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Immune Cells After Ischemic Stroke Onset: Roles, Migration, and Target Intervention

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Abstract

Ischemic stroke is one of the leading health issues and the major cause of permanent disability in adults worldwide. Energy depletion and hypoxia occurring after ischemic stroke result in cell death, which activates resident glia cells and promotes the peripheral immune cells breaching into brain performing various functions even contradictory effects. The infiltration of immune cells may mediate neuron apoptosis and escalate ischemic damage, while it enhances neuron repair, differentiation, and neuroregeneration. The central nervous system (CNS) is immune-privileged site as it is separated from the peripheral immune system by the blood-brain barrier (BBB). Pathologically, the diapedesis of peripheral immune cells to CNS is controlled by BBB and regulated by immune cells/endothelial interactions. As immune responses play a key role in modulating the progression of ischemic injury development, understanding the characteristics and the contribution on regulating inflammatory responses of glia cells and peripheral immune cells may provide novel approaches for potential therapies. This review summarizes the multistep process of periphery immune cell extravasation into brain parenchyma during immunosurveillance and chronic inflammation after ischemic stroke onset. Furthermore, the review highlights promising target intervention, which may promote the development of future therapeutics for ischemic stroke.

Keywords Ischemic stroke · Glia cells · Peripheral immune cells · Blood-brain barrier

Introduction

Stroke is classified into ischemic and hemorrhagic subtypes depending on its etiology (Yoo et al. 2016), which is 87% of stroke is attributed to ischemic stroke (Radu et al. 2017). Ischemic stroke is a devastating disease worldwide with high morbidity and mortality rate accounting for 5.5 million deaths annually (Holloway and Gavins 2016; Hu et al. 2017a). Recombinant tissue-plasminogen activator (rtPA) remains the only Food and Drug Administration (FDA) approved approach used in clinic to restore cerebral blood flow. There are many risk factors, causes, and mechanisms contributing to ischemic stroke (Fig. 1), which divided into modifiable factors and unmodifiable factors. The causes of ischemic stroke are divided into three categories: (1) vasculature dysfunction, (2) atherosclerosis (which falls into structural changes), and (3) BBB dysfunction (Kong et al. 2016).

In an ischemic event, there is a shortage of oxygen and/or nutrient delivery due to poor blood flow, which causes failure of oxidative phosphorylation and ATP synthesis (Khoshnam et al. 2017). Due to the depletion of energy, glycolysis arises in the ischemic brain, which generates lactic acid and results in subsequent tissue acidosis. Excessive lactate accumulation can cause edema, BBB dysfunction, extensive tissue necrosis, impairment of brain energetics, and oxidative stress (Leng et al. 2014).

Hypoxia and hypoglycemia adversely affect Na^+/K^+ ATPase pump, resulting in plasma membrane depolarization, release of potassium into the extracellular space, and entry of sodium into cells. In addition, the Ca^{2+} pump also fails causing a dramatic rise in intracellular calcium concentration during ischemia, which is called calcium overload. This activates several death-signaling proteins, such as calcium-dependent proteases, lipases, and DNases resulting in cell death in the ischemic core (Szeto et al. 2018).

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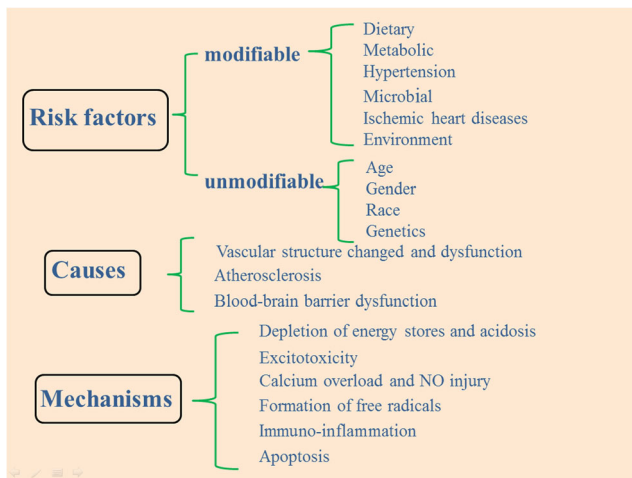
Fig. 1 The risk factors, causes and mechanisms of ischemic stroke. The risk factors are divided into two types: modifiable and unmodifiable. The modifiable types are regulated by medicine or changing habits. The unmodifiable types cannot be adjusted one way or another. Vascular structure changed; atherosclerosis and BBB dysfunction constitute to causes of ischemic stroke. Several pathological mechanisms are activated following ischemic stroke. These include depletion of energy stores and acidosis, excitotoxicity, calcium overload and NO injury, formation of free radicals, immuno-inflammation, and apoptosis resulting in ischemic stroke

Apoptosis is one of cell type-specific mechanisms in the pathology of ischemic stroke (Cheon et al. 2018). There are two pathways of cell death in penumbral cells: the intrinsic apoptotic pathway (also known as mitochondrion-mediated pathway) and the extrinsic apoptotic pathway (death receptor pathway) (Gupta and Ghosh 2017). Calcium overload may activate different enzyme in the cytoplasm and mitochondrion to damage lipids, proteins, and nucleic acids, which results in death receptor apoptosis. On the other hand, calcium overload destroys the structure and function of mitochondrion, which induces the release of cytochrome c from mitochondrion. Cytochrome c will activate death apoptosis like Bcl-2 to mediate intrinsic apoptosis. Activation of the *N*-methyl-D-aspartate (NMDA) when ischemic stroke occurs leads to membrane depolarization and facilitates the influx of calcium ions into neurons resulting in the neuronal damage, which is called excitotoxicity (Khoshnam et al. 2017; Wu and Tymianski 2018). NMDAR-mediated excitotoxicity, excessive of Ca^{2+} influx, mitochondrion metabolism, neuronal nitric oxide synthase (nNOS) activation, and acidosis lead to the free radical formation (Gupta and Ghosh 2017). Oxidative stress occurs when the production of free radicals, such as reactive oxygen/nitrogen species (ROS/RNS), overpowers the endogenous scavenging capacity of antioxidant defenses systems. ROS have substantial cellular effects, causing tissue devastation and cell death by processes including DNA damage, protein destruction, lipid peroxidation, release of Ca^{2+} from intracellular stores, cytoskeletal structural injury, and chemotaxis (Gupta and Ghosh 2017; Khoshnam et al. 2017). Despite depletion of energy stores and

acidosis, calcium overload, excitotoxicity, apoptosis, and formation of free radicals, the pathology of ischemic stroke also includes immuno-inflammation, which is the main point in this review (Hu et al. 2017b; Khoshnam et al. 2017).

When ischemic stroke occurs, death of cells especially neurons in the brain would be induced by hypoxia inducible factor-1α (HIF-1α) and Notch intracellular domain (NICD), which are co-expressed in the neuronal nucleus to engage pro-inflammatory and apoptotic signaling pathways (Chen et al. 2014; Cheng et al. 2014). The immune responses after ischemic stroke are separated into innate immunity and adaptive immunity. The glia cells activated by cell debris release a series of cytokines and chemokines to recruit peripheral immune cells into brain parenchyma in innate immune system, the first line of defense to cerebral damage (Guruswamy and ElAli 2017; Khoshnam et al. 2017; Kim and Cho 2016). Adaptive immunity following innate immune system is based on the antigen-specific defense mechanism, which includes the T and B lymphocytes that are related to the post-injury inflammatory response (Khoshnam et al. 2017). Actually, the first responders to central nervous system (CNS) injury are microglia and astrocytes. Microglia is the resident macrophages of the brain and a key modulator of immunologic responses after ischemic stroke. Once activated by extracellular signals, they function to sweep debris and toxic substances by phagocytosis. Astrocytes are the most abundant cells in the brain. In uninjured brain tissues, astrocytes provide structural and nutritive support for neurons. After ischemic stroke, astrocytes play an important role in wound healing and repair by mediating reactive gliosis and glial scar formation.

This review summarizes the performance and functions of cerebral resident glia cells as well as peripheral immune cells participated in the ischemic stroke. BBB constituted with endothelial cells (ECs) and the glia limitans perivascularis of the microvessels regulates the nutrition and toxic substance in and out of the CNS (Kong et al. 2016). Since a better understanding of the process that periphery immune cells breaching the BBB into brain parenchyma is helpful for researchers to discover targets with therapeutic potential for ischemic stroke. The migration of peripheral immune cells into brain is elaborated in the second part. Currently, emerging targets usually take a role in regulating cellular infiltration, decreasing inflammation, and extenuating ischemic injury. In this review, target intervention for stroke treatment based on immune responses is classified into three parts: cytokines, adhesion molecules, and related genes.

The Immune Cells in the Brain After Ischemic Stroke

The various immune cells contain microglia, neutrophils, monocyte, macrophage, and lymphocyte (Jones et al. 2018; Park et al. 2018b; Wattananit et al. 2016; Yu et al. 2018). All of

these cell types engage in cross-talk with each other using a multitude of signaling pathways that modulate activation/ suppression in response to ischemia (McDonough and Weinstein 2016). Infiltration of immune cells has double-sided effects (Table 1) (Jones et al. 2018). Previous researches have proved that neuronal injury from ischemic stroke is aggravated by invading peripheral immune cells (Jones et al. 2018; McDonough and Weinstein 2016; Neumann et al. 2015), while others have the contradictory idea. Because ischemic damage is time-dependent and ranges from negligible to massive, involving different cell types (Perez-Alvarez et al. 2018), it will be reasonable to get controversial consequences. The characteristics of glia cells and periphery immune cells are elaborated as follows.

Microglia and Monocyte-Macrophage System

Microglia is the only resident macrophage, which belongs to the monocyte-macrophage system in the brain gray matter, at the percentage of 15% (Kim et al. 2016). However, a series of recent findings has established that microglia is a unique cell population distinct from macrophages (Salter and Beggs 2014). Microglia is not activated normally and cannot exert immune function in resting state, which maintains the homeostasis of brain by controlling the synapse, neuronal firing, and removing debris (Salter and Beggs 2014). Microglia can be activated and will up to the peak 2–3 days after ischemic stroke (Kim and Cho 2016). The response repertoire of microglia includes cytoskeletal rearrangements leading to morphological changes, stereotypic transcriptional alterations, proliferation, apoptosis, and autophagy (Beggs and Salter 2016; Salter and Beggs 2014). Here, we mainly discuss about autophagy. Autophagy refers to as the cellular catabolic processes in which cytoplasmic proteins and organelles in the cell are "eaten" by itself (Wang et al. 2018). It is different from apoptosis, the programmed cell death. Autophagy is emerging as a core regulator of CNS neurodegeneration according to recent reports. Microglia, as the main innate immune cells in

Table 1 The functions of different immune cells in ischemic stroke

Cell types	Subtypes	Functions	
Microglia	M1	Physiology	Maintain homeostasis (Salter and Beggs 2014)
		Pathology	Drive apoptosis of neurons (Salter and Beggs 2014)
			Release pro-inflammatory mediators (Cheon et al. 2017; Kim et al. 2016)
	M2	Physiology	Maintain homeostasis (Salter and Beggs 2014)
		Pathology	Release anti-inflammatory mediators (Kim et al. 2016)
			Sweep debris and toxic substances (Kim et al. 2016)
			Promote transcription of NF-κB (Choi et al. 2017; Lu et al. 2018)
			Repair injury of neurons (Liu et al. 2017b)
			Enhance neurogenesis and differentiation of neurons (Choi et al. 2017)
Astrocytes		Physiology	Provide structural and nutritive support (Chisholm and Sohrabji 2016)
			Regulate glutamate levels (Chisholm and Sohrabji 2016)
			Release neutrophils (Chisholm and Sohrabji 2016)
			Component of BBB (Wang and Parpura 2016)
		Pathology	Heal wound and repair injured cells (Kim et al. 2016)
			Produce inflammatory cytokines and toxic mediators to exaggerate injury(Kim et al. 2016)
Lymphocytes	T		Amplify inflammation (Wang et al. 2017)
			Increase neurological deficits and infarct volume (Jin et al. 2018; Kim et al. 2016)
	B		Have little function (Kim et al. 2016)
	NK		Increase local inflammation and neural hyperactivity (Khoshnam et al. 2017)
	Treg		Decrease the infarct volume and neurological deficit (Kim et al. 2016)
Neutrophils			React with microglia and be in phagocytosis by microglia (Neumann et al. 2015, 2018)
			Release oxygen radical, proteases and pro-inflammatory mediators (Neumann et al. 2015)
			Activate immune cells to remove debris (Ruhnau et al. 2017)

CNS, also participated in autophagy, which finely regulates the innate immune response (Plaza-Zabala et al. 2017). Researchers have indicated that microglia autophagy may be mediated by Toll-like receptor 2 ligands (TLR2) (Arroyo et al. 2013), purinergic receptor (Takenouchi et al. 2009), microRNA (Song et al. 2015), and p53 up-regulated modulator of apoptosis (Zhang et al. 2012). The autophagy evoked by ischemic insult in microglia contributes to ischemia-induced brain injury and neurological recovery after ischemic stroke (Wang et al. 2018). Nevertheless, the role of autophagy may play on microglia and the possible impacts of autophagy dysregulation on the physiology and survival of these brain-resident macrophages have not been studied clearly yet (Plaza-Zabala et al. 2017). Microglia frequency was significantly reduced in the ischemic hemisphere compared to the contralateral hemisphere, while the number of activated microglia is increased (Jones et al. 2018). The activated microglia but not resting microglia can sweep debris and toxic substance, while it increases the level of cytokine and adhesion molecules (Kim et al. 2016). Microglia is not simple waste collector after ischemic stroke, but rather, it can drive the process of neuron death (Salter and Beggs 2014).

According to the microenvironment, the macrophages can differentiate into M1 and M2 subtypes (Cheon et al. 2017; Li et al. 2017b; Liu et al. 2017b). M2 subtype can be divided into M2a, M2b, and M2c. The M1 subtype with CD16, CD32, and CD68 expressed on the surface can promote the transcriptional activation of nuclear factor-κB (NF-κB) (Choi et al. 2017) and release pro-inflammatory mediators, which aggravate cerebral ischemic injury (Jiang et al. 2018). The M2 subtype releases anti-inflammatory mediators, such as interleukin-33 (IL-33) and IL-10, which protect the undamaged neurons from ischemia and hypoxia (Cheon et al. 2017; Jiang et al.

2018). M2a expresses arginase-1, Ym1, and Fizz. M2b expresses IL-10 and CD86. M2c expresses arginase-1, CD163, and CD206. In general, CD86, CD11b, and MHC-II are regarded as biomarkers of M1, while CD206 and ED-1 are regarded as biomarker of M2 (Fig. 2) (Choi et al. 2017; Espinosa-Garcia et al. 2017). The regulation of M1/M2 is extremely important to removing debris and protecting the undamaged neurons. It has been proved that M1 subtype produced in the early stage is deleterious, which activates the transcription of NF-κB to produce pro-inflammatory cytokines: tumor necrosis factor-α (TNF-α), IL-1β, and NO (McDonough and Weinstein 2016). However, in the late stage, M2 subtype produced later, which releases anti-inflammatory mediator: IL-4, IL-12, and grow factor is advantageous (Kim et al. 2016).

Ischemic stroke-induced neuroinflammation is mostly mediated by microglia. Numerous researches have focused on the states of microglia to find the signaling pathway of activation mechanism. For example, homocysteine (Hcy) exaggerates microglia activation and neuroinflammation after ischemic stroke through JAK2/STAT3 pathway (Chen et al. 2017b). After ischemic stroke, the injured neurons release peroxiredoxin2 binding to the Toll-like receptor4 (TLR4) on the microglia (McDonough and Weinstein 2016), which increases the expressions of MyD88 and NF-κB. The increased expressions of MyD88 and NF-κB contribute to the release of IL-1β and IL-6, thereby activating microglia (Lu et al. 2018).

Astrocytes

Astrocytes provide structural and nutritive support, regulate glutamate levels, and release neurotrophins under physiological condition (Chisholm and Sohrabji 2016). Astrocytes are

Fig. 2 The depolarization of microglia. The cell debris, such as broken DNA, RNA, and cytoplasmic protein after ischemic stroke, activates microglia and promotes the differentiation of microglia into M1 and M2 subtypes. M1 subtype releases pro-inflammatory mediators resulting in neurons apoptosis. M2 subtype releases anti-inflammatory mediators resulting in neurons neurogenesis and differentiation
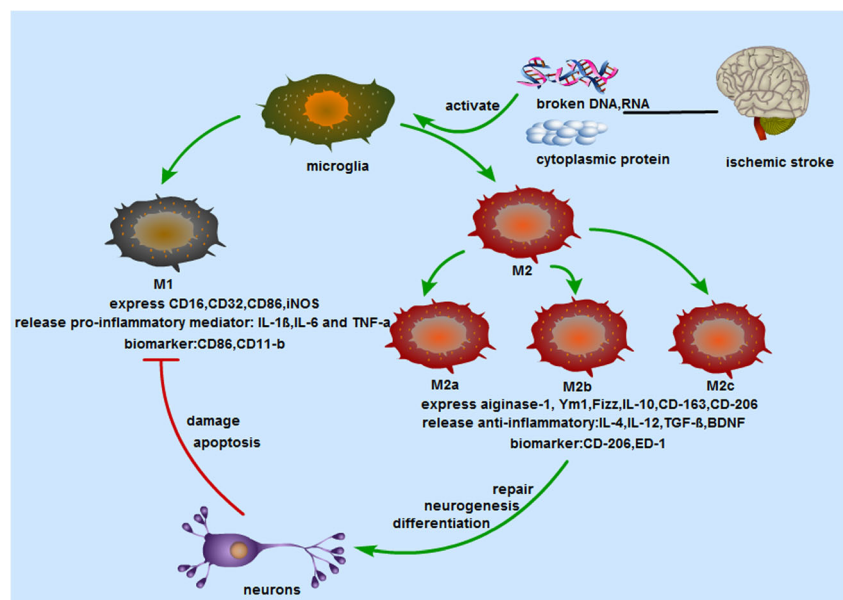
also one of the compositions of BBB, and their end feet cover more than 90% of brain capillaries to participate in BBB formation (Wang and Parpura 2016). Astrocytes have strong temporal and spatial features with astrocytic hypertrophy, reactive astrogliosis, or elongation occurring under ischemic stroke (Wang and Parpura 2016; Xie and Yang 2015). Astrocytic hypertrophy caused by re-oxygenation after reperfusion is also known as astrocytes swelling, which could be relieved by activated the Na$^+$, K$^+$, and 2Cl$^-$ transporter (NKCCl) (Hertz et al. 2014). Astrocytes have opposite effects on cerebral ischemic injury. For example, the monoamine metabolism regulated by monoamine oxidase (MAO) in astrocytes causes oxidative stress, which results in BBB dysfunction after ischemic stroke onset (Zou et al. 2017). Conversely, pentraxin 3 derived from astrocytes can support the BBB integrity, which can decrease the infract volume and infiltration of immune cells in the brain (Shindo et al. 2016). Accumulation of autophagy-like vacuoles containing electron-dense material, protein expression of LC3-II, Beclin-1, lysosome-associated membrane protein 2 (LAMP2), and lysosomal cathepsin B which are biomarkers of autophagy were observed in ischemic astrocytes in brain tissue (Wang et al. 2018), which indicates that autophagy exists in astrocytes as well as microglia. Although neuronal death is considered to be the most serious irreversible process, the apoptosis and autophagy induced by ischemic stroke is more deleterious to astrocytes than neurons (Pamenter et al. 2012). It has been demonstrated that protective autophagy in astrocytes induced by regulation of AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (m-TOR)/ULK1 (AMPK/mTOR/ULK1) signaling pathway promotes astrocyte proliferation and migration (Perez-Alvarez et al. 2018; Zhang and Miao 2018). What's more, PI3K/Akt-mTOR pathway, NF-κB, and AMPK also participate the regulation of autophagy after ischemic stroke onset (Wang et al. 2018). The response of astrocytes can be influenced by sex differences and impaired by aging. For example, estradiol, an anti-inflammatory and neuroprotective agent in ischemic stroke, increases the insertion of estradiol receptor α(ERα) into the cell membrane in female astrocytes, but fails in male astrocytes (Chisholm and Sohrabji 2016). Astrocytes also interact with different immune cells, such as lymphocytes, microglia, and neurons. In physiological condition, CD4$^+$ T cells activate astrocytes to release a kind of unknown substance, which drives the CD4$^+$ T cell polarization to Th1 and Treg. Under pathological conditions, astrocytes regulate the activity of T cell to protect or impair the tight junction (TJ) of vascular ECs. Another research has proved that IL-15 derived by astrocytes induces the accumulation of CD8$^+$ T and NK cells to exacerbate the brain injury after stroke (Li et al. 2017a). Astrocytes release pro- and anti-inflammatory cytokines after ischemic stroke depending on the temporal and spatial features in ischemic brain (Xie and Yang 2015). Astrocytes heal wounds and repair injured cells

by mediating reactive gliosis and glia scar formation, while they generate pro-inflammatory cytokines and toxic mediators to exaggerate the injury (Kim et al. 2016).

Lymphocytes

Lymphocyte is a kind of leukocytes and can be classified into T, B, natural killer cell (NK) and regulatory cells (Treg). When ischemic stroke occurs, the constitution of immune cells will change quickly in the brain and the periphery. It has been demonstrated that CD4$^+$ and CD8$^+$ T lymphocyte frequencies are significantly increased in the ischemic thalamus even 14 days post-stroke (Jones et al. 2018). T lymphocytes are a key player in amplifying inflammation after ischemic stroke, whereas B lymphocytes have been shown to play a lesser role (Kim et al. 2016). It has been demonstrated that the depletion of cytotoxic T cells including CD8$^+$ and CD4$^+$ T cells decreases the infarct volume after stroke (Mracsko et al. 2014). The main infiltrated T lymphocytes are CD4$^+$ T cells after ischemic stroke, while CD8$^+$ T cells are mainly involved in the CNS viral infection (Xie and Yang 2015). But, some studies have demonstrated that CD8$^+$ T cells can also worsen the injury of ischemic stroke mediated via perforin (Mracsko et al. 2014). Other immune cells, such as neutrophils and macrophages, will be up to the peak 2–3 days after ischemic stroke and gradually disappear in the brain 14 days after stroke, while infiltration of lymphocytes including CD4$^+$ T, CD8$^+$ T, B, and NK cells persists 14 days after stroke, which may be related to the injury of late-stage cerebral ischemia (Feng et al. 2017). The proportion of T and B cells in the periphery of stroke patients is lower than the level of healthy population, conversely in CNS. It is demonstrated that the frequencies of B and T lymphocytes in the periphery are negatively correlated with stroke severity including neurological deficits and infarct volume at the onset (Wang et al. 2017), which also indicates that the infiltration of lymphocytes may aggravate ischemic injury. Another research has proved that the cell death induced by toxic insults is reduced in the presence of lymphocytes, which indicates neuroprotection of lymphocytes (Shrestha et al. 2014). Actually, the functions of lymphocytes are controversial. Whether lymphocytes are detrimental or protective to CNS may depend on the pathological conditions under which these cells infiltrate in CNS. Despite neurons and glia cells, autophagy is found in blood-derived cells like lymphocytes and neutrophils after ischemic stroke (Perez-Alvarez et al. 2018). It has been proved that autophagy in lymphocytes as well as in glia cells is also regulated by mTORC1, a protein complex downstream of PI3K-Akt pathway, which is one of the players deregulated after ischemia (Perez-Alvarez et al. 2018).

Previous researches have demonstrated that NK cells have nothing to do with ischemic stroke. However, a recent study demonstrated that NK cells exacerbate the brain infarction by

increasing local inflammation and neuronal hyperactivity (Khoshnam et al. 2017). Similar to NK cells, the functions of Treg cells are also controversial. Previous research has proved that blocking the function of Treg with antibody increases the infarct volume and neurological deficit, while other studies could not show any modulatory role of Treg cells (Kim et al. 2016).

Neutrophils

Neutrophils, the first colony of immune cells form periphery to the brain parenchyma (Neumann et al. 2015; Ruhnau et al. 2017), are spherical in the brain parenchyma and they are elongated in the vessels (Neumann et al. 2018). Neutrophils also have contradictory functions in the brain. The pro-inflammatory characteristics of neutrophils exaggerate the damage of brain tissue and result in thrombosis to attribute the ischemic injury. For example, a research has proved a detrimental role of infiltrating neutrophils containing releasing oxygen radicals, proteases, and pro-inflammatory cytokines (Neumann et al. 2015). rtPA a reagent used in thrombolysis treatment has been proved to aggravate reperfusion injury and drug toxicity with a high neutrophils/lymphocytes ratio (Ruhnau et al. 2017). However, neutrophils activate immune cells to form complete immune functions, which indicates the advantageous role of infiltration of neutrophils (Ruhnau et al. 2017). Actually, neutrophils are migratory freely in the brain parenchyma and can be phagocytosed by microglia under conditions of oxygen and glucose deprivation (Neumann et al. 2015, 2018). Neutrophils react with endothelial adhesion molecules to decrease flow rate in the vessels and depolarization, which follows the neutrophils crossing the BBB with the help of a series of adhesion molecules such as P-, E-, and L-selectins, ICAM-1, and integrin(CD11b, a, c)(Kim et al. 2016). The process of periphery immune cells moving into CNS and the influence of neutrophils infiltration will be discussed later. Although there are few studies about autophagy of lymphocytes and neutrophils under ischemic condition, autophagy was observed in neutrophils (Perez-Alvarez et al. 2018). It has been demonstrated that autophagy of neutrophils in other neurodegenerative diseases like systemic sclerosis could enhance the survival of blood-derived cells (Maugeri et al. 2018).

T Cells Breach BBB to CNS

The process of periphery immune cells migrating into brain parenchyma after ischemic stroke is complex due to the participation of various kinds of adhesion molecules and immune cells. BBB protects CNS from the constantly changing milieu in the vascular compartment by strictly controlling the movement of molecules across its interface, which establishes the border between the immune system and CNS (Coisne et al. 2013). For lack of lymphatic vessels and absence of classical MHC-positive antigen presenting cells, CNS is considered an immunologically privileged site (Dudvarski Stankovic et al. 2016; Engelhardt 2006). There are many similarities between lymphocytes and other periphery immune cells, while some differences exist. For example, activated leukocyte cell adhesion molecule (CD166) is involved in extravasation of monocytes, but it does not participate in the migration of T cells across BBB (Lyck et al. 2017). The constitution of BBB and the process of periphery immune cells breaching BBB to CNS are elaborated after ischemic stroke (taking the classical T cell infiltration as an example) (Fig. 3).

BBB

A diffusion barrier is formed by the unique cellular and molecular characteristics of ECs and the glia limitans perivascularis of the microvessels in the CNS parenchyma.

Fig. 3 T cells cross BBB. The binding of PSGL on the surface of T cells and P-selectin expressed on ECs mediates T cell capture and rolling on ECs. Interaction of α4β1 and VCAM plays an important role in arrest and crawling against blood stream with the help of CCL19, CCL21 binding to CCR7. VCAM, ICAM, and PECAM are involved in the process of arrest. Furthermore, LFA binding to ICAM1/2 mediates T cells across BBB into brain parenchyma
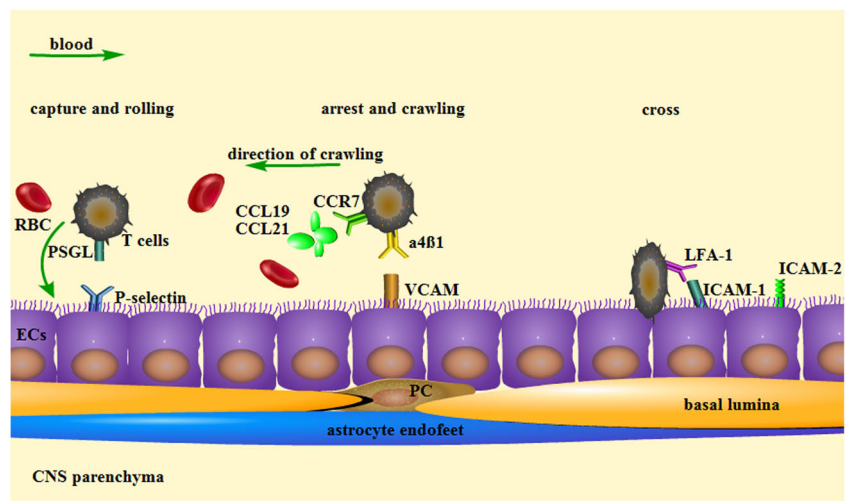
At the level of CNS capillaries, BBB forms a direct barrier (Engelhardt and Ransohoff 2012) in which blood vessels are made up of two main cell types: ECs that form the walls of the blood vessels and mural cells that sit on the ablumenal surface of the EC layer (Daneman and Prat 2015). Numerous factors contribute to the physical barrier of BBB like endothelial TJ and adherens junction (AJ) proteins. Despite ECs, other cells are involved in the constitution of BBB. Pericytes share a basement membrane with ECs and form direct synaptic-like peg-socket focal contacts with endothelium through N-cadherin and connexins. Astrocytes end feet cover more than 90% of brain capillaries to participate in BBB formation (Wang and Parpura 2016). Actually, small lipophilic molecules and drugs, with a molecular weight of < 400 Da and form of < 8 hydrogen bonds, can cross the BBB, which result in low proportion of periphery immune cell migration across it under physiological condition (Coisne et al. 2013; Zhao et al. 2015b). After ischemic stroke occurs, increased MMPs secretion can affect BBB permeability, with MMP-2 and -9 being associated with BBB breakdown following stroke, which activates the process of immune cells across BBB in CNS inflammation (Brilha et al. 2017). The process of T cell interactions with the inflamed BBB endothelium is dynamic before diapedesis (Lyck and Engelhardt 2012), which is divided into three parts: capture and rolling; arrest and crawl; and cross.

Capture and Rolling

P-Selectin glycoprotein ligand (PSGL) and its receptors: E-, P-, and L-selectins are essential for T cell capture and rolling in spinal cord microvessels (Engelhardt 2006; Sathiyanadan et al. 2014). The binding of PSGL expressed on the surface of T cells and P-selectin stored in Weibel-Palade bodies of meningeal blood vessel ECs mediates capture and rolling of T cells and blood vessels (Sathiyanadan et al. 2014). When E-, P-, and L-selectins bind to PSGL-1, T cells can be captured and roll along the EC surface at reduced velocity (Coisne et al. 2013). Despite this, it has been proved that elevated levels of soluble P-selectin in mice alters BBB function and promotes atherosclerosis to exacerbate stroke (Kisucka et al. 2009). However, there is another way for T cells binding to ECs without the help of selectins. α4/VCAM-1 interactions are not involved in transendothelial migration of T cells across the BBB but rather mediate earlier steps of T cells/BBB-interaction, such as firm adhesion in the spinal cord white matter, which is unique due to the lack of rolling of the T cells along the vascular wall (Engelhardt 2006). Some other adhesions including α4-integrin, α4β7-integrin, β7-integrin, β1-integrin, LFA-1, and CD44 may no longer required for the initial T cell capture or rolling but are still needed to mediate T cell adhesion (Engelhardt and Ransohoff 2012; Sathiyanadan et al. 2014).

Arrest and Crawl

T cells are activated via the binding of GPCRs expressed on the surface of periphery immune cells and the chemokine released by the ECs after capture and rolling (Engelhardt 2006). For example, the combination of CCL19 and CCL21 in the blood and CCR7 expressed on the surface of immune cells enhances T cells arrest and crawling on ECs (Alt et al. 2002; Steiner et al. 2011). T cell arrest and crawl on ECs in vitro under static conditions are mediated by the combination of α4β1 expressed on the surface of T cells and VCAM-1 and ICAM-1 expressed on ECs existing in BBB (Steiner et al. 2010). T cells crawl with a lower speed for a long distance against the direction of blood flow (Lyck and Engelhardt 2012). Normally, ECs express PECAM, ICAM-2, constitutive VCAM-1, and low-degree ICAM-1, in which the level of ICAM-1 and ICAM-2 increases after ischemic stroke occurs (Engelhardt 2006). Indeed, ICAM-1 and α4 integrin are important for T cell crawling and depolarization. It has been demonstrated that the speed and distance of T cells crawling on BBB are depended on the level of ICAM-1 expressed on the surface of ECs (Abadier et al. 2015). In the absence of endothelial ICAM-1, T cells lose their abilities to polarize and crawl, but a few that remain attached to the brain endothelium seems repeatedly to undergo α4β1-VCAM-1-mediated arrest (Steiner et al. 2010). Natalizumab, a α4 integrin antibody, is thought to exert its therapeutic efficacy by blocking the α4 integrin-mediated binding of periphery immune cells to BBB (Coisne et al. 2009), which indicates that blocking α4β1 leads to significantly reduced arrest and crawling interaction with the inflamed BBB, but not the capture or rolling of T cells (Sathiyanadan et al. 2014). It has been investigated that anti-VLA4 treatment reduces the cerebral infiltration of neutrophils, which may be the evidence that the binding of VLA-1 and VCAM-4 is also involved in the process of arrest and crawling (Neumann et al. 2015). Different subtypes of lymphocytes have their own migration characteristics. Although CD8^{+} T cells are able to initiate contact and maintain stable adhesion to the inflamed BBB compared to CD4^{+} T cell blasts (Coisne et al. 2013) and significantly larger numbers of CD8^{+} than CD4^{+} T cells arrest on primary mouse brain microvascular endothelial cells (pMBMECs), CD4^{+} T cells are prior to CD8^{+} in depolarization and crawling during the diapedesis (Rudolph et al. 2016).

Cross

There are two options for T cells diapedesis across BBB. Extravasation of immune cells across vascular beds into peripheral tissue usually occurs through endothelial junctions via paracellular pathway, while diapedesis of immune cell across the BBB into the inflamed CNS occurs through ECs via a transcellular pathway, leaving the TJs morphologically

intact (Engelhardt and Ransohoff 2012). A specific adaptation of T cell extravasation across the BBB appears to be the predominant diapedesis along the transcellular route (Lyck and Engelhardt 2012). Actually, the interaction of LFA and ICAM plays an important role in the migration of T cells into CNS, as previous research has proved that LFA-1 is involved in the transendothelial migration but not in capture or rolling during the process of T cell across BBB (Laschinger et al. 2002; Wang et al. 2007). It is demonstrated that infiltration of Th17 cells into the brain parenchyma therefore promoting glia activation and directly damaging to neurons is via LFA-1/ICAM-1 interaction on BBB (Liu et al. 2017a). Despite in ischemic stroke, in other diseases such as Alzheimer's disease, the binding of LFA-1 and ICAM-1 also mediates the diapedesis of peripheral immune cells into brain (Pietronigro et al. 2016). High level of endothelial ICAM-1 promotes rapid initiation of transcellular diapedesis of T cells across the BBB, while intermediate level of endothelial ICAM-1 favors paracellular T cells diapedesis. CD8$^+$ T cells are preferred to transcellular route for diapedesis compared to CD4$^+$ T cells (Rudolph et al. 2016). Furthermore, the route of T cell diapedesis across the BBB is independent of the loss of BBB barrier properties (Abadier et al. 2015). Upon breaching the EC layer, T cells prefer the site of α4-laminin and penetrate the basement membrane via α6β1 dependent pathway (Wu et al. 2009). In the immunosurveillance, APCs are located behind the BBB, which are upregulated in the healthy human and mouse CNS under pathological conditions (Ifergan et al. 2011). Cerebrospinal fluid containing macrophages expressing MHC is produced by choroid plexus and flows from ventricle to leptomeningeal space so that APCs are exposed to all antigens in the CNS. As a result, T cells breach BBB and recognize of APCs to trigger inflammation reactions (Engelhardt and Ransohoff 2012; Lyck and Engelhardt 2012).

Target Intervention for Ischemic Stroke Treatment Based on Immune Responses

Due to a narrow time window, as the only FDA approved approach, rtPA is suitable for a minority (< 10%) of stroke patients (Guruswamy and ElAli 2017). Pharmaceutical and cell-based therapies with immune responses, which play an important role in the outcome of ischemic stroke could be beneficial in treatment (Martinez and Peplow 2017). Despite the medicine on the market or regents under laboratory research designed based on immune responses, such as corticosteroids, non-steroidal anti-inflammatory drugs, inhibitors of scavenger receptor, and Toll-like receptors (TLRs) (Chen et al. 2014), target intervention for ischemic stroke treatment based on immune responses is elaborated by three aspects: cytokines, adhesion molecules, and genes related to migration of peripheral immune cells into CNS.

Cytokines

Inhibiting the pro-inflammatory cytokines can extenuate ischemic injury. TNF-α, a pro-inflammatory mediator released by astrocytes and some populations of neurons, plays a key role in inducing angiogenesis, increasing the expressions of adhesion molecules and enhancing inflammation (Cantatore et al. 2017; Figiel 2008). However, it has been demonstrated that TNF-α is a neuroprotective agent in the brain (Figiel 2008), which is contradictory to most research results. One explanation for the apparent discrepancies is that TNF-α is directly beneficial to neuronal viability; however, it can evoke responses from glia that are harmful to neurons in coculture especially under the ischemic condition. The level of TNF-α is increased in gingival fluid after ischemic stroke occurs, which aggravates neuroinflammation and neuronal damage in response to cerebral ischemia (Wytrykowska et al. 2016; Zarruk et al. 2018). The post-ischemic cerebral angiogenic response was inhibited by antibodies against TNF receptor-1(TNFR-1) after 4 and 7 days post-ischemia (Huang et al. 2016). Inhibition of TNF-α using a selective small molecule inhibitor of tumor necrosis factor-converting enzyme (TACE), which is a key sheddase releasing TNF-α from its inactive cell-bound precursor, DPH-067517, might have a salutary effect in ischemic stroke induced by embolic occlusion of the middle cerebral artery (MCAO) (Wang et al. 2004). Actually, etanercept, a TNF-α inhibitor used in rheumatism, also protects rat brain against ischemic stroke (Wu et al. 2016), which indicates that TNF-α inhibitor may be an efficacious therapeutic strategy for treatment of ischemic stroke.

IL-1β, a pro-inflammatory cytokine known as lymphocyte stimulating factor, generated by activated monocyte-macrophage system, regulates the immune responses after ischemic stroke occurs. IL-6, another pro-inflammatory cytokine, is involved in inflammation and enhances the development and differentiation of blood cells. However, angiogenesis mediated by astrocytic high-mobility group box-1 (HMGB1)/IL-6 promotes post-stroke functional recovery, which is contradictory with previous results (Chen et al. 2017a). Although the controversial results have not been explained yet, the pro-inflammatory characteristic of IL-6 is widely accepted, which indicates that inhibiting IL-6 may be play an important role in the therapy of ischemic stroke. As indicators of ischemic stroke, the level of IL-1β and IL-6 is increased after ischemic stroke occurs (Wytrykowska et al. 2016). Research has demonstrated that exercises downregulate pro-inflammatory mediators, such as IL-1β against cerebral ischemia-reperfusion injury (Zhang et al. 2016). Similarly, bilobalide has neuroprotective effects on cerebral ischemia and ischemia/reperfusion (I/R) by inhibiting pro-inflammatory mediator production (Jiang et al. 2014). As cell-based therapies are emerging as new promising treatments in stroke, a randomized controlled phase 2 trial has

proved that subcutaneous IL-1 receptor antagonist (IL-1Ra) improves clinical outcome by reducing inflammation (Smith et al. 2018), which suggest cell therapy centered on IL-1Ra is neuroprotective in experimental stroke (Clausen et al. 2016). As a result, inhibiting IL-1 and IL-6 may be another target invention for ischemic stroke.

The release of anti-inflammatory cytokines, such as IL13, IL10, IL-4, and TGF-β, extenuates ischemic injury. IL-13, an anti-inflammatory cytokines produced by CD4$^+$T cells and NK cells, causes increased mucus production by epithelial cells and increased collagen synthesis by fibroblasts and inhibits pro-inflammatory cytokines production. The level of IL-13 and IL-4 is increased after ischemic stroke onset (Arumugam et al. 2005). Transplantation of IL-13-producing mesenchymal stem cells (MSCs) increases the proportion of highly activated infiltrating macrophages and promotes the induction of alternatively activated microglia and macrophages, which provided pre-clinical rationale for the application of IL13-MSCs in future investigation of ischemic stroke (Hamzei Taj et al. 2018).

IL-4 is associated with diverse immune and inflammatory responses cellular activities via the interleukin-4 receptor α (IL-4Rα), which plays a role in long-term ischemic stroke recovery. Recent research has demonstrated neuronal IL-4Rα modulates neuronal apoptosis and cell viability during the acute phases of cerebral ischemia, which shows a neuroprotection role of IL-4Rα (Lee et al. 2018). Actually, the anti-inflammatory property of IL-4 is mediated by polarizing macrophages away from a pro-inflammatory M1 phenotype to a "healing" M2 phenotype (Zhao et al. 2015a). However, exogenous IL-4 does not protect against ischemic damage (Park et al. 2014), which suggests that IL-4Rα may represent a novel target for therapeutic development in ischemic stroke.

IL-10 is an important anti-inflammatory cytokine promoting neuronal and glia cells survival and dampening of inflammatory responses (Garcia et al. 2017). Significant association of IL-10 (− 1082A/G) gene polymorphism with the risk of ischemic stroke is observed in a meta-analysis (Kumar et al. 2016). It is proved that overexpressing IL-10 enhances the neuroprotective effects of MSC transplantation by anti-inflammatory modulation and thereby supports neuronal survival during the acute ischemic phase (Nakajima et al. 2017). What's more, a research has shown that the baseline serum level of IL-10 ≥ 14.5 pg/ ml is a predictor of post-stroke infection (Ashour et al. 2016), which indicates that IL-10 may help the clinic diagnosis and therapy of ischemic stroke.

Adhesion Molecules

Regulating adhesion molecules which control peripheral immune cell migration into brain parenchyma remains to be a potential therapeutic target (Rossi et al. 2011; Ruhnau et al. 2017). Research has proved that adhesion of bone marrow stromal cells (BMSC) in cerebral venules with middle cerebral artery occlusion and reperfusion (MCAO/R) is significantly increased. The binding of selectins and PSGL is the initial step mediating ECs capturing immune cells in the migration of periphery immune cells into brain parenchyma. Immunoneutralization of either E- or P-selectin blocked MCAO/R-induced recruitment of adherent BMSC (Yilmaz et al. 2011). What's more, the expression of P-selectin contributes to enhanced BBB dysfunction at 24 h after transient focal cerebral ischemic, which indicates that the relief of BBB breakdown mediated by P-selectin deficient following transient ischemic stroke is a future therapeutic target for treatment of ischemic stroke (Jin et al. 2010).

Integrin play an important role in the migration of periphery immune cells into CNS. Natalizumab, used in multiple sclerosis, is a humanized antibody against α-4 integrin (CD49d) that mediates arrest and crawling of periphery immune cells on ECs. The efficacy of natalizumab for ischemic stroke is evaluated, which indicates anti-integrin antibody treatment a new therapy for acute ischemic stroke (Simats et al. 2016). However, a previous research has demonstrated that blocking of α4 integrin does not protect from acute ischemic stroke in mice, although blocking of α4 integrin significantly reduced the invasion of T lymphocytes and neutrophils on day 5 after MCAO occlusion (Langhauser et al. 2014). The explanation is that anti-α4 therapy could reduce infarct volumes and improved functional deficits only after transient focal cerebral ischemia in rats, which suggests that the therapy of anti-integrin antibody may be applied on the acute phase after the ischemic challenge and should be studied further in the future.

The binding of LFA-1, CD11b/CD18, and ICAM is involved in the transendothelial migration, and inhibition of LFA-1 and CD11b/CD18 could be a promising target invention of ischemic stroke. In an experiment using mice with null mutations for LFA-1, significant reduction in infarct volume and improvement in the I/R-induced neurological deficit are reported (Arumugam et al. 2004). Absence of CD11b/CD18, also known as Mac-1, decreases the infarct volume and neutrophil infiltration (Kim et al. 2016).

Genes Related to the Cell Apoptosis and Inflammation

Regulation of gene expression related to the cell apoptosis and inflammation decreases the injury of ischemic stroke. The subfamilies of mitogen-activated protein kinase (MAPK), namely extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38-MAPKs respond to stress and regulate the apoptotic pathway (She et al. 2018). Actually, as the only approved pharmacological strategy for acute ischemic stroke, rt-PA exhibits vascular toxicity mainly due to endothelial damage through p38 MAPK pathways (Garraud et al. 2016). It is demonstrated that the activation of p38

contribute to the progression of tissue injury (Lehotsky et al. 2016). Brain cell exposure to lymphocytes can reduce p-p38 MAPK and p-ERK but not total protein associated with the neuroprotection of lymphocytes, which also indicates the activation of p38 may aggravate the ischemic injury (Shrestha et al. 2014). Compared to p38, the activation of ERK has double-sided functions. Transient activation of ERK plays a pivotal role in neuronal maturation, survival, and long-term potentiation, while sustained activation of ERK may play a critical role in triggering pro-apoptotic signals and neuronal cell death (Lehotsky et al. 2016). It is reported that many substances, such as gastrodin, sulfosuccinimidyl oleate sodium, and spatholobi caulis extract in preclinical study, exhibit neuroprotection and anti-apoptosis by modulation of MAPK signaling pathways (Dhungana et al. 2017; Liu et al. 2018; Park et al. 2018a). However, because the activation of MAPK signaling pathway is influenced by numerous factors, these substances have not entered into market, which indicates us the therapeutic potential of MAPK should be studied further.

Regulation of NF-κB, the gene associated with inflammatory chemokines, can also prevent neurons from the injury of ischemic stroke (Li et al. 2017b). Recombinant growth-arrest-specific protein 6 (rGas6) attenuates neuroinflammation by inhibiting the TLR/TRAF/NF-κB pathway after MCAO in rats (Wu et al. 2018). Preoxiredoxin2 (Prx2) released by injured neurons binding to the Toll-like receptor4 (TLR4) on the microglia increases the expressions of MyD88 and NF-κB, which enhance the release of IL-1β and IL-6 to activate microglia and induce neuron apoptosis (Lu et al. 2018). Therefore, inhibiting the expression of NF-κB may extenuate the ischemic injury. Actually, many factors could influence the expression of NF-κB, the downstream gene of the signaling pathway, which indicates that the therapy based on NF-κ B may be studied further in the future.

The phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) is a central mediator in the signal transduction pathways that helps to regulate cell growth, metabolism, and cell survival in response to growth factors. The binding of two grow factors activates class-1 PI3K-Akt signaling pathway, resulting in Akt phosphorylation, which phosphorylates a number of downstream proteins including some associated with apoptosis, such as BAD, glycogen synthase kinase-3 (GSK-3), and caspases (Ishrat et al. 2012). mTORC1, a downstream protein complex in the PI3K-Akt pathway deregulated after ischemia and OGD, enhances neuron growth and proliferation (Jiang et al. 2014; Perez-Alvarez et al. 2018). The apoptosis, proliferation, and growth of neurons extenuate the ischemic injury, which means that the activation of class-PI3K/Akt may be another promising target invention. Actually, there are so many signaling pathways and genes involved in cerebral ischemia such as Notch signaling pathway including Notch, NF-κB, p53, HIF-1α, and peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) (Arumugam et al. 2018) that could be therapeutic targets in the future.

Summary

We have discussed the form changed and functions of glia cells and peripheral immune cells after ischemic stroke onset at the early stage and the pro-long time. Cell death due to hypoxia and lack of energy after ischemic stroke occurs generates DAMPs, which activate resident glia cells. The activated glia cells release a series of cytokines and chemokines to recruit periphery immune cells across BBB into CNS. Whether anti-inflammation or pro-inflammation activated glia cells and peripheral immune cells performing depends on the stage of ischemic stroke. We have summarized the process of peripheral immune cells migration into brain parenchyma. Furthermore, we talked about target intervention for ischemic stroke treatment based on immune responses especially the regulation of immune response to decrease I/R injury. The regulation is also divided into three levels containing: cytokines (such as TNF-α, IL-1β, IL-6, IL-13, IL-10, and IL-4), adhesion molecules (such as P-selectin/PSGL, α4β1/VCAM, VLA/VCAM, and LFA/ICAM), and genes (such as MAPK, NF-κB, and PI3K/Akt) associated to ischemic stroke.

Stroke is one of the leading causes of death and disability in the world (Lin et al. 2018). Infiltration of peripheral immune cells into brain is known to modulate injury and repair processes (Jones et al. 2018). This review has summarized the performance of glia cells and peripheral immune cells after ischemic stroke onset systematically, which provides potential targets invention for ischemic stroke treatment in clinic. For example, researchers are eager to find immunotherapies applying for ischemic stroke treatment according to the performance of immune cells (Hocum Stone et al. 2016; Shepherd et al. 2017). The process of periphery immune cells across BBB into brain is discussed concisely and clearly in this review. As an important event after ischemic stroke, the migration of immune cells from periphery into brain can be a worthy research direction to find key points treating ischemic stroke. What's more, target intervention for ischemic stroke treatment based on immune responses is discussed for the first time, which will provide novel insights for developing new therapeutic strategies to treat acute ischemic stroke.

There are different types of immune cells, each with diverse subtypes. Future work should summarize the characteristics of subtypes after ischemic stroke onset, which can give us more information about ischemic stroke. Changes of BBB itself, a defense of the CNS after ischemia, should be elaborated later. As immune system plays an important role in the pathology of ischemic stroke, the details of immune responses should be discussed to find novel potential targets in the future.

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