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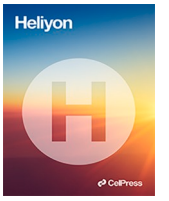

Review article

Neuroinflammation and anti-inflammatory therapy for ischemic stroke

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ABSTRACT

Stroke remains one of the most devastating and challenging neurological diseases worldwide. Inflammation, as well as oxidative stress is one of the main contributors to post-stroke injuries, and oxidative stress can further induce inflammation. Moreover, the inflammatory response is closely related to immune modulation in ischemic stroke progression. Hence, major ischemic stroke treatment strategies include targeting inflammatory responses, immune modulation (especially immune cells), and inflammatory response to suppress stroke progression. To date, several drugs have demonstrated clinical efficacy, such as Etanercept and Fingolimod. However, only edaravone dexborneol has successfully passed the phase III clinical trial and been approved by the National Medical Products Administration (NMPA) to treat ischemic stroke in China, which can restore redox balance and regulate inflammatory immune responses, thus providing neuroprotection in ischemic stroke. In this review, we will comprehensively summarize the current advances in the application of inflammatory biomarkers, neuroinflammation and neuroimmunotherapeutic scenarios for ischemic stroke, thus aiming to provide a theoretical basis and new prospects and frontiers for clinical applications.

1. Introduction

Stroke continues to be one of the most catastrophic neurological conditions, ranking as the second leading cause of death [1]. Moreover, as populations continue to age worldwide, the mean lifetime probability of experiencing a stroke has increased from 22.8% in 1990 to 24.9% in 2016 [2]. Furthermore, stroke incidences will undergo a 2.25-fold increase by the year 2050, with about one-third of the cases occurring in people over 85 years of age [3]. Undoubtedly, increasing stroke incidences and mortality would have drastic financial and emotional effects on patients, families, and society.

About 80% of all stroke cases are ischemic strokes (IS) [4]. To date, the most common therapeutic approach for IS was to rescue the penumbra through reperfusion using tissue plasminogen activator, intravenous thrombolysis, or mechanical thrombectomy (with a stent retriever or endovascular therapy) [5,6]. However, few patients benefited from mechanical thrombectomy and intravenous thrombolysis due to the short window of treatment opportunity and hemorrhagic complications [5]. Moreover, ischemic reperfusion may induce a series of injuries. Therefore, alternative therapeutic strategies are urgently needed.

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IS results from a major cerebral artery or its branches occlusion that decreases cerebral blood flow and kills neurons. A series of responses contribute to the pathological process of ischemia, such as inflammation, oxidative stress, immune cells recruitment, and microglia activation [7]. Among these factors, inflammation is considered as a critical factor in all phases of stroke development, from occlusion in the acute phase to post-ischemic repair [8]. Inflammation is a defense response that removes toxic substances and restricts their detrimental effects. There is increasing evidence to indicate that inflammation contributes significantly to brain ischemia during the post-ischemic phase. Furthermore, reperfusion injuries are primarily driven by oxidative stress and inflammation, and oxidative stress can also incite an inflammatory response [9]. Besides, an increasing amount of evidence demonstrates that continuous inflammation can damage neurons and the blood–brain barrier (BBB) during cerebral infarction, injuring tissue and deteriorating functional outcomes. Furthermore, the immune response is intimately linked to the modulation of inflammation in the development and progression of IS [10]. Hence, targeting the inflammatory response and restoring redox balance remain major strategies against IS.

We searched PubMed, EMBASE, and Web of Science to identify animal and clinical data with the following keywords, "immunotherapy or neuroinflammation or neuro-immunotherapeutic" and "ischemic stroke", which was published before August 01, 2022. The eligible study must provide robust and sufficient data (preclinical study), or be report following CONSORT Statement, otherwise were excluded. This review summarizes current knowledge and progresses on the pathophysiological changes of IS, IS inflammatory biomarkers, and neuroinflammation and anti-inflammatory therapies against IS, thus providing a theoretical basis and new prospects for clinical applications.

2. Pathophysiological changes in ischemic stroke

Typical pathophysiological changes in IS start with a sudden blood supply loss and result in a rapid onset of neurological deficits [11]. Clinical symptoms often evolve within 24–48 h, and are determined by the affected area and fate of the ischemic penumbra [12]. In general, staging of IS can be divided into three phases: the acute phase (which covers the first 2 weeks), the subacute stage (lasting up to 6 months following onset, when most changes occur), and the chronic phase (occurring over months to years and often accompanied by several sequelae) [13,14]. Of note, 6 h within the onset of stroke is termed as "hyperacute phase", widely regarding as the time window of mechanical thrombectomy and intravenous thrombolysis. The following sections discuss the detailed pathological features of the acute phase and subacute stage.

2.1. Acute phase

In the first hours after onset, the sudden block of blood supply leads to endothelial dysfunction, leukocyte adhesion, and coagulation [15]. The endothelial cells respond to shear stress-induced injuries by changing selectin and adhesion molecules expressions, recruiting peripheral circulating leukocytes, and promoting platelet agglutination. Adhering leukocytes and aggregated platelets may block vessels, preventing reperfusion [16]. Later, peripheral monocytes cross the BBB and penetrate the parenchyma, releasing inflammatory cytokines and inducing oxidative stress, exacerbating ischemic damage [17].

Following ischemia, microglial cells become activated within a few hours and migrate to the site of the lesion. This activation is induced by the leakage of plasma proteins and mediated by various downstream signaling effectors, including nuclear factor κB (NF-κB), hypoxia-inducible factor 1 (HIF-1), and signal transducer and activator of transcription 3 (STAT3) [18]. Numerous studies have revealed that microglia are the main inflammation contributors exhibiting neurotoxic activity [19]. However, microglial depletion induces poorer stroke outcomes. This could be due to the fact that microglia provide a protective effect by producing the neurotrophic factor IGF-1, eliminating dead cells and neutrophils, and suppressing the formation of reactive astrocytes [20]. Prevailing notion recognizes that microglia polarize and differentiate into M1 and M2 phenotypes. While the single cell transcriptional maps depict more complex phenotypic alterations. Furthermore, this data does not reveal any subpopulation that entirely corresponds to either the classical M1 or M2 subsets at the single-cell level [21,22]. Therefore, the complexity of microglial polarization may partially explain the failure of pan-microglial suppression in the treatment of IS.

Astrocytes, being the most abundant cell type in the brain, play a vital role in neuronal metabolism, providing structural support, forming the blood-brain barrier (BBB), and maintaining the extracellular environment [23]. During the acute phase of IS, astrocytes recognize injury signals through Toll-like receptors and transform their morphology and functions to take on a "reactive" phenotype, which involves the secretion of proinflammatory factors and chemokines via the NF-κB pathway to encourage the recruitment of neutrophils [24,25]. Under ischemic conditions, the number of cerebral vessels wrapped with astrocytic end-feet is dramatically reduced, enabling peripheral substances like pro-apoptotic and inflammatory factors to diffuse into the parenchyma. This can result in the secondary spread of brain injuries [26]. In addition, serum albumin may leak and aggregate in the extracellular space to contribute to tissue swelling [27]. Of note, in analogy to the "M1"/"M2" microglia/macrophage, reactive astrocytes are also divided into two subsets, termed "A1 (neurotoxic)" and "A2 (neuroprotective)", and A2 astrocytes are found in acute phase on cerebral ischemic insults [28]. Hoverer, this dichotomy requires further tested and potentially misleading for A1 marker genes was seldom found in various neurodegenerative disease and brain injury [29]. Astrocytes in a state of ischemia during a stroke exhibit more A1 properties, while those in a hemorrhagic brain do not exhibit characteristics of either A1 or A2-like cells [30]. Further evidence is warranted to achieve a better understanding.

After IS, peripheral immune cells infiltrate lesion sites and contribute to the subsequent inflammatory responses. Neutrophils and macrophage/monocytes migrate to the ischemic brain within the first hours. They can further release reactive oxygen species (ROS) and proteolytic enzymes that damage the BBB, causing severe endothelial impairment, integrity reduction, and hemorrhagic transformation [31,32]. Components of the adaptive system in IS have dual effects. T helper (Th) 2 and regulatory T cells (Treg) cells secrete

Table 1
Inflammatory biomarkers in IS.

Category	Biomarker	Source cells	IS stage	Clinical use	Reference
Cytokines	IL-1b	Neutrophil, monocyte/macrophage	Acute phase	1. Plasma level elevated in cardioembolic stroke but decreased in lacunar subtype 2. Worse outcomes in the presence of the -+3953 T and 511 T alleles	[66,67]
	IL-6	Macrophage, microglia	Acute phase	1. Plasma level elevated in cardioembolic stroke but decreased in lacunar subtype 2. CSF levels for prognosis in acute phase of IS 3. Higher plasma levels associated with worse MRI performance 4. High-sensitivity interleukin-6 as an early indicator of survival in IS 5. A marker of futile reperfusion in IS patients with large vessel occlusion after MT	[61, 66–70]
	TNF-a	Neutrophil, monocyte/macrophage	Acute phase	1. Plasma level elevated in cardioembolic stroke but decreased in lacunar subtype 2. Poor 1-year outcome with −850 T and −308 A alleles 3. Prediction of small arterial lesions caused by stroke	[67,71, 72]
	IL-10	T cell	Acute phase	1. Higher serum IL-10 associated with poor outcome 2. Predictor of early neurobehavioral outcome after acute IS. 3. Lower IL-10 plasma levels associated with early worsening after acute IS	[73–75]
	IL-33	fibroblasts, mast cells, dendritic cells, macrophages, osteoblasts, endothelial cells, and epithelial cells [76].	Acute phase	1.Independently predict hemorrhage transformation (HT) and outcome in acute IS	[76]
Other proteins	CRP	Liver synthesis	Acute phase, post stroke stage	1. Plasma levels for early detection or prediction of post-stroke infections 2. Prognostic biomarker	[77]
	VCAM-1	Endothelial cell	Acute phase	1. Higher serum VCAM-1 levels indicate worse outcome 2. Independent predictors of IS outcome 3. Intracranial VCAM1 is related to comorbidities, severity, functional outcomes in patients undergoing MT	[62,78, 79]
	Lp-PLA2	Endothelial cell	Predicted value	1. Prediction of stroke risk in postmenopausal women	[80]
	NT-pro BNP	the atrium	Acute phase	1. Prediction of 90-day all-cause mortality.	[81]
	MMP2/ MMP9	Gelatinase Proteolytic enzymes-expressing cells	Acute phase	1. Positively correlated with severity	[82]
Seletin	*P*-selectin	/	progressive ischemic stroke	1. Plasma level closely correlated with the onset time of IS.	[59]
	P-selectin	/	Acute phase	1.Early change by 1 unit increased the incidence of poststroke infections	[56]
	P-selectin	/	/	1. M62I polymorphism was associated with decreased risk of incidence IS in African Americans.	[58]
	E-selectin	/	/	1. AC genotype of *E*-selectin gene polymorphism (S128R) are more prone to stroke	[57]
	E-selectin	/	/	1. *E*-selectin SNP A561C is associated with increased risk for the development of ischemic stroke in this subset of the Han Chinese population.	[83]
	E-selectin	/	/	1. C allele, AA and AC genotypes of *E*-Selectin gene rs5361 variants were related to an increased risk of IS in overall populations.	[84]
	L-selectin	/		1. PP genotype of L-selectin gene polymorphism (P213S) are more prone to stroke in Chinese population	[85]

Abbreviations: CRP: *C*-reactive protein; CSF: cerebrospinal fluid; IL: interleukin; IS: ischemic stroke; Lp-PLA2: Lipoprotein-associated phospholipase A2; MMP: matrix metalloproteinases; MT: mechanical thrombectomy; NT-pro BNP: amino-terminal pro-B-type natriuretic peptide; VCAM-1: vascular cell adhesion molecule 1.

cytokines such as IL-4, IL-5, IL-10, and IL-13 to promote tissue repair, but also play a role in limiting immune responses [33,34]. Furthermore, Th1, Th17, $CD8^+$ T cells, and γδT cells may exacerbate ischemic injuries by releasing cytokines such as IL-2, IL-12, IL-17, and interferon (IFN)-γ [35,36]. The roles of B cells in IS remain unclear, but they do not seem to exert major effects in the acute phase [37].

In addition, a recent study has indicated the crucial involvement of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in the inflammatory damage following IS. The NLRP3 inflammasome is an intracellular multi-protein complex that can stimulate the production of various pro-inflammatory cytokines and chemokines. NLRP3 inhibition has been shown effective in mitigating infarction and neurological deficits by different team [38,39]. However, contradictory reports showed that neither genetic nor pharmalogical suppression of NLRP3 restricts injury extension in thrombotic stroke [40]. More recent data reveals a time-dependent dual role of NLRP3 in the acute phase of IS [41].

2.2. Subacute phase and post-stroke repair

Because cerebral inflammation lasts about 1 week after onset, identifying therapeutics that suppress post-ischemic inflammation and promote tissue repair in the subacute phase is primordial. Post-ischemic inflammation in the brain can last for months, and macrophages play a crucial role in this process. When activated by damage-associated molecular patterns (DAMPs), infiltrating macrophages produce inflammatory cytokines like TNF-α and IL-1β, leading to neuronal death. Additionally, macrophages release IL-23 and IL-12, which trigger T cell activation and contribute to subacute phase inflammation [42]. During this stage, microglia can act like monocytic macrophages and phagocyte dead cells or debris, which helps the resolution of the infarct and is considered beneficial.

The functions of microglia in post-stroke repair are greatly influenced by their phenotype. On one hand, microglia can secrete pro-inflammatory cytokines such as IL-1β, IL-6, IFN-γ, TNF-α, chemokines, and matrix metalloproteinases including MMP-9. They can interact with the endothelium via integrin Mac-1 and endocytic receptor LRP1, leading to the disruption of the BBB [43,44]. On the other hand, microglia release the brain-derived neurotrophic factor (BDNF), which promotes neurogenesis via the P2X purinoceptor 4 (P2X4R) [45,46]. Neutrophils also undergo phenotypic conversions, from a detrimental one in the acute phase, to a beneficial one that scavenges dead cells, debris and provides a favorable repair microenvironment [47].

Glial scar formation is another pathological feature in the subacute phase. In the acute phase, astrocytes are activated and exhibit elongated processes surrounding the ischemic lesions, forming a glial scar within a few days after the injury [48]. Reactive astrocytes play a role in protecting existing vessels and aiding in vascular repair and remodeling following an IS [49]. This scar separates the injury site from normal tissue, preventing harmful factors secreted from the damaged region from diffusing into remote areas [48]. However, this structure lacks tight junctions. Thus, serum substances, such as albumin and antibodies, remain in the parenchyma, possibly inducing neuronal injury [50].

3. Inflammatory biomarkers and signaling pathways in ischemic stroke

3.1. Inflammatory biomarkers in ischemic stroke

IS is sudden, debilitating, and lethal, thus requiring early diagnosis and intervention. However, prompt detection and diagnosis of stroke remain challenging when clinical symptoms are vague and magnetic resonance neuroimaging is not readily available. Silent brain infarctions, or silent stroke cases without corresponding clinical symptomatology represent 10%–20% of all cases [51]. Therefore, establishing biofluid biomarkers associated with IS can accelerate IS diagnosis and clinical decision-making.

Biomarker detection is an objective measure of the pathogenic processes or pharmaceutical effects. Usually, stroke biomarkers are molecules in body fluids such as serum, urine, or saliva that can provide diagnostic and prognostic values [52,53].

Biomarkers related to inflammation, including IL-1β, IL-6, IL-10, TNF-a, *C*-reactive protein (CRP), and VCAM-1, have proven to be valuable in diagnosing IS early and predicting clinical outcomes (as shown in Table 1). Additionally, the neutrophil-to-lymphocyte ratio (NLR) can forecast neurological outcome deterioration and recurrent IS [54]. Another kind of molecules that indirectly modulates inflammatory responses is the selectin family, which mediates the adhesion of leukocytes to endothelial cells and platelets, consisting of L-selectin (leukocyte selectin), *P*-selectin (platelet selectin), and *E*-selectin (endothelial selectin) [55]. Several lines of evidence have shown that these members can be used as prognostic factors of IS onset and outcomes [56–59]. Recent study also shows that inflammatory biomarkers can be used to predict clinical outcomes in patients experienced intravenous thrombolysis and mechanical thrombectomy. NLR tested at 24 h after ictus or intervention can predict 3-month functional outcome [60]. After MT, IL-6 is an indicator of unsuccessful reperfusion in stroke patients with occlusion of a large blood vessel [61]. A correlation has been found between intracranial VCAM1 and comorbidities, severity, and functional outcomes in patients undergoing MT [62]. Additionally, serum IL-33 has been identified as an independent predictive biomarker for hemorrhage transformation (HT) and outcome in acute IS [63].

Apart from peripheral inflammatory biomarkers, computed tomography imaging has been utilized to evaluate local neuroinflammation. For example, an increase in mitochondrial translocator protein 18 kDa (TSPO) expression has been observed in neurodegenerative and psychiatric disorders following various types of injuries [64]. This makes TSPO an ideal biomarker to monitor and quantify glial activation through positron emission tomography. However, although some TSPO ligands, such as 18 F-GE-180 and 11C-PBR28, are good and safe tracers [65], none have been applied to stroke progression monitoring.

3.2. Inflammatory signaling pathways in ischemic stroke

Signaling pathways are critical processes for immune cell activation and function in response to infections or diseases in AIS (Fig. 1). For example, the TLR4/NF-κB and JAK/STAT pathways participate in the cerebral ischemic response. TLR4/NF-κB is one of the major signaling pathways regulating inflammation and apoptosis after ischemic insults. This pathway is activated in immune cells, such as peripheral monocyte/macrophage, leukocyte T cells, as well as vascular endothelial cells in the brain, and microglia. Once activated, NF-κB *trans*-locates to the nuclei and induces the expression of a series of genes, such as iNOS, COX-2, ICAM-1, Nox-2, cytokines, and chemokines, which enhances the recruitment of peripheral immune cells to the lesion sites [86].

JAK/STAT is another critical intracellular signal transduction pathway mediated by cytokines, oxidative stress, etc. The JAK and STAT families include several members, and JAK2/STAT3 is the most extensively studied pair. In cerebral ischemia, it is activated early after infarction and promotes the expression of proinflammatory factors, exacerbating cerebral injury [87]. The roles of STAT signaling in inflammatory reactions are still in debate as STAT activation can also have protective effects during ischemic insults [87, 88]. Recent studies have shown that JunD, a transcription factor of the activated protein-1 (AP-1) family, can regulate inflammation by targeting IL-1β synthesis and macrophage activation, thus mitigating I/R injury [89].

Of note, intracellular signaling is activated by extracellular signals. Under ischemic conditions, cellular debris from dead cells, called DAMPs, are a major extracellular signal source. They are taken up by immune cells, triggering sterile inflammation. Known DAMPs involved in cerebral inflammation are proteins, such as high mobility group box 1 (HMGB1) and heat shock proteins (HSPs), and non-protein alarmins, such as adenosine triphosphate (ATP) [90]. HMGB1 is a nuclear protein released from necrotic cells and recognized by the receptor for advanced glycation end products (RAGE) or toll-like receptors (TLRs), which further trigger local peripheral inflammatory responses via NF-κB signaling in the acute phase [91]. However, HMGB1 also promotes angiogenesis and neurogenesis in the late phase of stroke, indicating its protective role in stroke recovery [90]. Moreover, HMGB1 release in the circulation induces bone marrow cells egress and bone marrow-derived suppressor cells splenic proliferation, inhibiting the adaptive immune responses [92].

HSPs are molecular chaperones that ensure the correct folding of proteins in response to stress or high temperatures. Among them, Hsp70 has been most extensively studied and elicits dual effects in IS depending on its cellular location. Intracellular Hsp70 inhibits NF-κB signaling, and extracellular Hsp70 potentiates NF-κB signaling activation by binding to TLRs [93]. Extracellular nucleotides

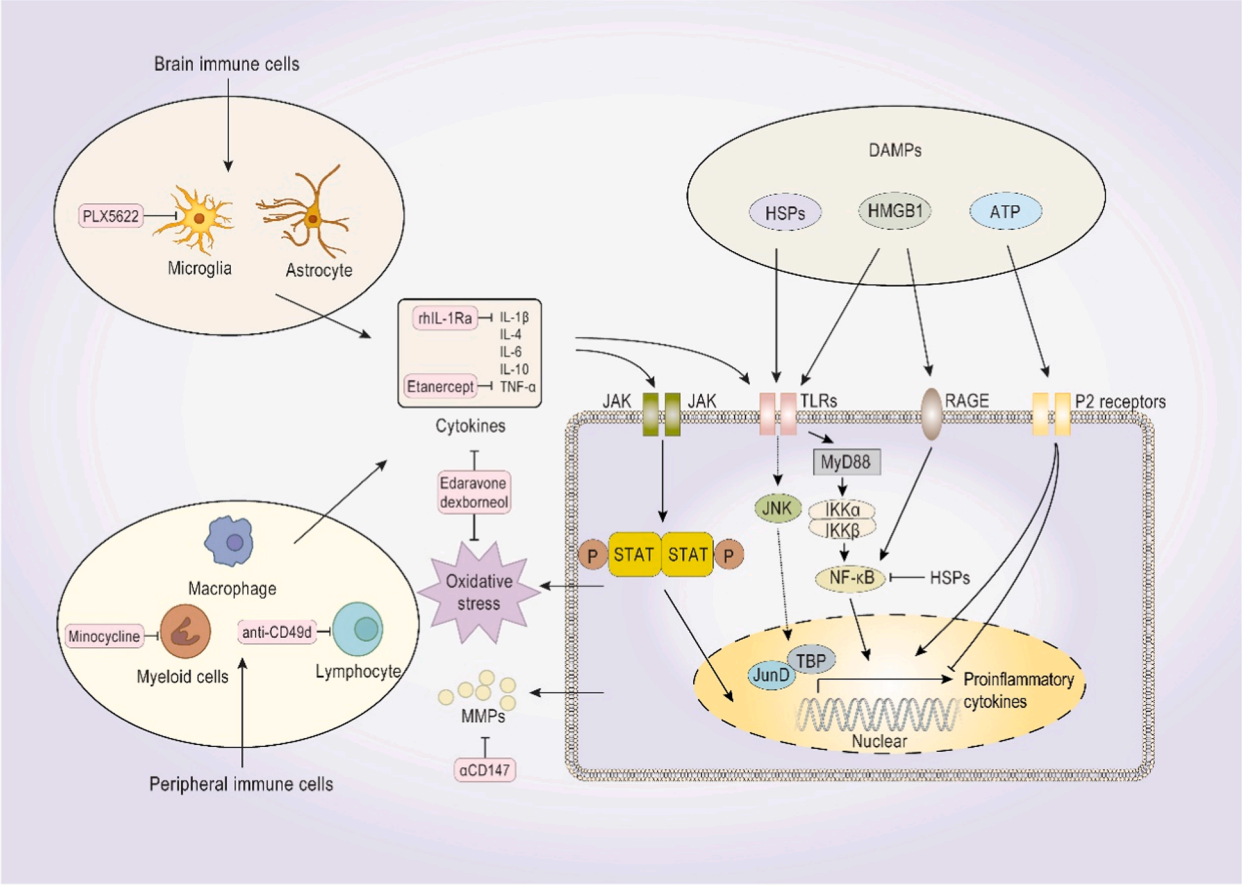

Fig. 1. Inflammatory signaling in IS.

such as ATP, either released from injured cells or actively secreted by glial cells, can be recognized by P2 receptors, highly expressed on myeloid cells. The P2 receptors family comprises both ligand-gated P2X cation channels and G protein-coupled P2Y receptors. Multiple P2 receptors participate in cerebral ischemic responses. For instance, P2Y6R-mediated microglial phagocytosis facilitates debris clearance and functional recovery after IS [94]. In addition, P2X4R activation yields detrimental acute and chronic effects after stroke [95]. The different cellular distribution of these receptors may explain this contradiction.

While many drugs aim to affect these signaling pathways and provide neuroprotection, the majority of them are still in preclinical stages. The only anti-inflammatory drug to successfully complete a phase III clinical trial and be approved by the National Medical Products Administration (NMPA) to treat IS is Edaravone dexborneol. This drug comprises two active compounds, edaravone, and dexborneol, both of which inhibit NF-κB signaling, ultimately shielding neurons from inflammation-related harm [96,97]. Furthermore, edaravone and dexborneol can stimulate the Nrf2/HO-1 signaling pathway, which helps eliminate excess oxidative stress and protects against hypoxic injury [98,99]. Edaravone dexborneol, with an optimal proportion of 4:1, exerts synergistic effects against oxidative, inflammatory, and apoptotic insults and has demonstrated its superior clinical efficacy to edaravone alone.

Brain is vulnerable to ischemic insults, and suffers prominent necrosis soon after oxygen and glucose insufficiency. Then DAMPs, such as HSPs, HMGB1 and ATP are passively released from lesions, recognized by microglia and astrocytes and trigger inflammation via different pathways, which results in proinflammatory cytokines generation. This recruits peripheral immune cell to the site of injury and may further exacerbate damage. Various therapeutics have been designed against different targets in inflammatory responses.

Abbreviations: DAMP, Damage-associated molecular pattern; HMGB1, High mobility group box protein 1; HSPs, Heat shock proteins; JAK, Janus kinase; JNK, *c*-Jun N-terminal kinase; RAGE, Receptor for advanced glycation end products; STAT, the Janus kinase (JAK)-signal transducer and activator of transcription; TRAF6, TNF Receptor Associated Factor 6.

4. Immunomodulatory therapeutic strategies to treat ischemic stroke

4.1. Targeting inflammatory responses

4.1.1. Cytokine modulation

Experimental and clinical studies have focused on developing strategies to reduce cell death and inflammation. A key area of investigation has been cytokines and the potential to neutralize or eliminate them. Cytokine therapies involve the use of engineered antibodies, soluble cytokine receptors, and recombinant proteins that bind to and inhibit specific cytokines [100].

Clinical therapeutics targeting proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-10, have been administrated to treat non-neurological diseases, such as rheumatoid arthritis and inflammatory bowel disease [101]. Because cytokines exhibit both beneficial and detrimental effects on IS, down-regulating them can have undesired effects. Four cytokines are potential therapeutic targets of IS treatments: the detrimental cytokines TNF-α and IL-1, and the beneficial cytokines IL-6 and IL-10, which boost angiogenesis and functional recovery. IL-1 and TNF-α are two major proinflammatory cytokines regulating important inflammatory processes involving cellular adhesion molecules and chemokines in IS. Several studies have demonstrated that IL-1 and TNF-α can worsen ischemic damage during the acute phase and impede post-stroke recovery during the subacute phase [102,103]. Furthermore, the use of the IL-1 recombinant human IL-1 receptor antagonist (rhIL-1Ra) and the TNF-α receptor antagonist Etanercept has shown to significantly decrease infarct size and improve neurological outcomes in clinical settings [104]. Other cytokine therapies for IS, such as IL-6 and IL-10 supplements, yielded similar effects. It is commonly accepted that IL-6 and IL-10 are negative immune regulators in ischemic brains, and higher plasma IL-6 or IL-10 levels are correlated with better outcomes after stroke [105,106]. In addition, *in vitro* experiments have shown that IL-6 and IL-10 can improve behavioral performance, limit ischemic-related pathological alterations, and promote neuronal proliferation and differentiation. However, there are no reports on their clinical use.

4.1.2. Matrix metalloproteinase blockage

MMPs are a large family of zinc-dependent endopeptidases participating in extracellular protein degradation. In the acute phase of IS, MMPs degrade the basal lamina and weaken the BBB [107]. In rats, cerebral ischemia dramatically elevates pro/active MMP-9 levels [108]. Several MMPs activators have been identified. For example, CD147, a cell surface glycoprotein, modulates the synthesis and activity of MMPs [109]. MMP-9, an inducible MMP expressed in neutrophils, is a 92-kDa type IV-collagenase acting in the extracellular space [110]. Hence, modulating CD147 levels can prevent MMP-induced BBB leakage.

4.2. Targeting immune cells

4.2.1. Reactive microglia inhibition

Resident microglia are the primary immune cells in the brain; they are the first to react to the pathophysiological alterations caused by IS [111]. There is increasing evidence that activated microglia are detrimental in IS, and therapies inhibiting their activation have been extensively investigated [98]. However, their roles in IS remain controversial. Several studies suggest that microglial activation induces angiogenesis, neurogenesis, and myelin remodeling, thereby fostering neurological recovery after IS [112]. For example, pharmacological and genetic manipulations of microglial depletion exacerbated ischemic lesions [113,114]. Microglia undergo multiple phenotype changes under pathological conditions [115], and microglial phenotype transformation during different stages of a specific disease contributes to its complexity [116]. However, this complexity allows us to consider new treatment strategies aimed at converting microglia to a protective phenotype.

Table 2
Neuro-Immunomodulatory therapies in animal experiments.

Drug	Subject	Administration	Effects	Ref
IL-1				
IL-1R antagonist	Rat tMCAO	subcutaneous (s.c.) either acutely (at reperfusion) or in a delayed manner (24 h after reperfusion)	Alleviates neurological deficits, antidepression	[133]
IL-1R antagonist	Rat tMCAO	s.c. 3 and 6 h post reperfusion	Neurogenesis	[134]
IL-1RA-PEP	Rat tMCAO	intravenous (i.v.) at reperfusion (2 h)	p65/NF-κB and p38/MAPK	[72]
TNFα				
exDCs transduced to overexpress soluble TNFR1	rat, proximal tMCAO (60 min, filament)	administration (i.v.) of TNFR1 overexpressing exDCs 6 h post reperfusion	The administration of TNFR1-expressing dendritic cells resulted in a reduction in both the size of the infarct and the level of inflammation.	[135]
TNF monoclonal antibody	mice, proximal tMCAO (60 min, filament)	After occlusion, 1 mg/kg Etanercept or cTfRMab-TNFR was injected i.v. At either 45 or 90 min.	The application of cTfRMAb-TNFR led to a decrease in both the volume of the infarct and neural impairments.	[136]
IL-6				
IL-6	mice, distal pMCAO (electrocoagulation)	Participants were administered with an intravenous injection of either 500 ng IL-6, sIL-6R, or 500 ng IL-6, followed by 500 ng IL-6R, either at 5 min after occlusion or at both 5 and 60 min after occlusion.	The behavioral outcome was improved by IL-6, but there was no effect on infarct size. However, when IL-6 was combined with solIL-6R, there was an increase in both infarct volume and PMN count.	[137]
IL-6	mice, proximal tMCAO (60 min, filament)	The injection of 10 ng *anti*-IL6 mAb via intracerebroventricular (i.c.v.) or the administration of 0.1 μg rIL-6 via intranasal route every 24 h for a period of 2 weeks, starting 14 days after occlusion.	The injection of *Anti*-IL-6 mAb through the intracerebroventricular route resulted in reduced proliferation and neuronal differentiation of neural progenitor cells in the ipsilateral SVZ and also impacted functional recovery. However, the intranasal administration of rIL-6 showed the opposite effect.	[138]
IL-6	rat, tMCAO (120 min, filament)	The administration of rIL-6 was done through intraperitoneal injection at a dose of either 50 or 500 ng.	The injection of rIL-6 resulted in a reduction of infarct volume.	[139]
IL-10				
IL-10	mice, distal pMCAO (electrocoagulation)	After occlusion, an injection of 100 ng of rmIL-10 was given via i.c.v.	The injection of 100 ng of rmIL-10 directly into the cerebral ventricles 5 min after occlusion resulted in a reduction of infarct volume.	[140]
IL-10	mice, proximal tMCAO (60 min, filament)	The administration of IL-10-producing B cells via intravenous injection was performed either 24 h before or 4 h after occlusion.	The administration of IL-10-producing B cells via intravenous injection led to decreased infarct volumes and reduced post-stroke inflammation.	[141]
IL-10	rat, distal tMCAO (90 min, filament)	Intravenous injection of mesenchymal stem cells overproducing IL-10 was performed at 0 or 3 h after reperfusion.	The administration of intravenous mesenchymal stem cells that overproduce IL-10 resulted in a decrease in infarct volumes, improvement in motor functions, and reduction in inflammation.	[142]
Microglia				
PLX5622	aged mice, tMCAO	chow diet for 21 days	increased infarct volume and decreased neurons, enhanced neuroinflammation after IS	[143]
PLX3397	mice, MCAO	The AIN-76 A standard diet was administered at a dose of 40 mg/kg/day for 21 consecutive days.	The absence of microglia led to an increase in the severity of stroke.	[109]
Myeloid cells inhibition				
Minocycline	rat, photothrombosis-induced focal stroke	Administered intraperitoneally at a dosage of 50 mg/kg, the drug was given 1 h after stroke induction, followed by subsequent doses of 50 mg/kg at 12, 24, 36, and 48 h.	The decrease in the count of CD68-positive cells and astrogliosis resulted in functional improvement.	[144]
MMP				
CD147 Antagonistic peptide	mice, tMCAO	An intravenous injection of 2.5 mg/kg APN in a total volume of 100 μL was initiated at 1 h after the induction of tMCAO.	The administration of APN via intravenous injection at a dose of 2.5 mg/kg led to an improvement in acute stroke outcome on the third day.	[145]
αCD147	mice, tMCAO	once daily i.v. Injection for 3 days beginning 4 h after ischemia onset.	CD147 inhibition promotes long-term functional repair after stroke	[146]
αCD147	mice, tMCAO	Tail vein injection of 100 μL PBS was used to administer the antibody treatment, which was initiated 4 h after ischemia onset and repeated at 24 and 48 h.	CD147 inhibition ameliorates acute IS by reducing thrombo-inflammation	[147]

(*continued on next page*)

Table 2 (*continued*)

Drug	Subject	Administration	Effects	Ref
T lymphocytes invasion				
anti-CD49d (VLA4)	mice, tMCAO	An administration of anti-CD49d antibody (300 μg) was carried out either 24 h before or 3 h after the onset of cerebral ischemia.	failed to positively influence the stroke outcome	[148]
anti-CD49d (Natalizumab)	mice, thromboembolic stroke	A single intravenous dose of 250 μg was administered either 1 h or 48 h after occlusion.	The intervention did not have any impact on the lesion volume or long-term neurological deficit.	[149]
Fingolimod				
	tMCAO, mice	1 mg/kg on reperfusion	anti-inflammation, but did not improve endpoint outcomes at 24 h after tMCAO	[150]
	tMCAO, mice	FTY720 (1 mg/kg, i.p.) 30 min after reperfusion,	The administration of Fingolimod resulted in improvement of neurological performance, a reduction of infarct size and edema.	[85]
	tMCAO, rat	The treatment protocol involved the administration of FTY720 (0.5 mg/kg, sigma) 24 h after reperfusion, with subsequent doses given every other day.	The enhancement of memory performance after MCAO was observed with FTY720, which induced LTP via post-synaptic mechanisms.	[151]
	Photothrombotisis-induced cortical IS in mice.	Administered intraperitoneally at a dose of 0.3 mg/kg for 1, 7, or 14 consecutive days.	FTY720 exerted neuroprotection and promoted angiogenesis by inducing microglial M2 polarization.	[152]
	Chronic WM ischemic injury induced by bilateral carotid artery stenosis in mice	FTY720 (0.3 mg/kg in PBS; Cayman Chemical Company) i.p. Administration for 3, 10, or 30 consecutive days	FTY720 reduced cognitive decline and prevented WM integrity disruption.	[153]

Abbreviations: cTfRMAb: chimeric monoclonal antibody against the mouse transferrin receptor; exDCs: ex vivo-derived dendritic cells; IL: interleukin; IL-1RA-PEP: Interleukin-1 receptor antagonist peptide; IS: ischemic stroke; mAb: monoclonal antibody; MMP: matrix metalloproteinases; NT-pro BNP: amino-terminal pro-B-type natriuretic peptide; PMN: polymorphonuclear neutrophils; SVZ: subventricular zone; t/pMCAO: transient/permanent middle cerebral artery occlusion; TNFR1: tumor necrosis factor receptor 1; VLA4: very late antigen-4.

4.2.2. Myeloid cell inhibition

Myeloid cells originate from hematopoietic stem cells in the bone marrow. They include macrophages, dendritic cells, and neutrophils, which are recruited to the ischemic sites after IS. Leukocytosis is an inflammatory response marker after IS [117]. Following a stroke, neutrophils are the initial peripheral immune cells to migrate towards the lesion, followed by monocytes. Subsequently, both neutrophils and monocytes undergo morphological alterations [118]. Then, chemokine concentration gradients attract neutrophils and monocytes to the lesions, where they cause secondary injuries by secreting noxious molecules [119]. Minocycline is a tetracycline antibiotic able to cross the BBB, which can inhibit microglial activation and peripheral neutrophil invasion in IS. In addition, the anti-inflammatory effects of Minocycline are associated with TLR-mediated pathways [120].

4.2.3. T lymphocyte invasion

T lymphocytes participate in the later stages of IS. T cells infiltrate the lesions between days 3 and 7 [32]. T lymphocytes need to cross the BBB to cause ischemic injury in the brain. However, the effects of different T cell subpopulations in IS vary. Th1 cells secrete proinflammatory cytokines, such as IFN-γ and chemokines, and ROS, which can harm the BBB. Conversely, Th2 cells release anti-inflammatory cytokines, including IL-4 and IL-10, which stimulate the production of nerve growth factor, facilitate debris removal, tissue repair, and angiogenesis [35,121]. While γδT cells and natural killer T cells have been shown to be harmful in IS [122,123], Treg cells have been found to limit inflammatory responses and therefore reduce brain injury [34]. Immune cell migration across the vasculature into the parenchyma involves various adhesion receptors located on both endothelial and immune cells [124]. T lymphocyte invasion into the brain largely depends on the interaction between two critical molecules, the leukocyte very late antigen-4 (VLA-4) and the vascular cell adhesion molecule-1 (VCAM-1), expressed on endothelial cells. Therefore, blocking VLA-4 or VACA, for example, using monoclonal antibodies could theoretically prevent IS progression. However, recent randomized, placebo-controlled, double-blind clinical trials proved that Natalizumab, a monoclonal antibody of VLA-4 failed to limit infarct volume or improve clinical outcomes [125,126]. This may be due to the late involvement of T cells when myeloid cells dominate the lesion area or to the participation of T cells in a compensatory mechanism against ischemic injuries.

Fingolimod acts as a sphingosine-1-phosphate receptor (S1PR) modulator that prevents lymphocytes from leaving lymph nodes and reduces mitochondrial dysfunction, which is a major source of ROS [127]. A randomized, multicenter, pilot trial showed that the combined administration of Fingolimod and alteplase lowered circulating lymphocytes levels, reduced lesion volumes, and improved neurological performance [128].

4.3. Targeting the redox balance and inflammatory responses

Inflammation and oxidative stress are two major pathological features of reperfusion injuries and are closely associated with each other [107]. In addition, inflammation can trigger aberrant intracellular oxidation states. Continuous neuroinflammation and redox state imbalance compromise the BBB, exacerbating parenchyma impairment and worsening functional outcomes [129]. Borneol (Bing-Pian or Long-Nao) (a Traditional Chinese Medicine herb) was believed to possess “orifice-opening” activity, and studies revealed

Table 3
Clinical trials of Neuro-Immunomodulatory therapies.

Drug	Subject	Treatment	Effects	Reference
IL-1				
recombinant human IL-1 receptor antagonist (rhIL-1Ra)	Patients with acute stroke (<6 h)	An intravenous injection of a 100 mg bolus of rhIL-1Ra was followed by a continuous infusion of 2 mg/kg per hour for 72 h.	rhIL-1Ra can partially rescue the inhibition of peripheral innate immune system in the acute phase of stroke.	[154]
rhIL-1Ra (anakinra)	Patients with acute stroke (<5 h)	A subcutaneous injection of 100 mg of rhIL-1Ra (anakinra) was administered twice daily for a duration of 3 days.	RhIL-1Ra treatment decreased plasma inflammatory markers, but it did not have an effect on the modified Rankin Scale (mRS) score at three months.	[155]
TNF				
Etanercept	Chronic stroke patients (3–120 months)	Etanercept was administered via perispinal, interspinous, and extrathecal injection at a dose of 25 mg.	The intervention resulted in improvements in motor impairment, spasticity, sensory impairment, cognition, psychological/behavioral function, aphasia, and pain.	[156]
Etanercept	Chronic stroke patients (13–36 months)	25 mg of Etanercept was injected via perispinal, interspinous, and extrathecal ways.	Neurological improvement in all patients	[157]
Etanercept	Patients with stroke occurred between 1 and 5 years	Perispinal administration	Ongoing trial	ACTRN12620001011976
Microglia				
Minocycline	patients	i.v. 100 mg minocycline injection at 24 h after a stroke	Safe but not efficacious	[158]
leukocyte infiltration				
Natalizumab	AIS patients, double-blind, phase 2 study	300 mg i.v. Injection	Natalizumab administered up to 9 h after stroke onset did not halt infarct growth	[125]
anti-ICAM-1 (Enlimomab)	IS patients (within 6 h)	Enlimomab on the first day followed by a maintenance bolus of 40 mg of Enlimomab over 5 min or placebo for 4 days	Enlimomab is not an effective IS treatment	[159]
Fingolimod				
	Randomized, open-label, evaluator-blind, multicenter pilot trial	Fingolimod and alteplase combination orally once daily for 3 consecutive days	The administration of the combined therapy was well-tolerated and resulted in a reduction of reperfusion injury, ultimately leading to an improvement in clinical outcomes among patients diagnosed with acute IS.	[128]
	Open-label, evaluator-blind, parallel-group clinical pilot trial	Within 72 h of disease onset, Fingolimod was administered orally.	The intervention was safe and resulted in a limited amount of secondary cerebral injury from baseline to day seven. Additionally, it led to decreased leakage from microvessels, attenuated neurological deficits, and facilitated neuronal repair.	[160]
Edaravone dexborneol				
	Phase III RCT, AIS patients	14-day infusion of edaravone dexborneo injection, first injection within 48 h	Higher rate of mRS $\leq$1 on day 90, and greater reduction in NIHSS	[131]
	phase II study	30 min i.v. Infusion every 12 h, for 14 consecutive days	Safe and well tolerated at all doses, although no significant neurological improvement at day 90	[132]
	Phase IV study	Not reported	Ongoing trial	ChiCTR2100053196 ChiCTR2100045950 ChiCTR2100048153
	Phase IV study	30 mg/7.5 mg twice daily i.v. Injection for 12 $\pm$ 2 days	Ongoing trial	ChiCTR2100048812
Dimethyl Fumarate	Phase II study	Dimethyl fumarate 240 mg orally, twice daily for 3 consecutive days	Ongoing trial	NCT04891497 NCT04890366 NCT04890353
Methylprednisolone + prednisolone	Phase III study	Methylprednisolone 20 mg/kg i.v. Infusion daily for 5 consecutive days followed by a 4-week course of tapering Prednisolone orally once daily	Ongoing trial	NCT03249844

Abbreviations: AIS: acute ischemic stroke (IS); ICAM-1: intercellular adhesion molecule-1; mRS: the Modified Rankin Scale; NIHSS: the National Institutes of Health Stroke Scale; rhIL-1Ra: recombinant human IL-1 receptor antagonist; RCT: randomized clinical trial.

that borneol might enhance drug delivery via BBB [130]. Simultaneous blockage of ROS and inflammation by edaravone dexborneol (combination of edaravone and dexborneol) exerts synergistic effects and protects the brain from ischemic injury more effectively than edaravone alone [131,132]. (Table 2 and Table 3). In addition, edaravone dexborneol could delay neuroinflammation-induced or associated immune cascades and inflammatory modulation to further exert neuroprotective effects.

Besides its anti-oxidative stress effect, this combination delayed neuroinflammation-induced immune cascades and inflammatory modulation to exert neuroprotective effects, indicating that the combination was more potent than the single compounds.

5. Conclusions

The application of immunomodulatory therapy in ischemic cerebrovascular diseases attracts increasing attention. The number of studies on the involvement of the inflammatory immune response in IS pathogenesis has gradually increased. Some immunomodulators or immunomodulatory measures have been used in animal experiments and shown effects in clinical trials. For example, Fingolimod, an S1PR modulator, showed promising results against IS in several small-scale clinical trials. However, It's worth noting that the trials with small sample sizes were not conducted with a double-blind approach. Therefore, confirming the role of Fingolimod in IS still requires extensive work. Another promising drug, Etanercept, a monoclonal antibody preventing TNF-α from binding to its receptors, has been extensively studied in animal stroke models. It is currently undergoing a phase II randomized controlled trial assessing its efficacy and safety for post-stroke recovery. Edaravone dexborneol is the only approved inflammatory cytokine-inhibiting drug against AIS, but further studies are still needed to precise its anti-inflammatory mechanism.

Although immunomodulatory therapies achieved positive results in most experimental ischemic cerebrovascular disease studies, most of them failed clinical trials. These may be attributed to the following reasons.

1. In the case of brain ischemia, multiple damage pathways progress concurrently in the ischemic cascade and may have interactions with each other. Consequently, the crucial question is whether disrupting a single injury mechanism can lead to clinical benefits. Utilizing combination therapies that target multiple pathways of ischemic injury may offer advantages compared to strategies that focus on a single pathway [161].
2. The large differences between cerebral ischemia animal models and the human body and dose variations in immunomodulatory preparations resulted in imprecision regarding the time window, bioavailability, effectiveness, and safety, limiting the application of immunotherapy in clinical ischemic cerebrovascular disease [162].
3. Current drugs focus on peripheral immune effectors, such as PMC or cytokines. However, ischemic insults also induce profound inflammatory responses in the brain parenchyma, and crossing the BBB remains the biggest current challenge in drug delivery to the brain [163].
4. Most neuroprotective drugs have to act in a narrow time window—less than 12 h [131]. However, ischemic damage may not be final at that stage because the subsequent inflammatory response may last months or even years. Hence, neuro-immunomodulatory therapies used beyond the first few hours of IS are of great value.

Overall, future studies should focus on the specific mechanisms of inflammatory immune responses in the central nervous system, explore appropriate cerebral ischemia models, assess reasonable dosing time windows, establish standardized intervention measures and measurement methods, and develop specific central nervous system. Furthermore, new approaches enhancing BBB penetration and inducing endogenous expression will improve IS treatment efficacy. In the near future, immunotherapy could become an essential new adjuvant treatment strategy against IS.

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Significance statement

Ischemic stroke remains one of the most devastating and challenging diseases worldwide, imposing an enormous burden on patients and the society. Inflammatory responses have been considered to be included in all stroke pathogenesis stages. Various

inflammatory modulators have been designed to target pathological factors during this process to suppress stroke progression. However, these efforts and progresses haven't been systemically summarized and discussed. Therefore, the current advances in the application of inflammatory biomarkers, neuroinflammation and neuro-immunotherapeutic scenarios for ischemic stroke will be summarized in this review, aiming to provide a theoretical basis and new prospects/frontiers for clinical choice and practice.

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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