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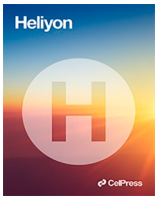

Review article

Effects of peripheral blood cells on ischemic stroke: Greater immune response or systemic inflammation?

Huanhuan Gong [a,1], Zheng Li [b,1], Guoqing Huang [c], Xiaoye Mo [c,*]

[a] Department of Critical Care Medicine, The Third Xiangya Hospital, Central South University, Changsha, China
[b] Department of General Surgery, The Third Xiangya Hospital, Central South University, Changsha, China
[c] Department of Emergency, Xiangya Hospital, Central South University, PR China

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ABSTRACT

Ischemic stroke is still one of the most serious medical conditions endangering human health worldwide. Current research on the mechanism of ischemic stroke focuses on the primary etiology as well as the subsequent inflammatory response and immune modulation. Recent research has revealed that peripheral blood cells and their components are crucial to the ensuing progression of ischemic stroke. However, it remains unclear whether blood cell elements are principally in charge of systemic inflammation or immunological regulation, or if their participation is beneficial or harmful to the development of ischemic stroke. In this review, we aim to describe the changes in peripheral blood cells and their corresponding parameters in ischemic stroke. Specifically, we elaborate on the role of each peripheral component in the inflammatory response or immunological modulation as well as their interactions. It has been suggested that more specific therapies aimed at targeting peripheral blood cell components and their role in inflammation or immunity are more favorable to the treatment of ischemic stroke.

1. Introduction

Ischemic stroke (IS) is a leading cause of mortality and morbidity worldwide, the pathogenesis of which has been studied in both animal models and human stroke patients [1,2]. Clinical research often focuses on the initial mechanism of cerebral infarction, such as cerebral artery thrombosis, with a hypercoagulable state of blood constituents, or the occurrence of cardiac embolism. The inflammatory response and immune regulation are critical during the progression of ischemic injury [3,4]. These two processes are inseparable from the participation of peripheral leukocytes, platelets, and vascular endothelial cells, all of which are capable of releasing

Abbreviations: IS, Ischemic stroke; RBC, Red blood cell; AM, Adhesion molecule; RDW, RBC distribution width; TNF-α, Tumor necrosis factor alpha; TIA, Transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale; LFA-1, Lymphocyte function-associated antigen-1; MAC-1, Macrophage antigen-1; ICAM-1, Intercellular cell adhesion molecule-1; EAST, Enlimomab Acute Stroke Trial; PSGL-1, *p*-selectin glycoprotein ligand 1; NLR, Neutrophil-to-lymphocyte ratio; SAI, Stroke-associated infection; Treg, Regulatory T; Th, Helper T; CTL, Cytotoxic T lymphocytes; IFN-γ, Interferon-gamma; IP-10, Interferon-gamma-inducible protein 10; IL, Interleukin; RPR, RDW to platelet ratio; MPV, Mean platelet volume; PDW, Platelet distribution width; TGF-β, Transforming growth factor-beta; CCL2, chemokine (C–C motif) ligand 2; MIP, Macrophage inflammatory protein; WBC, White blood cell; Plt, Platelet.

* Corresponding author. No.87, Xiangya Road, Kaifu District, Xiangya Hospital, Central South University, Changsha, Hunan, China.
E-mail address: moxiaoye@csu.edu.cn (X. Mo).

[1] Contributed equally.

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inflammatory cytokines and chemokines [2,5,6]. In the normal state, peripheral leukocytes roll along the endothelial surface in the vessel, with few adhering to the endothelium. After an ischemic attack, some neutrophils, lymphocytes, and monocytes in circulation adhere to endothelial cells and infiltrate the endothelium, resulting in infarction and damaging ischemic tissue through the physical obstruction of vessels, release of oxygen radicals, and secretion of cytokines and proteinases [7,8]. Un-infiltrated cells and constituents in the peripheral blood also undergo a series of alterations, such as red blood cell (RBC) damage, T lymphocyte shift, increased platelet-leukocyte aggregation, and elevated soluble adhesion molecule (AM), all of which are involved in the inflammatory response and immune function [2,9]. As peripheral blood is readily available, recent studies have concentrated on peripheral blood components to estimate prognosis and explore the mechanisms of IS.

Peripheral blood components are diverse and may play distinct functions in different stages of brain ischemia-reperfusion damage. Some are involved in immunosuppression, others in pro-inflammatory and anti-inflammatory responses, and yet others are considered to be involved in both, which is difficult to discern. Limited research has been undertaken to investigate the effect of peripheral blood components after IS. Here, we summarize the findings from previous animal experiments and clinical observations to form a clear picture of the alterations in peripheral blood cells and constituents in cerebral ischemic disorders, drawing attention to the novel treatments that target the activities of peripheral blood constituents.

1.1. Red blood cells (RBCs)

The value of the RBC distribution width (RDW) indicates the extent of variation in RBC volume. The RDW is frequently higher in situations of impaired red cell generation, such as deficiency of iron, vitamin B_{12}, or folate. A higher RDW could be considered a sign of diminished capacity for systemic repair and recovery [10]. Furthermore, an increased RDW may reflect an underlying inflammatory state, which is supported by the fact that tumor necrosis factor alpha (TNF-α), a pro-inflammatory cytokine, leads to an elevated RDW [11,12]. A high RDW may also be a symptom of RBC damage, which is relevant to the induction of inflammation. Indeed, recent studies reported that an elevated RDW was related to a higher incidence of stroke, transient ischemic attack (TIA), unfavorable functional outcomes, and increased mortality [13].

Erythrocyte membrane band 3 protein is thought to be an indicator of RBC destruction, which is modified by proteolytic cleavage, clustering, or exposure of an unusual epitope [14]. Early studies have reported a different band 3 profile in peripheral blood from patients with IS, along with a dramatic increase in membrane-bound hemoglobin [15,16], which was attributed to the oxidative and proteolytic environment created by activated peripheral leukocytes [16,17]. Erythrocyte membrane band 3 distributions may weaken the structure of the membrane and cause a loss of membrane deformability, which would slow blood flow in small blood vessels, extend the time that leukocyte activation products interact with nearby cells, and increase inflammation after ischemia.

A higher RDW or increased membrane band 3 distribution suggests that, following cerebral ischemia, RBCs in the circulation are injured, which correlates with the inflammatory response. Considering the importance of RBCs as oxygen carriers and providers, maintaining RBCs after ischemia and preventing RBC damage may be one of the most effective ways to preserve ischemic brain tissue. RBC preservation may also be a possible target for IS treatment.

1.2. Neutrophils

Neutrophils are the most prevalent leukocytes in circulation and are crucial to the inflammatory process. During IS, peripheral blood neutrophils are activated, as evidenced by an increase in cell numbers, upregulation of AM expression, and an increase in the release of chemokines and inflammatory mediators connected to this process [18,19]. In this section, we mainly explore the increased

Table 1
Representative clinical investigations on the increase in peripheral neutrophils in acute ischemic stroke within the past 5 years.

Clinical studies	Neutrophil count (10^9/L)	Sampling time	Number of patients	Clinical findings of peripheral neutrophils after ischemic stroke
Wei Cai[20]	>7.5[a]	Within 24 h	225	Neutrophil constitution in the peripheral blood increased soon after stroke onset, and a higher neutrophil count indicated detrimental stroke outcomes.
Petrone[21]	9.01 ± 0.42[a]	48–72 h	72	Neutrophil count was significantly higher in the poor outcome group than in the favorable outcome group.
Xing Zhang [23]	4.10[a]	Unknown	1363	Neutrophils may play a role in the pathogenesis of stroke related to intracranial atherosclerotic stenosis.
Nguyen[22]	6[a]	Within 48 h	156	Elevations in post-stroke WBC and neutrophils from 24 to 48 h were associated with better cognitive outcomes at 3 and 12 months after stroke, independent of age and baseline stroke severity.
Zhibing Hu [24]	Unknown	Unknown	503	Neutrophil count was associated with an increased risk of fatal all-stroke occurrence.
Roy-O'Reilly [25]	6.05 ± 2.95[a]	Within 24 h	508	Neutrophil counts were significantly higher in patients with ischemic stroke compared to TIA controls, and were positively correlated with stroke severity.

The table illustrates that various clinical trials involving stroke patients have indicated an enhanced peripheral neutrophil count, as well as their activation, including some representative investigations conducted within the last 5 years.
a Compared to control, $P < 0.05$, WBC: white blood cell, TIA: Transient ischemic attack.

neutrophil numbers and enhanced expression of AM. The inflammatory agents and chemokines produced by centrioles are discussed in a subsequent article.

Numerous clinical studies involving stroke patients have revealed an elevated peripheral neutrophil count, accompanied by their activation, among which some representative investigations within the past 5 years are shown in Table 1 [20–25]. In a clinical setting, a high score on the National Institutes of Health Stroke Scale (NIHSS), a widely accepted measure of the severity of stroke patients, was found to be positively linked to increased peripheral neutrophil counts [24]. Similarly, a greater neutrophil count was positively correlated with both larger ultimate infarct volumes on CT/MRI and early infarct volumes evaluated by diffuse MRI [25,26]. Similarly, a stroke patient with an entrance leukocyte count of 11,000 may be considered to be at a high risk of dying [27]. Increased peripheral neutrophils are associated with disease severity and a poor prognosis in patients with IS.

The ability of peripheral neutrophils to adhere to vascular endothelial cells is one of their key roles in the pre-inflammatory stage. Due to the expression of AM on their surface, adhesion enables neutrophils to receive information and respond appropriately to regulate cell function. After the onset of IS, AMs expressed on neutrophils aid in leukocyte rolling, firm adhesion, and transmigration [28]; the increase in AM expression has been identified as yet another crucial component of cell activation [29]. Previous research has demonstrated that the AM family, which mostly consists of integrins, immunoglobin gene superfamily, and selectins, is important in the adhesion of neutrophil-endothelial cells. The intergrins involved in neutrophil adhesion are mainly from the β2 subgroup of the beta subgroup and include lymphocyte function-associated antigen-1(LFA-1, CD11a/CD18), macrophage antigen-1 (MAC-1, CD11b/CD18), and GP150, 95 [30]. Neutrophil adhesion is mainly mediated by LFA-1, with MAC-1 playing a minor role. After IS, patients' peripheral neutrophils were found to express more LFA-1 [31]. According to one study, MAC-1 increased from day 1 to day 7 following cerebral ischemia, but LFA-1 remained at the normal level, with stroke patients and healthy controls showing differential expression of AM on circulating neutrophils [32]. According to Arumugam et al., rats with MAC-1 and LFA-1 defects showed decreases in leukocyte and platelet adhesion ability, infarct size, and mortality [33]. Additionally, intercellular cell adhesion molecule-1 (ICAM-1), as a member of the immunoglobulin superfamily, which is expressed on endothelial cells and is a receptor for LFA-1, MAC-1, and hyaluronic acid, among others, serves as a mediator of the adhesion reaction between cells [34]. Increased expression of ICAM-1 has also been found on micro vessels of infarcts in patients who survived stroke onset [35]. Based on the above, a clinical trial of agents modulating the leukocyte adhesion in IS had been performed. Moreover, treatment with a murine anti–ICAM-1 antibody (Enlimomab) has been investigated in patients with acute cerebral ischemia in the Enlimomab Acute Stroke Trial (EAST) [36]. The Enlimomab antibody is a murine IgG2a mAb to human ICAM-1, which represents a foreign protein for humans. According to the trial findings, Enlimomab-treated individuals had a greater mortality rate and a higher propensity to experience neurological impairments [36]. Fever, infections, aseptic meningitis, cutaneous reactions, and other negative occurrences were also reported. As a result, the clinical outcomes of Enlimomab are unsatisfactory, which may be attributed to a nonspecific complement activation induced by the presentation of Fc fragments or a specific humoral or cytotoxic immune response against the murine origin [37].

L-selectin, part of the selectin family, is expressed in neutrophils, where it rolls and binds to CD18 to promote leukocyte adhesion to endothelial cells [38,39]. However, inhibition of neutrophil L-selectin failed to reduce cerebellar infarct volume [40]. P-Selectin Glycoprotein Ligand 1 (PSGL-1, CD162) has also been shown to be involved in neutrophil-endothelium adhesion [41]. After an acute vascular event, activated neutrophils increase PSGL-1 on the surface and then adhere to the endothelium with the help of platelet interaction via P-selectin binding to PSGL-1 [42,43]. Mediating AM expression on peripheral neutrophils could potentially affect ischemic injury in the acute phase and influence chronic brain recovery and repair.

The neutrophil-to-lymphocyte ratio (NLR) has been previously reported as a biomarker of inflammatory response and could serve as an outstanding predictor in patients with IS [44]. Indeed, Xue et al. investigated 280 patients with acute cerebral ischemia and discovered that NLR upon admission was positively connected with stroke severity [45]. Compared to individuals with TIA, those with IS have a significantly increased NLR [46]. Similarly, Switonska et al. evaluated 58 patients with acute cerebral infarction treated by various techniques and revealed that individuals with higher NIHSS scores were likely to have more severe neurological deficits [47]. In addition to the severity of neurological damage, the NLR is linked to the onset and progression of cerebral infarction sequelae [48]. For example, in acute cerebral infarction, the risk of intracranial hemorrhage increases with increasing NLR [48]. Animal research and clinical studies have also indicated that the higher NLR, the higher the incidence of stroke-associated infection (SAI), presumably because acute cerebral ischemia triggers a hematogenous anti-inflammatory response, lowering the immune system's antimicrobial function [49–51]. Furthermore, NLR can be employed as a possible marker for the occurrence of early delirium, post-stroke depression, and stroke recurrence in patients with acute cerebral infarction [45,52,53]. It is clear that NLR, an easily accessible inflammatory marker in clinical practice, is associated with the severity of acute cerebral infarction, the occurrence of associated sequelae, and prognosis, but further study is still required to determine the precise mechanism of action.

1.3. Lymphocytes

Lymphocytes are divided into three groups based on their origin, morphological structure, surface markers, and immune functions: T cells, B cells, and NK cells. T cells and B cells, in particular, control cellular and humoral immunity, respectively [42]. The significance of lymphocytes in IS has been demonstrated by previous animal studies and clinical research. A previous study demonstrated that after a stroke, mice showed an increase in T and B cells that were terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeled positive in circulation [43]. In a clinical setting, stroke patients with no history of infection were shown to have decreased peripheral blood levels of all types of T lymphocytes, including regulatory T (Treg) cells, helper T (Th) cells, and cytotoxic T lymphocytes (CTL) [5,6]. Although the total T cell count decreased, the percentage of activated T cells in the peripheral blood increased in clinical cerebral ischemia [54,55]. Moreover, lymphocyte-deficient $Rag1^{-/-}$ mice have been shown to have smaller infarct volumes

and better neurological function than wild-type rats after suffering from ischemic events [56]. Furthermore, adoptive transfer of T cells into $Rag1^{-/-}$ mice was shown to reverse the beneficial effects of lymphocyte deficiency on infarct volume [57]. It is clear that cerebral ischemia reduces various T lymphocyte subtypes in peripheral blood, and this reduction may be a defense mechanism for brain tissue.

Specific to various T cell subtypes, Th cells decrease, and switch from Th1 to Th2 responses, with reductions in TNF-α and interferon-gamma (IFN-γ) production after stroke, indicating that T cell-mediated immune responses are important in both stroke pathogenesis and outcome [58]. Mice with depleted Th cells have been shown to have a reduction in IFN-γ and IFN-γ-inducible protein 10 (IP-10) levels, along with an improved neurological outcome [59]. These changes could contribute to the likelihood of infections in post-stroke patients [58,60]. Patients with large strokes have been shown to develop SAI more frequently, which occurred in association with a lower TNF-α/interleukin (IL)-10 ratio resulting from a Th2 shift and a decrease in Th lymphocytes [61]. Patients who showed the most striking decrease in T cells in the peripheral blood were susceptible to developing infections after stroke onset [62]. CTLS can kill target cells and emit several cytokines to help with immune response. Peripheral CTLs have been shown to decrease in stroke patients; however, the evidence of their correlation with patient prognosis is insufficient [5,6].

Treg cells, which have generalized suppressive effects over other lymphocytes and secrete anti-inflammatory cytokines, have recently been examined in the context of cerebral ischemia [63,64]. In an experimental stroke, a threefold increase in Treg cells was found 96 h after stroke, concurrent with a reduction in the spleen size and number of T cells [65,66]. In clinical studies, Yan et al. and Gelderblom et al. reported that the percentage of Treg cells elevated profoundly on day 7 after stroke [67,68]. The main mechanisms whereby Treg cells control cerebral ischemic damage include the following: augmenting the activation of resident and invading blood cells, with increased release of deleterious TNF–α and IFN-γ [67,68]; mediating effects through CCR5 signaling, enhancing the immunosuppressive function of Tregs, and increasing the interactions between Tregs and endothelial cells [69]; and enhancing the repair activity of microglia and consequently promoting oligodendrogenesis and white matter repair [70,71]. Depleting Treg cells has been shown to conspicuously increase brain damage and deteriorate functional outcomes [68]. Moreover, IL-33 treatment has been shown to increased Treg cells and improve outcomes after IS [72,73]. The adoptive transfer of Treg cells 2 h after ischemia reduced infarct volumes at 3 days after stroke [69]. It is accepted that Treg cells function as cerebral protective regulators of ischemic brain injury and merit further attention when developing targets for therapeutic approaches for IS.

In addition to T lymphocytes, B lymphocytes and NK cells are two other types of lymphocytes, although limited studies have investigated their roles in cerebral ischemia. Although the number of B lymphocytes has been shown to decrease overall in the context of cerebral ischemia, they do not appear to be activated after IS. Further, a previous study that adoptively transferred B cells among $Rag1^{-/-}$ mice revealed no significant impact on infarct volume or functional outcomes [5,6,54,55,57]. NK cells, which are distinct from T and B cells, are a class of lymphocytes that have a non-specific killing ability without pre-sensitization. NK cells are necessary to fight SAI [74], and the number of NK cells decreased in patients with SAI [5,6]. However, the significance of peripheral lymphocytes cannot be generalized, as the various subtypes have different roles. For example, while it is evident that T lymphocytes play an important role after IS, B lymphocytes and NK cells do not. Therefore, treatment targeting lymphocytes, particularly T cells, should be carefully designed to reduce deleterious effects and enhance the protective actions lymphocytes.

1.4. Monocytes

Monocytes are a type of inflammatory cell, which become stationary tissue macrophages after migrating into the infarct [75,76]. Macrophages contribute to ischemia damage by producing proteinases and exhibiting procoagulant activity [77]. Prior research has focused primarily on the pathogenic function of macrophages in the injured brain, but the role of circulating monocytes remains uncertain.

Most studies have focused on the adhesive activities and counts of circulating monocytes after cerebral ischemia. Monocyte counts in the peripheral blood of stroke patients have been reported to significantly increase in some studies, while monocyte genes have been shown to be downregulated in patients with IS, but not in others [78–80]. Although the monocyte count was controversial, the investigators prospectively studied 129 patients who had experienced their first acute stroke and reported that high monocyte count, together with current smoking and hyperlipidemia, were prothrombotic factors related to lacunar infarcts [81]. Lee et al. showed that monocyte depletion reduced the infarct size and mitigated neurological deficits in mice following IS [82]. Moreover, the percentage of $CD163^{+}/CD16^{+}$ monocytes 24 h after stroke was found to be positively associated with NIHSS score and Modified Rankin Scale score at admission [83]. As a result, variations in monocyte counts following cerebral infarction cannot be generalized and must instead be evaluated by subtype.

Neopterin is a recognized marker for monocyte activation. Stroke patients showed a higher level of neopterin in the blood after cerebral ischemia, which paralleled the time course of monocyte accumulation in the ischemic brain [84]. Monocyte activation enhances their infiltrating activity. Additionally, circulating monocytes mediate AM expression on their surface, resulting in a significant increase in MAC-1 and LFA-1 on days 1 and 7 after stroke; PSGL-1 expression on monocytes also increased from day 1 to day 90, forming increased platelet aggregates [32]. Moreover, MAC-1 expression on circulating monocytes has been shown to be positively correlated with NIHSS scores on admission [85]. Activated monocytes attract neutrophils, stimulate and modulate AM-dependent transendothelial migration of T lymphocytes, and contribute to lymphocyte apoptosis by producing various cytokines [86]. The persistent activation of circulating monocytes seems to contribute to stroke evolution in chronic phases. Consequently, it will be of interest to compare the therapeutic effects of suppressing monocyte activation at the acute and chronic stages after ischemia.

1.5. Platelets

Despite being only circulating cellular fragments, platelets are an essential component of peripheral blood because they can adhere to plaques and blood vessel walls after activation, take part in thrombin-mediated external signaling, encourage ischemia or infarction, and play a crucial role in the pathogenesis of IS [87]. Activation of platelets can lead to changes in the morphology and number of platelets. Most acute cerebral infarction is focused on the ratio of RDW to platelet ratio (RPR), mean platelet volume (MPV), and platelet distribution width (PDW), whereas the Platelet count is more disrupted [88,89].

The RPR has recently been identified as a new marker of the severity of inflammation and has the potential to predict the severity, activity, prognosis, and mortality of various diseases, including acute pancreatitis, myocardial infarction disease, severe burns, and active systemic lupus erythematosus [89–93]. In IS, the platelet count is reduced, the RDW is higher, and a high level of RPR is linked with a poor prognosis [94,95]. The MPV is currently one of the most extensively utilized and clinically significant platelet biological function indicators, and is linked to platelet reactivity and aggregation [96]. The increase in MPV is associated with an increase in the release of chemicals by active platelets, which improves their adhesion, aggregation, and release activities [96]. Studies have shown that the MPV is significantly larger in patients with acute cerebral ischemia than in healthy individuals and is positively connected with NIHSS scores [97,98]. Additionally, Lim et al. discovered that the MPV at admission might be used as a monitoring indicator of disease severity in patients with acute stroke [99]. The PDW mostly depicts constant variation in platelet size and volume [97]. Similar to the RDW, a higher PDW is a sign of weaker platelet volume consistency. Studies have shown that, in patients with acute stroke, the PDW is significantly higher than that in healthy patients, and is significantly lower in patients with mild disease than in patients with severe disease. These findings suggest that an increase in PDW may be related to the occurrence of acute stroke and has some clinical value and predictive value for the severity of the disease [97].

In conclusion, platelets play a critical role in the development of acute cerebrovascular events, particularly thrombosis and chronic inflammatory responses. However, more research is needed to determine whether it is linked to immunological variables.

1.6. Cytokines and chemokines

After IS onset, inflammatory cytokines and chemokines, produced by activated leukocytes and platelets in both circulation and ischemic lesions, affect both themselves and other blood cells. Neutrophils release pro-inflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-α, to promote T lymphocyte activation and migration, upregulate AM expression, and influence platelet glutamate uptake.

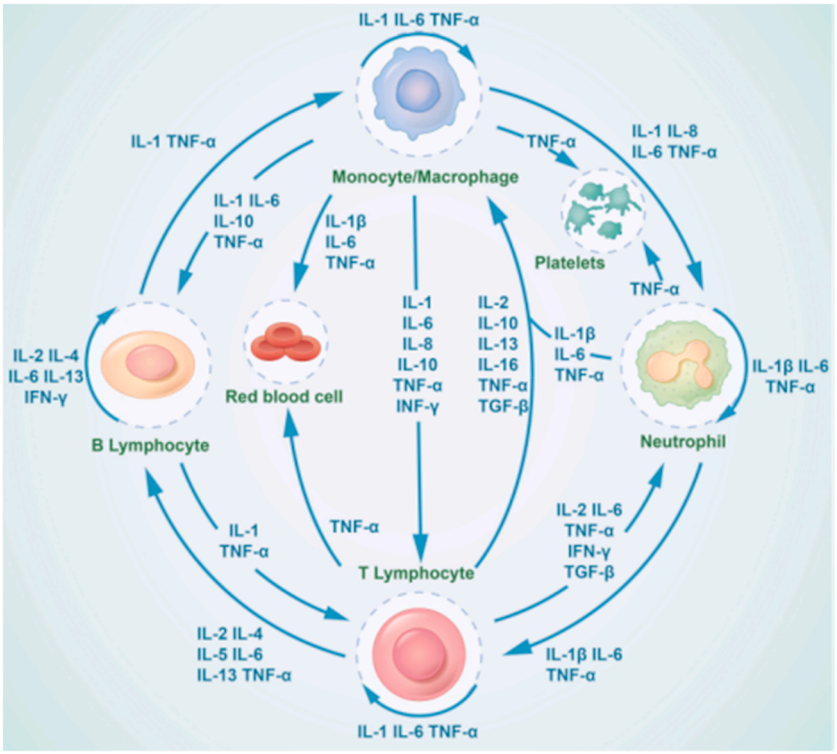

Fig. 1. Alterations and interactions of cytokines secreted by peripheral blood cells after ischemic stroke
After an ischemic stroke, peripheral blood cells and platelets interact by secreting several types of cytokines and chemokines, which jointly govern the inflammatory and immunological states.
TNF-α: Tumor necrosis factor alpha, IFN-γ: Interferon-gamma, IP-10: Interferon-gamma-inducible protein 10, IL: Interleukin.

Neutrophils also secrete reactive oxygen species, matrix metalloproteinases, and other substances that work in conjunction with cytokines to accelerate ischemia-reperfusion injury [2,5,6]. Different lymphocytes produce different types and quantities of cytokines. Th1 cells mostly secrete IFN-γ; Th2 cells mainly secrete IL-4, IL-5, IL-9, IL-13, and IL-25; and Th17 cells mainly secrete IL-17A, IL-17F, and IL-22. Tregs primarily secrete transforming growth factor-beta (TGF-β), IL-10, IL-35, STAT6, and FOXP3, whereas cytotoxic T cells identify their antigens and, upon activation, release cytokines such as TNF-α and IFN-γ. B cells also have an impact on immunological responses by generating cytokines such as lymphotoxin, IL-6, IL-10, TGF-β, IL-4, IFN-γ, and IL-12[5,6,63,64]. However, it is important to note that the differentiation status and activation circumstances of B cells determine whether they can create cytokines. Additionally, IS mostly impacts T lymphocyte-produced cytokines, including IL-2, IL-6, TNF-α, and IFN-γ, as pro-inflammatory molecules, and the released cytokines IL-4, IL-5, IL-13, and TGF-β, as anti-inflammatory agents [100,101].

Circulating monocytes are another important source of chemokines [86]. The mRNA levels of CXC-chemokines in peripheral monocytes (e.g., IL-1β, IL-8, and IL-17) have been shown to be correlated with neurological impairment after stroke [86,102,103]. Neutralizing IL-8 has been shown to reduce brain edema and infarct size in an ischemia-reperfusion model in rabbits [104]. However, the number of monocytes expressing CC-chemokine mRNA, such as chemokine (C–C motif) ligand 2 (CCL-2), macrophage inflammatory protein (MIP)-1α, and MIP-1β, was not elevated in patients with IS [105]. The related cytokines and chemokines from peripheral blood cells, along with their network after IS were shown in Fig. 1.

1.7. Conclusions and prospects

In this review, we summarized the alterations and roles of peripheral blood cells after IS and concluded that these changes are closely related to inflammatory and immunomodulatory processes in the development of cerebrovascular ischemic diseases (see Fig. 2). The activation of neutrophils is thought to be the core of the inflammatory response, whereas lymphocytes are mainly responsible for the immune mechanism. However, several limitations were exposed in the mentioned clinical studies. For example, there is a lack of a precise description of the time course for blood sampling and the absence of exclusion criteria for patients who suffer a history of previous vascular risk factors, which may interfere with the detection of peripheral blood cells. Meanwhile, it is important to note that peripheral blood components contribute to the inflammation and immunosuppression observed after cerebral ischemia, while the disease course will also impact this shift; hence, it is difficult to generalize and separate each change in blood composition into primary and secondary causes. These problems need to be solved urgently before conducting clinical studies on peripheral blood cells from patients with IS.

Here, several problems are proposed as future directions. First, the innate mechanisms of immune activation and immunosuppression induced by IS remain unclear. Developing a more specific profile for immunoregulation after ischemic events could allow the

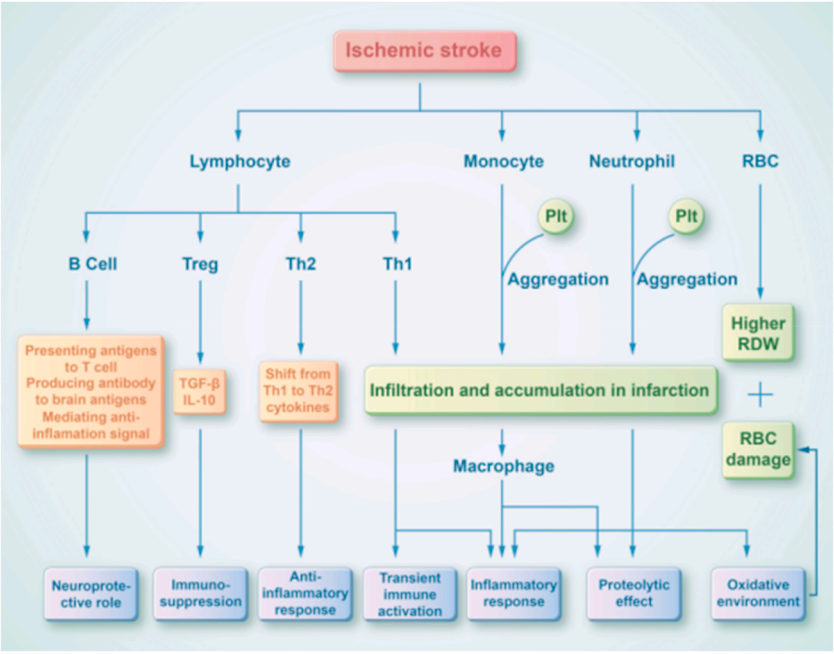

Fig. 2. Involvement of peripheral blood cells in the pathogenesis of ischemic injury
This diagram summarizes the changes and roles of peripheral blood cells following ischemic stroke, concluding that these changes are directly related to inflammatory and immunomodulatory processes in the development of cerebral ischemia disorders. RBC: Red blood cell, RDW: RBC distribution width, Treg: Regulatory T, Th: Helper T, Plt: platelet, IL-10: Interleukin-10, TGF-β: Transforming growth factor-beta. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

development of a new and useful immune therapy for stroke patients. Second, neutrophils and lymphocytes both play core roles in the ischemic process, but interfering with their functions during treatment inevitably leads to deleterious outcomes, such as higher mortality from SAI. More research is necessary to determine how to relieve or avoid such deleterious effects. Third, whether RBC damage and higher volume variation directly potentiate the ischemic injury effect requires more evidence, as RBCs are the main carrier and source of oxygen and nutrients. As the important roles of RBCs have been previously ignored, we propose that protecting and maintaining the normal functions of RBCs may be an effective treatment for individuals suffering from stroke.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Huanhuan Gong: Writing – original draft, Resources, Formal analysis, Data curation. **Zheng Li:** Writing – original draft, Resources, Investigation, Formal analysis, Data curation. **Guoqing Huang:** Software, Methodology. **Xiaoye Mo:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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