion [61]. The focal ischemic stroke model is a closer approximation to human stroke and produces a heterogeneous pathology that includes a necrotic core and salvageable penumbra [62]. However, small differences in surgical technique may account for different effects on the infarct [63, 64]. Furthermore, due to variances in cerebral vascular anatomy, different mouse strains show a different outcome [65, 66]. In addition, conditions of animals during surgery, such as blood pressure, blood gases, body temperature, and anesthesia influence outcome. Thus, standardization and quality control are very important when using this animal model.

**4.3. Hypertensive Mice with Salt Loading.** There are a lot of hypertensive animal models [67]; however, surgical intervention is needed to induce stroke in these models. Recently, these hypertensive mice have been used to research spontaneous stroke. Excessive salt intake induced frequent thoracic or abdominal cavity hemorrhage in Tsukuba hypertensive mice, which are human renin and angiotensinogen transgenic mice [68]. Hemorrhaging occurred due to the development of aortic aneurysms and rupture at the aortic arch and aorta near the renal arteries. Vascular lesions progressed with structural degeneration of the aortic media. Unfortunately, cerebral pathology was not assessed in this model [68]. Subsequently, a spontaneous stroke model using human renin and angiotensinogen transgenic hypertensive mice, but not Tsukuba hypertensive mice, was reported [69]. In this report, high-salt diet and L-NAME diet induced hemorrhage in the brain stem, cerebellum, and basal ganglia, which were reasonably similar to those observed in patients with hypertension. It is not clarified whether these mice models show ischemic stroke; however, these hypertensive mice, especially renin and angiotensinogen transgenic mice, are useful for experimental stroke research.

## 5. Inflammatory Cytokines

Inflammatory cytokines, such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , are secreted by activated microglial cells and macrophages in stroke lesions and induce the expression of chemokines, which recruit more circulating monocytes/macrophages into lesions and lead to further brain damage. However, the role of each cytokine in stroke is complicated.

**5.1. Interleukin-1 $\beta$ .** Recently, IL-1 $\beta$  has been considered a therapeutic target for stroke. Chronic increases in IL-1 $\beta$  expression in the brain led to leukocyte infiltration and increased MCP-1 and ICAM-1 expressions in a mouse model

[70], which is a phenotype also seen in stroke lesions. In addition, a number of studies have demonstrated that inhibiting the release or action of IL-1 markedly reduced ischemic cerebral damage in animal models. IL-1 $\alpha$  and IL-1 $\beta$  double knockout mice exhibited dramatically reduced ischemic infarct volume compared with wild-type mice [71]. In a meta-analysis of animal model studies, IL-1 receptor antagonist (IL-1Ra), which represents the most advanced approach to modify IL-1 action, reduced infarct volume in models of focal cerebral ischemia [72]. In humans, a phase II clinical trial of intravenous IL-1Ra compared with placebo in patients with acute stroke is currently underway [73]. Further, IL-1Ra gene polymorphism represents a risk factor for ischemic stroke [74, 75]. These reports suggest that inhibition of IL-1 $\beta$  signals can prevent the onset of stroke.

**5.2. Interleukin-6.** A prospective cohort study and systemic review revealed that plasma levels of IL-6 were associated with poor outcome after both ischemic and hemorrhagic strokes [76]; however, it was not clear whether IL-6 increased before or after stroke onset. Animal models showed less association between IL-6 and stroke. IL-6 could not induce adhesion molecules and MCP-1 mRNA expressions in cerebrovascular endothelial cells derived from SHRSP [31]. Mice deficient in IL-6 showed similar stroke lesion volume and neurological function as control mice in an acute ischemic injury model [77]. Furthermore, IL-6 mediates anti-inflammatory effects in addition to its proinflammatory role [78]. Therefore, its manipulation can have either detrimental or beneficial effects. Further studies are required to clarify the role of IL-6 in stroke.

**5.3. Tumor Necrosis Factor- $\alpha$ .** Increased serum and cerebrospinal fluid levels of TNF- $\alpha$  have been found in patients 24 hours, 1 week, and 2 weeks after stroke, and these increases correlate with infarct volume and severity of neurological impairment [79]. However, previous reports suggest that TNF- $\alpha$  has a dual role in brain injury [80, 81]. Blockade of TNF- $\alpha$  actions reduced infarct volume after permanent middle cerebral artery occlusion in BALB/C mice with the dimeric type I soluble TNF receptor, which binds to TNF- $\alpha$  and antagonizes its action [82]. In contrast, TNF- $\alpha$  pretreatment was neuroprotective against permanent middle cerebral artery occlusion in BALB/C mice with reduction of infarct size, macrophages, and CD11b-positive neutrophils [83]. In addition to these observations, pentoxifylline, an anti-inflammatory agent, attenuated damage of stroke via the dual role of TNF- $\alpha$ . Pentoxifylline treatment increased serum levels of TNF- $\alpha$ , but not IL-1 $\beta$  and IL-6, and dose dependently prevented the occurrence of spontaneous brain damage by reducing macrophage infiltration into lesion in SHRSP [84], suggesting a protective role of TNF- $\alpha$ . On the other hand, pentoxifylline reduced brain edema in a rat model of transient focal cerebral ischemia through a decline in TNF- $\alpha$  production [85], suggesting a deleterious role of TNF- $\alpha$ . Although anti-TNF- $\alpha$  strategies have proved beneficial in other clinical settings such as inflammatory bowel disease, there are no clinical trials of anti-TNF- $\alpha$  agents

in stroke. Further studies are required to clarify the role of TNF- $\alpha$  in stroke.

**5.4. MCP-1.** CC chemokine ligand (CCL2) is known as MCP-1 and is a potent mononuclear cell attractant. MCP-1 is synthesized by several cell types, such as monocytes/macrophages, T-lymphocytes, smooth muscle cells, endothelial cells, and even cerebrovascular endothelial cells. Expression of MCP-1 is upregulated by inflammatory cytokines. Serum levels of MCP-1 are high in patients with ischemic stroke and myocardial infarction [5, 6], which might be interpreted as a stroke-induced increase in inflammatory events. On the other hand, there is one report that serum CCL2 levels in acute ischemic stroke patients did not differ from that in controls at 1 to 3 days after stroke onset [86]. In this paper, details of controls were not shown, but one of the possibilities is that control subjects were hypertensive. It is reported that plasma levels of MCP-1 were elevated in patients with essential hypertension in the absence of other diseases [13]. The MCP-1-deficient mice model is a unique model to elucidate the role of macrophages in stroke [87]. Compared with control mice, infarct volume was smaller in MCP-1-deficient mice 24 hours after middle cerebral artery occlusion, and a reduction of phagocytic macrophage accumulation within infarcts and the infarct border in MCP-1 deficient mice 2 weeks after middle cerebral artery occlusion. In addition, MCP-1 deficient mice produced less IL-1 $\beta$  in ischemic tissue. This means that MCP-1 and IL-1 $\beta$  are key factors of macrophages in stroke lesions.

**5.5. Adipokines.** Obesity is also recognized as the risk factor for stroke, because obesity is associated with hypertension and inflammation via secretion of adipokines, such as adiponectin, leptin, resistin, adipisin, plasminogen activator inhibitor-1, and inflammatory cytokines [88–90]. It is well known that macrophage infiltration into adipose tissue induces inflammation in adipose tissue and influences these adipokine secretions [91, 92]. The most commonly studied adipocytokines are leptin and adiponectin. There are a lot of reports about the association of leptin and adiponectin with stroke, and leptin and adiponectin show differential association patterns with ischemic stroke [93]. It is reported that higher leptin levels and lower adiponectin levels were found in stroke patients [94]. On the other hand, there are controversial reports that adiponectin, but not leptin, levels are recognized as a predictor of the risk for stroke [95], or that leptin, but not adiponectin, levels are recognized as a predictor of the risk for stroke in men, but not women [96]. It is not clear whether adiponectin and leptin are useful predictors of stroke in obese subjects; however, adiponectin and leptin might directly influence stroke incidence. It is reported that leptin stimulates macrophages and that adiponectin suppresses it. Leptin increases the mRNA and protein levels of IL-1 $\beta$ , IL-6, IL-12, TNF- $\alpha$ , cyclooxygenase-2, and MCP-1 in macrophages and endothelial cells [97, 98]. Adiponectin inhibits pro-inflammatory signaling in human macrophages [99] and promotes macrophage polarization toward an anti-inflammatory phenotype [100]. Adiponectin also increases

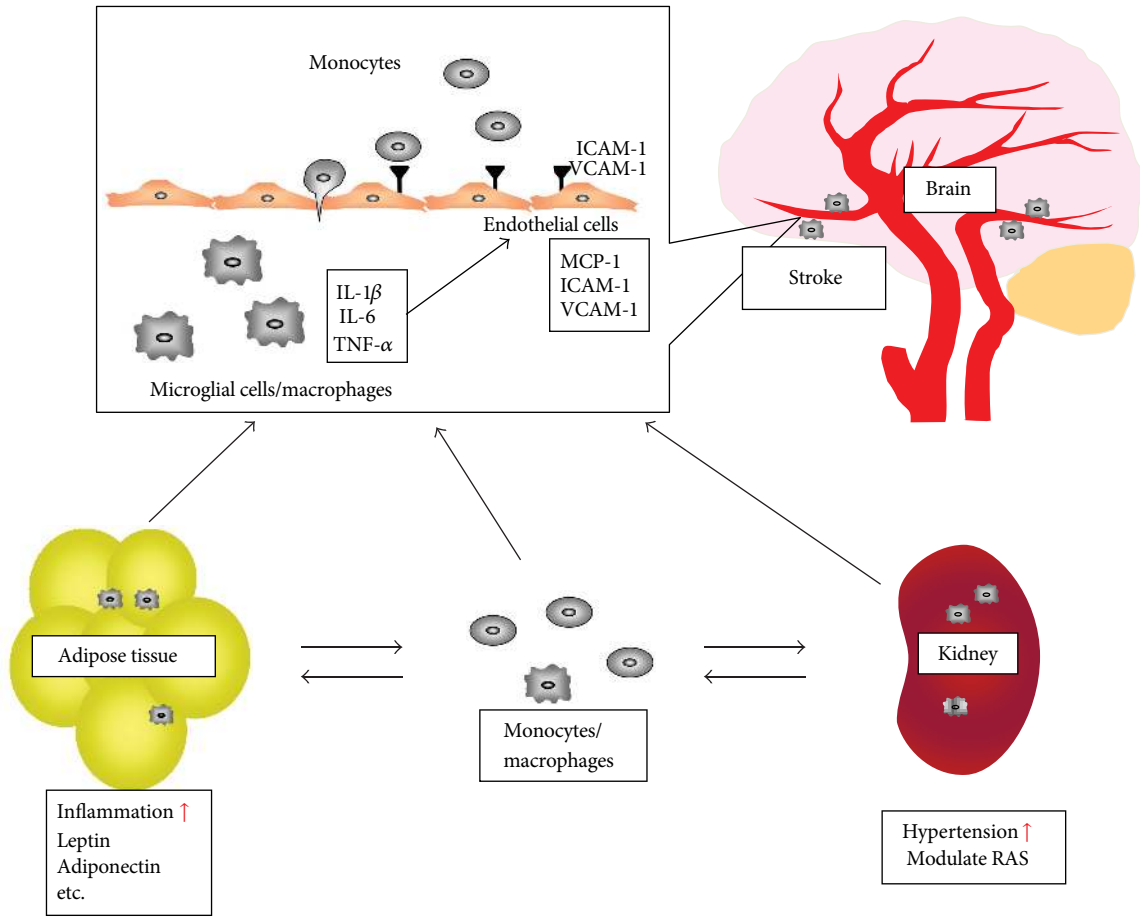


FIGURE 1: Monocytes/macrophages modulate adipose tissue and kidney functions and accelerate stroke. Monocytes/macrophages infiltration into adipose tissue stimulates secretion of leptin and inflammatory cytokines and suppresses secretion of adiponectin, which induce systemic inflammation, endothelial cell dysfunction, and monocytes/macrophages activation. Monocytes/macrophages infiltration into kidney modulates renin-angiotensin system and increase blood pressure, which also induces endothelial cell dysfunction and monocytes/macrophages activation. Endothelial cells express MCP-1 and adhesion molecules, which induce monocytes chemotaxis, adhesion, and migration into subendothelial lesions. Microglial cells and infiltrated monocytes/macrophages in brain induce cerebrovascular damages and cause stroke onset.

IL-10, an anti-inflammatory cytokine, as well as mRNA expression in human monocyte-derived macrophages [101]. In addition, both adiponectin and leptin receptors are expressed in the brain, suggesting that these adipokines might be directly associated with stroke [102, 103].

## 6. Anti-Inflammatory Strategies

There are several reports that treatment with drugs that have anti-inflammatory properties can prevent stroke not only in animal models, but also in humans.

**6.1. Statins.** Rosuvastatin treatment significantly delayed the onset of stroke and attenuated the transcription of inflammatory biomarkers [57]. Clinical studies using statins already use inflammatory events as endpoints for stroke prevention. In healthy persons without hyperlipidemia but with elevated high-sensitivity CRP levels, rosuvastatin, which lowered high-sensitivity CRP as well as cholesterol levels, reduced the

incidence of stroke and myocardial infarction by 50% relative to placebo [104]. A meta-analysis of statin trials showed that statins might reduce the incidence of all strokes by decreasing LDL-cholesterol without increasing the incidence of hemorrhagic stroke [105]. In addition to cholesterol-dependent effects, cholesterol-independent effects of statins on stroke have also been recognized [106, 107]. However, statin treatment increases the risk of hemorrhagic stroke in patients with a history of cerebrovascular disease, even though it also clearly decreased the risk of ischemic stroke [108]. Therefore, patients undergoing statin treatment should be carefully monitored to avoid achieving very low level of cholesterol, which are known risk for hemorrhagic stroke [109].

**6.2. Thiazolidinediones.** Thiazolidinediones, including rosiglitazone and pioglitazone, are peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) agonists used in the treatment of type 2 diabetes. A systemic review showed that

rosiglitazone and pioglitazone were similarly effective in reducing infarct volume and protecting neurologic function in a rodent model of focal or global cerebral ischemia [110]. Pioglitazone delayed the onset of stroke by improving vascular endothelial dysfunction and brain inflammation in SHRSP. Pioglitazone suppressed macrophage infiltration, MCP-1 and TNF- $\alpha$  gene expressions in the brain [59]. Rosiglitazone induced upregulation of CD36 in macrophages and enhanced the ability of microglia to phagocytose red blood cells, which helped to improve hematoma resolution, and improved functional deficits in an intracerebral hemorrhage mouse model [111]. In humans, the PROspective pioglitazone Clinical Trial In macroVascular Events (PROACTIVE) [112] showed that pioglitazone significantly reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes [58]. On the other hand, one report showed that compared with pioglitazone, rosiglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of acute myocardial infarction, stroke, heart failure, or all-cause mortality in patients of 65 years or older [113].

**6.3. Other Anti-Inflammatory Drugs.** Low-dose acetylsalicylic acid (aspirin) also delayed the onset of stroke in SHRSP via suppression of inflammation [60]. Aspirin reduced salt-induced macrophage accumulation and MMP-9 activity at the stroke-negative area in the cerebral cortex of SHRSP [60]. Frequent aspirin use might also confer a protective effect for risk of stroke in humans [114, 115]. Terutroban, a specific thromboxane/prostaglandin endoperoxide receptor antagonist, decreased cerebral mRNA expressions of IL-1 $\beta$ , transforming growth factor- $\beta$ , and MCP-1 and increased survival in SHRSP [116]. These effects were similar to rosuvastatin and aspirin [116]. The Prevention of cerebrovascular and cardiovascular Events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack (PERFORM) study was started in February 2006 [117]. Recently, it was reported that PERFORM study did not meet the predefined criteria for noninferiority, but showed similar rates to terutroban and aspirin for the primary endpoint, such as a composite of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction, or other vascular death [118]. These reports indicate that antiplatelet agents, which also have anti-inflammatory properties, could suppress inflammation and prevent stroke onset.

## 7. Beneficial Roles after Stroke

It is generally believed that the activated microglial cells in ischemic injury are neurotoxic, and results of several recent studies revealed that microglial cells might exert neuroprotective effects in certain conditions [119, 120]. In addition to the primary role of macrophages, which is the phagocytosis of cellular and fibrillar debris resulting from stroke, activated microglial cells and macrophages are involved in regulation of the regenerative state and remodeling of the brain by producing brain-derived neurotrophic factor [121, 122], insulin growth factor 1 [123, 124], several other

growth factors [125], neuroprotective gene Ym1 [126], and nitric oxide which are known to regulate synaptic functions [127]. As described previously, some cytokines secreted from microglial cells and macrophages, such as IL-6 and TNF- $\alpha$ , and attenuate brain damage. In addition to these mediators, intracranial transplantation of monocyte-derived multipotential cells enhances recovery after ischemic stroke [128]. Whether activated microglial cells and macrophages act as toxic or neuroprotective factors might depend on the time and severity of stroke lesions.

## 8. Summary

Microglial cells and monocytes/macrophages play important roles in the onset and aggravation of stroke via expression of several inflammatory cytokines at the brain, adipose tissue, and kidney (Figure 1). However, it is also reported that these inflammatory events are important in the reduction of and recovery from brain damage. However, it is clear that suppression of inflammation is effective in the prevention of primary stroke, and macrophages might be therapeutic targets to prevent stroke.

## Conflict of Interests

The authors have no conflict of interests to disclosure.

## References

- [1] W. Rosamond, K. Flegal, G. Friday et al., "Heart disease and stroke statistics—2007 Update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee," *Circulation*, vol. 115, no. 5, pp. e69–e171, 2007.
- [2] L. B. Goldstein, C. D. Bushnell, R. J. Adams et al., "Guidelines for the primary prevention of stroke: a Guideline for Healthcare Professionals from the American Heart Association/American Stroke Association," *Stroke*, vol. 42, no. 2, pp. 517–584, 2011.
- [3] G. J. Blake and P. M. Ridker, "Inflammatory bio-markers and cardiovascular risk prediction," *Journal of Internal Medicine*, vol. 252, no. 4, pp. 283–294, 2002.
- [4] K. Fassbender, T. Bertsch, O. Mielke, F. Mühlhauser, and M. Hennerici, "Adhesion molecules in cerebrovascular diseases: evidence for an inflammatory endothelial activation in cerebral large- and small-vessel disease," *Stroke*, vol. 30, no. 8, pp. 1647–1650, 1999.
- [5] C. Sánchez-Moreno, J. F. Dashe, T. Scott, D. Thaler, M. F. Folstein, and A. Martin, "Decreased levels of plasma vitamin C and increased concentrations of inflammatory and oxidative stress markers after stroke," *Stroke*, vol. 35, no. 1, pp. 163–168, 2004.
- [6] A. Arakelyan, J. Petrakova, Z. Hermanova, A. Boyajyan, J. Lukl, and M. Petrek, "Serum levels of the MCP-1 chemokine in patients with ischemic stroke and myocardial infarction," *Mediators of Inflammation*, vol. 2005, no. 3, pp. 175–179, 2005.
- [7] R. L. Prentice, T. P. Szatrowski, H. Kato, and M. W. Mason, "Leukocyte counts and cerebrovascular disease," *Journal of Chronic Diseases*, vol. 35, no. 9, pp. 703–714, 1982.
- [8] M. Fava, "Leukocytes and the risk of ischemic diseases," *JAMA*, vol. 258, no. 7, pp. 907–908, 1987.

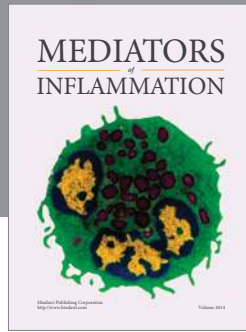
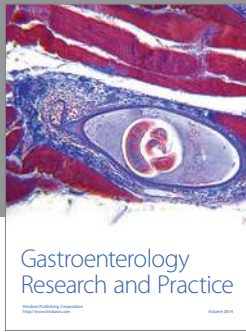
- [9] R. F. Gillum, D. D. Ingram, and D. M. Makuc, "White blood cell count and stroke incidence and death: the NHANES I epidemiologic follow-up study," *American Journal of Epidemiology*, vol. 139, no. 9, pp. 894–902, 1994.
- [10] A. J. Grau, A. W. Boddy, D. A. Dukovic et al., "Leukocyte count as an independent predictor of recurrent ischemic events," *Stroke*, vol. 35, no. 5, pp. 1147–1152, 2004.
- [11] A. D. Blann, W. Tse, S. J. R. Maxwell, and M. A. Waite, "Increased levels of the soluble adhesion molecule E-selectin in essential hypertension," *Journal of Hypertension*, vol. 12, no. 8, pp. 925–928, 1994.
- [12] C. A. Desouza, D. R. Dengel, R. F. Macko, K. Cox, and D. R. Seals, "Elevated levels of circulating cell adhesion molecules in uncomplicated essential hypertension," *American Journal of Hypertension*, vol. 10, no. 12, pp. 1335–1341, 1997.
- [13] A. Madej, B. Okopień, J. Kowalski, M. Haberka, and Z. S. Herman, "Plasma concentrations of adhesion molecules and chemokines in patients with essential hypertension," *Pharmacological Reports*, vol. 57, no. 6, pp. 878–881, 2005.
- [14] A. C. Newby, "Metalloproteinase expression in monocytes and macrophages and its relationship to atherosclerotic plaque instability," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 12, pp. 2108–2114, 2008.
- [15] R. Ross, "Atherosclerosis—an inflammatory disease," *The New England Journal of Medicine*, vol. 340, no. 2, pp. 115–126, 1999.
- [16] C. M. Dollery and P. Libby, "Atherosclerosis and proteinase activation," *Cardiovascular Research*, vol. 69, no. 3, pp. 625–635, 2006.
- [17] A. Bar-Or, R. K. Nuttall, M. Duddy et al., "Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis," *Brain*, vol. 126, no. 12, pp. 2738–2749, 2003.
- [18] A. C. Newby, "Dual role of matrix metalloproteinases (matrixins) in intimal thickening and atherosclerotic plaque rupture," *Physiological Reviews*, vol. 85, no. 1, pp. 1–31, 2005.
- [19] J. L. Johnson, G. B. Sala-Newby, Y. Ismail, C. M. Aguilera, and A. C. Newby, "Low tissue inhibitor of metalloproteinases 3 and high matrix metalloproteinase 14 levels defines a subpopulation of highly invasive foam-cell macrophages," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 9, pp. 1647–1653, 2008.
- [20] A. C. Newby, "Do metalloproteinases destabilize vulnerable atherosclerotic plaques?" *Current Opinion in Lipidology*, vol. 17, no. 5, pp. 556–561, 2006.
- [21] M. Schilling, M. Besselmann, C. Leonhard, M. Mueller, E. B. Ringelstein, and R. Kiefer, "Microglial activation precedes and predominates over macrophage infiltration in transient focal cerebral ischemia: a study in green fluorescent protein transgenic bone marrow chimeric mice," *Experimental Neurology*, vol. 183, no. 1, pp. 25–33, 2003.
- [22] R. Tanaka, M. Komine-Kobayashi, H. Mochizuki et al., "Migration of enhanced green fluorescent protein expressing bone marrow-derived microglia/macrophage into the mouse brain following permanent focal ischemia," *Neuroscience*, vol. 117, no. 3, pp. 531–539, 2003.
- [23] K. Nakajima and S. Kohsaka, "Microglia: activation and their significance in the central nervous system," *Journal of Biochemistry*, vol. 130, no. 2, pp. 169–175, 2001.
- [24] R. B. Banati, J. Gehrmann, P. Schubert, and G. W. Kreutzberg, "Cytotoxicity of microglia," *GLIA*, vol. 7, no. 1, pp. 111–118, 1993.
- [25] F. C. Barone, B. Arvin, R. F. White et al., "Tumor necrosis factor- $\alpha$ : a mediator of focal ischemic brain injury," *Stroke*, vol. 28, no. 6, pp. 1233–1244, 1997.
- [26] N. Rothwell, S. Allan, and S. Toulmond, "The role of interleukin 1 in acute neurodegeneration and stroke: pathophysiological and therapeutic implications," *The Journal of Clinical Investigation*, vol. 100, no. 11, pp. 2648–2652, 1997.
- [27] M. Schilling, M. Besselmann, M. Müller, J. K. Strecker, E. B. Ringelstein, and R. Kiefer, "Predominant phagocytic activity of resident microglia over hematogenous macrophages following transient focal cerebral ischemia: an investigation using green fluorescent protein transgenic bone marrow chimeric mice," *Experimental Neurology*, vol. 196, no. 2, pp. 290–297, 2005.
- [28] M. Schilling, J. K. Strecker, W. R. Schäbitz, E. B. Ringelstein, and R. Kiefer, "Effects of monocyte chemoattractant protein 1 on blood-borne cell recruitment after transient focal cerebral ischemia in mice," *Neuroscience*, vol. 161, no. 3, pp. 806–812, 2009.
- [29] K. G. Petry, C. Boiziau, V. Dousset, and B. Brochet, "Magnetic resonance imaging of human brain macrophage infiltration," *Neurotherapeutics*, vol. 4, no. 3, pp. 434–442, 2007.
- [30] Y. Yamori, "Predictive and preventive pathology of cardiovascular diseases," *Acta Pathologica Japonica*, vol. 39, no. 11, pp. 683–705, 1989.
- [31] T. Chiba and O. Ezaki, "Dietary restriction suppresses inflammation and delays the onset of stroke in stroke-prone spontaneously hypertensive rats," *Biochemical and Biophysical Research Communications*, vol. 399, no. 1, pp. 98–103, 2010.
- [32] M. Gelderblom, F. Leyboldt, K. Steinbach et al., "Temporal and spatial dynamics of cerebral immune cell accumulation in stroke," *Stroke*, vol. 40, no. 5, pp. 1849–1857, 2009.
- [33] J. Huang, U. M. Upadhyay, and R. J. Tamargo, "Inflammation in stroke and focal cerebral ischemia," *Surgical Neurology*, vol. 66, no. 3, pp. 232–245, 2006.
- [34] T. V. Arumugam, D. N. Granger, and M. P. Mattson, "Stroke and T-cells," *NeuroMolecular Medicine*, vol. 7, no. 3, pp. 229–242, 2005.
- [35] B. Dahlöf, "Prevention of stroke in patients with hypertension," *American Journal of Cardiology*, vol. 100, no. 3, supplement, pp. S17–S24, 2007.
- [36] A. J. Palmer, C. J. Bulpitt, A. E. Fletcher et al., "Relation between blood pressure and stroke mortality," *Hypertension*, vol. 20, no. 5, pp. 601–605, 1992.
- [37] P. J. Marvar, H. Lob, A. Vinh, F. Zarreen, and D. G. Harrison, "The central nervous system and inflammation in hypertension," *Current Opinion in Pharmacology*, vol. 11, no. 2, pp. 156–161, 2011.
- [38] C. Iadecola and R. L. Davisson, "Hypertension and cerebrovascular dysfunction," *Cell Metabolism*, vol. 7, no. 6, pp. 476–484, 2008.
- [39] M. Pate, V. Damarla, D. S. Chi, S. Negi, and G. Krishnaswamy, "Endothelial cell biology. Role in the inflammatory response," *Advances in Clinical Chemistry*, vol. 52, pp. 109–130, 2010.
- [40] H. Wang, J. Nawata, N. Kakudo et al., "The upregulation of ICAM-1 and P-selectin requires high blood pressure but not circulating renin-angiotensin system in vivo," *Journal of Hypertension*, vol. 22, no. 7, pp. 1323–1332, 2004.
- [41] C. A. Lemarié, B. Esposito, A. Tedgui, and S. Lehoux, "Pressure-induced vascular activation of nuclear factor- $\kappa$ B: role in cell survival," *Circulation Research*, vol. 93, no. 3, pp. 207–212, 2003.
- [42] I. Palomo, P. Marin, M. Alarcón et al., "Patients with essential hypertension present higher levels of sE-selectin and sVCAM-1 than normotensive volunteers," *Clinical and Experimental Hypertension*, vol. 25, no. 8, pp. 517–523, 2003.
- [43] Y. Liu, T. Liu, R. M. McCarron et al., "Evidence for activation of endothelium and monocytes in hypertensive rats," *American Journal of Physiology*, vol. 270, no. 6, pp. H2125–H2131, 1996.

- [44] G. W. Schmid-Schonbein, D. Seiffge, F. A. DeLano, K. Shen, and B. W. Zweifach, "Leukocyte counts and activation in spontaneously hypertensive and normotensive rats," *Hypertension*, vol. 17, no. 3, pp. 323–330, 1991.
- [45] M. Clozel, H. Kuhn, F. Hefti, and H. R. Baumgartner, "Endothelial dysfunction and subendothelial monocyte macrophages in hypertension: effect of angiotensin converting enzyme inhibition," *Hypertension*, vol. 18, no. 2, pp. 132–141, 1991.
- [46] Y. Dörffel, C. Lätsch, B. Stuhlmüller et al., "Preactivated peripheral blood monocytes in patients with essential hypertension," *Hypertension*, vol. 34, no. 1, pp. 113–117, 1999.
- [47] E. M. A. Mervaala, D. N. Müller, J. K. Park et al., "Monocyte infiltration and adhesion molecules in a rat model of high human renin hypertension," *Hypertension*, vol. 33, no. 1, part 2, pp. 389–395, 1999.
- [48] J. Theuer, R. Dechend, D. Müller et al., "Angiotensin II induced inflammation in the kidney and in the heart of double transgenic rats," *BMC Cardiovascular Disorders*, vol. 2, article 3, 2002.
- [49] T. Imakiire, Y. Kikuchi, M. Yamada et al., "Effects of renin-angiotensin system blockade on macrophage infiltration in patients with hypertensive nephrosclerosis," *Hypertension Research*, vol. 30, no. 7, pp. 635–642, 2007.
- [50] M. A. Saleh, E. I. Boesen, J. S. Pollock, V. J. Savin, and D. M. Pollock, "Endothelin-1 increases glomerular permeability and inflammation independent of blood pressure in the rat," *Hypertension*, vol. 56, no. 5, pp. 942–949, 2010.
- [51] U. N. Das, "Is angiotensin-II an endogenous pro-inflammatory molecule?" *Medical Science Monitor*, vol. 11, no. 5, pp. RA155–RA162, 2005.
- [52] H. R. Vianna, C. M. Soares, M. S. Tavares, M. M. Teixeira, and A. C. Silva, "Inflammation in chronic kidney disease: the role of cytokines," *Jornal Brasileiro de Nefrologia*, vol. 33, no. 3, pp. 351–364, 2011.
- [53] L. Sironi, E. Nobili, A. Gianella, P. Gelosa, and E. Tremoli, "Anti-inflammatory properties of drugs acting on the renin-angiotensin system," *Drugs of Today*, vol. 41, no. 9, pp. 609–622, 2005.
- [54] K. Okamoto, Y. Yamori, and A. Nagaoka, "Establishment of the stroke prone spontaneously hypertensive rat (SHR)," *Circulation Research*, vol. 34, no. 1, pp. 143–153, 1974.
- [55] L. Sironi, U. Guerrini, E. Tremoli et al., "Analysis of pathological events at the onset of brain damage in stroke-prone rats: a proteomics and magnetic resonance imaging approach," *Journal of Neuroscience Research*, vol. 78, no. 1, pp. 115–122, 2004.
- [56] M. Volpe, G. Iaccarino, C. Vecchione et al., "Association and cosegregation of stroke with impaired endothelium-dependent vasorelaxation in stroke prone, spontaneously hypertensive rats," *The Journal of Clinical Investigation*, vol. 98, no. 2, pp. 256–261, 1996.
- [57] L. Sironi, E. Gianazza, P. Gelosa et al., "Rosuvastatin, but not simvastatin, provides end-organ protection in stroke-prone rats by antiinflammatory effects," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 25, no. 3, pp. 598–603, 2005.
- [58] R. Wilcox, M. G. Bousser, D. J. Betteridge et al., "Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitazone Clinical Trial In macroVascular Events 04)," *Stroke*, vol. 38, no. 3, pp. 865–873, 2007.
- [59] T. Nakamura, E. Yamamoto, K. Kataoka et al., "Pioglitazone exerts protective effects against stroke in stroke-prone spontaneously hypertensive rats, independently of blood pressure," *Stroke*, vol. 38, no. 11, pp. 3016–3022, 2007.
- [60] T. Ishizuka, A. Niwa, M. Tabuchi, K. Ooshima, and H. Higashino, "Acetylsalicylic acid provides cerebrovascular protection from oxidant damage in salt-loaded stroke-prone rats," *Life Sciences*, vol. 82, no. 13-14, pp. 806–815, 2008.
- [61] M. Schroeter, S. Jander, O. W. Witte, and G. Stoll, "Local immune responses in the rat cerebral cortex after middle cerebral artery occlusion," *Journal of Neuroimmunology*, vol. 55, no. 2, pp. 195–203, 1994.
- [62] D. L. Small and A. M. Buchan, "Animal models," *British Medical Bulletin*, vol. 56, no. 2, pp. 307–317, 2000.
- [63] Y. Chen, A. Ito, K. Takai, and N. Saito, "Blocking pterygopalatine arterial blood flow decreases infarct volume variability in a mouse model of intraluminal suture middle cerebral artery occlusion," *Journal of Neuroscience Methods*, vol. 174, no. 1, pp. 18–24, 2008.
- [64] D. Tsuchiya, S. Hong, T. Kayama, S. S. Panter, and P. R. Weinstein, "Effect of suture size and carotid clip application upon blood flow and infarct volume after permanent and temporary middle cerebral artery occlusion in mice," *Brain Research*, vol. 970, no. 1-2, pp. 131–139, 2003.
- [65] N. Beckmann, "High resolution magnetic resonance angiography non-invasively reveals mouse strain differences in the cerebrovascular anatomy in vivo," *Magnetic Resonance in Medicine*, vol. 44, no. 2, pp. 252–258, 2000.
- [66] F. C. Barone, D. J. Knudsen, A. H. Nelson, G. Z. Feuerstein, and R. N. Willette, "Mouse strain differences in susceptibility to cerebral ischemia are related to cerebral vascular anatomy," *Journal of Cerebral Blood Flow and Metabolism*, vol. 13, no. 4, pp. 683–692, 1993.
- [67] W. C. Dornas and M. E. Silva, "Animal models for the study of arterial hypertension," *Journal of Biosciences*, vol. 36, no. 4, pp. 731–737, 2011.
- [68] N. Nishijo, F. Sugiyama, K. Kimoto et al., "Salt-sensitive aortic aneurysm and rupture in hypertensive transgenic mice that overproduce angiotensin II," *Laboratory Investigation*, vol. 78, no. 9, pp. 1059–1066, 1998.
- [69] S. Iida, G. L. Baumbach, J. L. Lavoie, F. M. Faraci, C. D. Sigmund, and D. D. Heistad, "Spontaneous stroke in a genetic model of hypertension in mice," *Stroke*, vol. 36, no. 6, pp. 1253–1258, 2005.
- [70] S. S. Shaftel, T. J. Carlson, J. A. Olschowka, S. Kyrkanides, S. B. Matousek, and M. K. O'Banion, "Chronic interleukin-1 $\beta$  expression in mouse brain leads to leukocyte infiltration and neutrophil-independent blood-brain barrier permeability without overt neurodegeneration," *Journal of Neuroscience*, vol. 27, no. 35, pp. 9301–9309, 2007.
- [71] H. Boutin, R. A. LeFeuvre, R. Horai, M. Asano, Y. Iwakura, and N. J. Rothwell, "Role of IL-1 $\alpha$  and IL-1 $\beta$  in ischemic brain damage," *Journal of Neuroscience*, vol. 21, no. 15, pp. 5528–5534, 2001.
- [72] V. Banwell, E. S. Sena, and M. R. Macleod, "Systematic review and stratified meta-analysis of the efficacy of interleukin-1 receptor antagonist in animal models of stroke," *Journal of Stroke and Cerebrovascular Diseases*, vol. 18, no. 4, pp. 269–276, 2009.
- [73] H. C. A. Emsley, C. J. Smith, R. F. Georgiou et al., "A randomised phase II study of interleukin-1 receptor antagonist in acute stroke patients," *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 76, no. 10, pp. 1366–1372, 2005.
- [74] A. A. Rezaei, S. M. Hoseinipناه, M. Hajilooi, A. R. Rafiei, N. Shikh, and M. Haidari, "Interleukin-1 receptor antagonist gene polymorphism and susceptibility to ischemic stroke,"



- Immunological Investigations*, vol. 38, no. 3-4, pp. 220–230, 2009.
- [75] S. Olsson, L. Holmegaard, K. Jood et al., “Genetic variation within the interleukin-1 gene cluster and ischemic stroke,” *Stroke*, vol. 43, no. 9, pp. 2278–2282, 2012.
- [76] W. Whiteley, C. Jackson, S. Lewis et al., “Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6,” *PLoS Medicine*, vol. 6, no. 9, Article ID e1000145, 2009.
- [77] W. M. Clark, L. G. Rinker, N. S. Lessov et al., “Lack of interleukin-6 expression is not protective against focal central nervous system ischemia,” *Stroke*, vol. 31, no. 7, pp. 1715–1720, 2000.
- [78] J. Scheller, A. Chalaris, D. Schmidt-Arras, and S. Rose-John, “The pro- and anti-inflammatory properties of the cytokine interleukin-6,” *Biochimica et Biophysica Acta*, vol. 1813, no. 5, pp. 878–888, 2011.
- [79] J. Zaremba and J. Losy, “Early TNF- $\alpha$  levels correlate with ischaemic stroke severity,” *Acta Neurologica Scandinavica*, vol. 104, no. 5, pp. 288–295, 2001.
- [80] E. Shohami, I. Ginis, and J. M. Hallenbeck, “Dual role of tumor necrosis factor alpha in brain injury,” *Cytokine and Growth Factor Reviews*, vol. 10, no. 2, pp. 119–130, 1999.
- [81] J. M. Hallenbeck, “The many faces of tumor necrosis factor in stroke,” *Nature Medicine*, vol. 8, no. 12, pp. 1363–1368, 2002.
- [82] H. Nawashiro, D. Martin, and J. M. Hallenbeck, “Inhibition of tumor necrosis factor and amelioration of brain infarction in mice,” *Journal of Cerebral Blood Flow and Metabolism*, vol. 17, no. 2, pp. 229–232, 1997.
- [83] H. Nawashiro, K. Tasaki, C. A. Ruetzler, and J. M. Hallenbeck, “TNF- $\alpha$  pretreatment induces protective effects against focal cerebral ischemia in mice,” *Journal of Cerebral Blood Flow and Metabolism*, vol. 17, no. 5, pp. 483–490, 1997.
- [84] C. Banfi, L. Sironi, G. De Simoni et al., “Pentoxifylline prevents spontaneous brain ischemia in stroke-prone rats,” *Journal of Pharmacology and Experimental Therapeutics*, vol. 310, no. 3, pp. 890–895, 2004.
- [85] A. Vakili, S. Mojarrad, M. M. Akhavan, and A. Rashidy-Pour, “Pentoxifylline attenuates TNF- $\alpha$  protein levels and brain edema following temporary focal cerebral ischemia in rats,” *Brain Research*, vol. 1377, pp. 119–125, 2011.
- [86] J. Zaremba, J. Ilkowski, and J. Losy, “Serial measurements of levels of the chemokines CCL2, CCL3 and CCL5 in serum of patients with acute ischaemic stroke,” *Folia Neuropathologica*, vol. 44, no. 4, pp. 282–289, 2006.
- [87] P. M. Hughes, P. R. Allegrini, M. Rudin, V. H. Perry, A. K. Mir, and C. Wiessner, “Monocyte chemoattractant protein-1 deficiency is protective in a murine stroke model,” *Journal of Cerebral Blood Flow and Metabolism*, vol. 22, no. 3, pp. 308–317, 2002.
- [88] P. Mathieu, P. Poirier, P. Pibarot, I. Lemieux, and J. P. Després, “Visceral obesity the link among inflammation, hypertension, and cardiovascular disease,” *Hypertension*, vol. 53, no. 4, pp. 577–584, 2009.
- [89] J. E. Hall, A. A. Da Silva, J. M. Do Carmo et al., “Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins,” *The Journal of Biological Chemistry*, vol. 285, no. 23, pp. 17271–17276, 2010.
- [90] F. Yiannikouris, M. Gupte, K. Putnam, and L. Cassis, “Adipokines and blood pressure control,” *Current Opinion in Nephrology and Hypertension*, vol. 19, no. 2, pp. 195–200, 2010.
- [91] S. P. Weisberg, D. McCann, M. Desai, M. Rosenbaum, R. L. Leibel, and A. W. Ferrante, “Obesity is associated with macrophage accumulation in adipose tissue,” *The Journal of Clinical Investigation*, vol. 112, no. 12, pp. 1796–1808, 2003.
- [92] A. Bouloumié, C. A. Curat, C. Sengenès, K. Lomède, A. Miranville, and R. Busse, “Role of macrophage tissue infiltration in metabolic diseases,” *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 8, no. 4, pp. 347–354, 2005.
- [93] B. J. Kim, S.-H. Lee, W.-S. Ryu, C. K. Kim, and B.-W. Yoon, “Adipocytokines and ischemic stroke: differential associations between stroke subtypes,” *Journal of the Neurological Sciences*, vol. 312, no. 1-2, pp. 117–122, 2012.
- [94] S. Gerdes, S. Osadtschy, M. Rostami-Yazdi, N. Buhles, M. Weichenthal, and U. Mrowietz, “Leptin, adiponectin, visfatin and retinol-binding protein-4—mediators of comorbidities in patients with psoriasis?” *Experimental Dermatology*, vol. 21, no. 1, pp. 43–47, 2012.
- [95] C. Prugger, G. Luc, B. Haas et al., “Adipocytokines and the risk of ischemic stroke: the PRIME Study,” *Annals of Neurology*, vol. 71, no. 4, pp. 478–486, 2012.
- [96] S. Söderberg, D. Colquhoun, A. Keech et al., “Leptin, but not adiponectin, is a predictor of recurrent cardiovascular events in men: results from the LIPID study,” *International Journal of Obesity*, vol. 33, no. 1, pp. 123–130, 2009.
- [97] S. I. Yamagishi, D. Edelstein, X. L. Du, Y. Kaneda, M. Guzmán, and M. Brownlee, “Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinase A,” *The Journal of Biological Chemistry*, vol. 276, no. 27, pp. 25096–25100, 2001.
- [98] S. Loffreda, S. Q. Yang, H. Z. Lin et al., “Leptin regulates proinflammatory immune responses,” *The FASEB Journal*, vol. 12, no. 1, pp. 57–65, 1998.
- [99] E. J. Folco, V. Z. Rocha, M. López-Illasaca, and P. Libby, “Adiponectin inhibits pro-inflammatory signaling in human macrophages independent of interleukin-10,” *The Journal of Biological Chemistry*, vol. 284, no. 38, pp. 25569–25575, 2009.
- [100] K. Ohashi, J. L. Parker, N. Ouchi et al., “Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype,” *The Journal of Biological Chemistry*, vol. 285, no. 9, pp. 6153–6160, 2010.
- [101] M. Kumada, S. Kihara, N. Ouchi et al., “Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages,” *Circulation*, vol. 109, no. 17, pp. 2046–2049, 2004.
- [102] J. Thundyil, D. Pavlovski, C. G. Sobey, and T. V. Arumugam, “Adiponectin receptor signalling in the brain,” *British Journal of Pharmacology*, vol. 165, no. 2, pp. 313–327, 2012.
- [103] J. M. Friedman, “Leptin, leptin receptors and the control of body weight,” *European Journal of Medical Research*, vol. 2, no. 1, pp. 7–13, 1997.
- [104] P. M. Ridker, E. Danielson, F. A. H. Fonseca et al., “Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein,” *The New England Journal of Medicine*, vol. 359, no. 21, pp. 2195–2207, 2008.
- [105] P. Amarenco, J. Labreuche, P. Lavallée, and P. J. Touboul, “Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis,” *Stroke*, vol. 35, no. 12, pp. 2902–2909, 2004.
- [106] J. K. Liao, “Beyond lipid lowering: the role of statins in vascular protection,” *International Journal of Cardiology*, vol. 86, no. 1, pp. 5–18, 2002.
- [107] C. J. Vaughan, “Prevention of stroke and dementia with statins: effects beyond lipid lowering,” *American Journal of Cardiology*, vol. 91, no. 4, supplement, pp. 23–29, 2003.

- [108] M. D. I. Vergouwen, R. J. De Haan, M. Vermeulen, and Y. B. W. E. M. Roos, "Statin treatment and the occurrence of hemorrhagic stroke in patients with a history of cerebrovascular disease," *Stroke*, vol. 39, no. 2, pp. 497–502, 2008.
- [109] I. B. Puddey, "Low serum cholesterol and the risk of cerebral haemorrhage," *Atherosclerosis*, vol. 119, no. 1, pp. 1–6, 1996.
- [110] A. T. White and A. N. Murphy, "Administration of thiazolidinediones for neuroprotection in ischemic stroke: a pre-clinical systematic review," *Journal of Neurochemistry*, vol. 115, no. 4, pp. 845–853, 2010.
- [111] X. Zhao, J. Grotta, N. Gonzales, and J. Aronowski, "Hematoma resolution as a therapeutic target: the role of microglia/macrophages," *Stroke*, vol. 40, no. 3, pp. S92–S94, 2009.
- [112] J. A. Dormandy, B. Charbonnel, D. J. Eckland et al., "Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAZone Clinical Trial in macroVascular Events): a randomised controlled trial," *The Lancet*, vol. 366, no. 9493, pp. 1279–1289, 2005.
- [113] D. J. Graham, R. Ouellet-Hellstrom, T. E. Macurdy et al., "Risk of acute myocardial infarction, stroke, heart failure, and death in elderly medicare patients treated with rosiglitazone or pioglitazone," *JAMA*, vol. 304, no. 4, pp. 411–418, 2010.
- [114] J. E. Buring, "A perspective on the women's healthy study: aspirin prevents stroke but not MI in Women; Vitamin E has no effect on CV disease or cancer," *Cleveland Clinic Journal of Medicine*, vol. 73, no. 9, pp. 863–870, 2006.
- [115] M. Tymianski, "Aspirin as a promising agent for decreasing incidence of cerebral aneurysm rupture," *Stroke*, vol. 42, no. 11, pp. 3003–3004, 2011.
- [116] P. Gelosa, R. Ballerio, C. Banfi et al., "Terutroban, a thromboxane/prostaglandin endoperoxide receptor antagonist, increases survival in stroke-prone rats by preventing systemic inflammation and endothelial dysfunction: comparison with aspirin and rosuvastatin," *Journal of Pharmacology and Experimental Therapeutics*, vol. 334, no. 1, pp. 199–205, 2010.
- [117] M. G. Bousser, P. Amarenco, A. Chamorro et al., "Rationale and design of a randomized, double-blind, parallel-group study of terutroban 30 mg/day versus aspirin 100 mg/day in stroke patients: the prevention of cerebrovascular and cardiovascular events of ischemic origin with terutroban in patients with a history of ischemic stroke or transient ischemic attack (PERFORM) study," *Cerebrovascular Diseases*, vol. 27, no. 5, pp. 509–518, 2009.
- [118] M. G. Bousser, P. Amarenco, A. Chamorro et al., "Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): a randomised, double-blind, parallel-group trial," *The Lancet*, vol. 377, no. 9782, pp. 2013–2022, 2011.
- [119] Y. Kitamura, D. Yanagisawa, M. Inden et al., "Recovery of focal brain ischemia-induced behavioral dysfunction by intracerebroventricular injection of microglia," *Journal of Pharmacological Sciences*, vol. 97, no. 2, pp. 289–293, 2005.
- [120] Y. Kitamura, K. Takata, M. Inden et al., "Intracerebroventricular injection of microglia protects against focal brain ischemia," *Journal of Pharmacological Sciences*, vol. 94, no. 2, pp. 203–206, 2004.
- [121] P. E. Batchelor, G. T. Liberatore, J. Y. F. Wong et al., "Activated macrophages and microglia induce dopaminergic sprouting in the injured striatum and express brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor," *Journal of Neuroscience*, vol. 19, no. 5, pp. 1708–1716, 1999.
- [122] K. Nakajima and S. Kohsaka, "Microglia: neuroprotective and neurotrophic cells in the central nervous system," *Current Drug Targets*, vol. 4, no. 1, pp. 65–84, 2004.
- [123] S. L. O'Donnell, T. J. Frederick, J. K. Krady, S. J. Vannucci, and T. L. Wood, "IGF-I and microglia/macrophage proliferation in the ischemic mouse brain," *GLIA*, vol. 39, no. 1, pp. 85–97, 2002.
- [124] M. LaThe Lancette-Hébert, G. Gowing, A. Simard, C. W. Yuan, and J. Kriz, "Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain," *Journal of Neuroscience*, vol. 27, no. 10, pp. 2596–2605, 2007.
- [125] U. K. Hanisch and H. Kettenmann, "Microglia: active sensor and versatile effector cells in the normal and pathologic brain," *Nature Neuroscience*, vol. 10, no. 11, pp. 1387–1394, 2007.
- [126] H. Ohtaki, J. H. Ylostalo, J. E. Foraker et al., "Stem/progenitor cells from bone marrow decrease neuronal death in global ischemia by modulation of inflammatory/immune responses," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 105, no. 38, pp. 14638–14643, 2008.
- [127] C. L. Gibson, T. C. Coughlan, and S. P. Murphy, "Glial nitric oxide and ischemia," *GLIA*, vol. 50, no. 4, pp. 417–426, 2005.
- [128] H. Hattori, S. Suzuki, Y. Okazaki, N. Suzuki, and M. Kuwana, "Intracranial transplantation of monocyte-derived multipotential cells enhances recovery after ischemic stroke in rats," *Journal of Neuroscience Research*, vol. 90, no. 2, pp. 479–488, 2012.



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