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Review

The Roles of Circular RNAs in Ischemic Stroke through Modulating Neuroinflammation

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Abstract

Ischemic stroke (IS) remains a serious threat to human health. Neuroinflammatory response is an important pathophysiological process after IS. Circular RNAs (circRNAs), a member of the non-coding RNA family, are highly expressed in the central nervous system and widely involved in regulating physiological and pathophysiological processes. This study reviews the current evidence on neuroinflammatory responses, the role of circRNAs in IS and their potential mechanisms in regulating inflammatory cells, and inflammatory factors affecting IS damage. This review lays a foundation for future clinical application of circRNAs as novel biomarkers and therapeutic targets.

Keywords: ischemic stroke; neuroinflammation; circRNA; inflammatory cytokine; therapeutic target

1. Introduction

According to the Global Burden of Disease Study 2019, stroke is the second leading cause of level 3 death worldwide in 2019, after ischemic heart disease, and the third leading cause of level 3 death and disability, posing a serious threat to human health and social development [1]. Ischemic stroke (IS) is a clinical syndrome characterized by cerebral tissue ischemia, hypoxia, and necrosis resulting from arterial narrowing or occlusion in the brain's blood supply (carotid and vertebral arteries) [1,2]. In 2019, IS accounted for 62.4% of all new strokes worldwide, making it the predominant type of stroke [1].

Following IS, brain inflammation is the major pathological event causing secondary cerebral tissue injury and poor functional recovery [3–7]. Post-stroke inflammation is initiated after the initial ischemia, marked by innate immune responses and the breakdown of the blood-brain barrier (BBB), releasing proinflammatory cytokines and infiltrating immune cells. Additionally, many studies on neuroinflammation have revealed that glial cells regulate the release of inflammatory cytokines and the progression of the inflammatory cascade [8,9].

Circular RNAs (circRNAs), belonging to the non-coding RNA family, have a stable structure and high tissue-specific expression. CircRNAs are highly expressed and widely involved in regulating physiological and pathophysiological processes in the nervous system [10,11].

CircRNAs are involved in neuronal injury and repair, glial cell protection, and BBB injury after IS [12–18]. However, the potential roles of different circRNAs in inflammatory responses remain unclear. Therefore, this review aims to provide new insights into the role of circRNAs in modulating neuroinflammatory responses in IS to enhance our understanding of its severity and prognosis.

2. Pathological Mechanism of Neuroinflammation after IS

2.1 Inflammatory Role of Immune Cells

Currently, excitotoxicity, calcium dysregulation, oxidative and nitrosative stress, cortical spreading depolarizations, and inflammation are used to explain the pathophysiology of IS [19,20]. Ischemic neuroinflammation is a pathological process of IS that significantly affects clinical prognosis [21]. Notably, cytokines, secreted by different brain immune cells, are key players in the inflammatory response, exhibiting both proinflammatory and anti-inflammatory effects [22,23]. Fig. 1 shows the inflammatory response of immune cells.

After ischemic brain injury, ischemia-anoxic necrosis cells release a series of danger signals commonly called

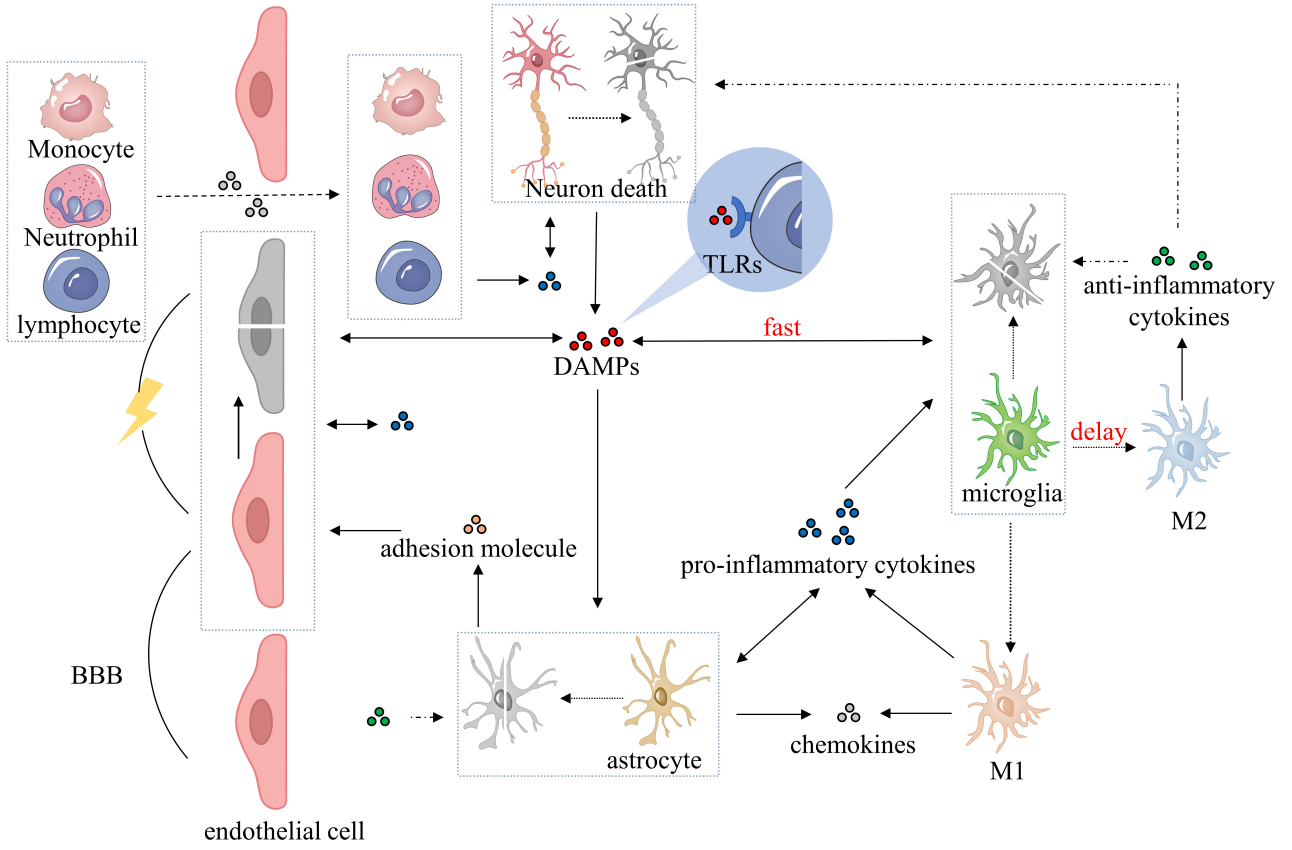

Fig. 1. Pathophysiological process of neuroinflammatory response after ischemic stroke. After ischemic brain injury, DAMPs are released during cell ischemia, hypoxia, and necrosis, promoting the activation of microglia, astrocytes, brain endothelial cells, and perivascular immune cells. Microglia polarize into classical (M1) or alternative (M2) microglia and secrete proinflammatory cytokines, anti-inflammatory cytokines, adhesion molecules, and chemokines. Activated astrocytes initially secrete proinflammatory cytokines, followed by anti-inflammatory cytokines, chemokines, and adhesion molecules. Proinflammatory cytokines contribute to the BBB breakdown and exacerbate the inflammatory response, while anti-inflammatory cytokines counteract this process and play a neuroprotective role. Adhesion molecules and chemokines facilitate the infiltration of peripheral immune cells into the BBB and promote the inflammatory response. DAMPs, damage-associated molecular patterns; BBB, blood-brain barrier; TLRs, Toll-like receptors; M1, classical microglia; M2, alternative microglia.

damage-associated molecular patterns (DAMPs), such as the high-mobility group box 1 protein (HMGB1) [24–26]. These DAMPs are released into the extracellular environment to activate the innate immune system and further stimulate the inflammatory cascade reaction [27]. Toll-like receptors (TLRs), located on microglia, astrocytes, perivascular macrophages, and brain endothelial cells, detect DAMPs and activate corresponding cells in response [28–31].

Microglia, the brain's most predominant resident macrophages, account for approximately 10% of all brain tissue cells that become highly activated early after stroke [32–34]. After activation, microglia polarize into two types, classical (M1) and alternative (M2) microglia, which play different roles, secreting cytokines that promote or relieve inflammation and affecting tissue repair [35,36]. This process increases microglial phagocytosis activity [37]. Currently, microglial cells secrete a variety of inflammatory cytokines and chemokines, including interleukin(IL)-1β, IL-4, IL-6, IL-8, IL-10, IL-12, IL-15, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, macrophage inflammatory protein (MIP)-1, monocyte chemoattractant protein-1 (MCP-1), chemokines interferon-γ-inducible protein 10 (CXCL10, also called IP-10), and proteolytic enzymes including matrix metalloproteinase (MMP)-3 and MMP-9 [38–40].

In the central nervous system, astrocytes are the main type of glial cells, accounting for approximately 50% of brain cells. In addition to playing a supporting role, astrocytes are important regulatory factors of brain function [41–43]. When activated by proinflammatory factors secreted by activated microglia, astrocytes lose their neuroprotective and homeostatic ability and induce neuron and oligodendrocyte death [44]. After brain tissue ischemia, astro-

cytes reduce brain nerve damage by producing antioxidants and glutamine and regulating extracellular potassium concentration [45]. Activated astrocytes secrete large amounts of inflammatory cytokines and chemokines, such as IL-1, TNF-α, interferon-γ (IFN-γ), and MCP-1, which contribute to BBB destruction [46,47]. While astrocyte death leads to decreased expression of tight junction proteins, leading to BBB breakdown and brain tissue edema [48]. Inflammatory factors such as IL-1, TNF-α, and MCP-1 increase in the early stages of cerebral ischemic injury, while IL-6 and macrophage migration inhibitory factors (MIF) increase at later stages [49]. Moreover, proinflammatory factors enhance the expression of adhesion molecules, including E-selectin, P-selectin, intercellular cell adhesion molecule (ICAM)-1, ICAM-2, and vascular endothelial cell adhesion molecule (VCAM)-1 [50–53].

Neutrophils are one of the peripheral immune cells. Neutrophils also release cytokines that promote glial scarring, phagocytic debris, and edema resolution [54]. Following BBB damage, neutrophils penetrate the brain through the action of cell adhesion molecules, including selectin, integrin, and immunoglobulin [55]. Neutrophils have a strong ability to destroy brain tissue, as they generate reactive oxygen species (ROS) and proteolytic enzymes, inducing direct neurotoxic effects. Additionally, their accumulation indirectly leads to cerebral ischemia and hypoxia by blocking capillary blood flow [56,57].

Another peripheral cells, (such as mononuclear phagocytes, natural killer cells (NK cells), and lymphocytes) also release cytokines and participate in ischemic inflammation [23,58]. Monocytes are innate immune cells that serve as important effectors and regulatory factors in inflammation [59], crossing the BBB, accumulating in damaged brain tissue, and exhibiting microglia-like phenotypic changes [60,61]. NK cells are important innate immune cells in peripheral blood that mobilize quickly in the initial stage of inflammatory responses, thereby promoting neuroinflammatory and inducing neuronal death [62].

A growing body of literature has begun to elucidate that lymphocytes can assume in IS pathology. Lymphocytes cross the BBB and enter ischemic brain parenchyma under the influence of P-selectin, VCAM-1, and ICAM-1 signaling [63]. The degree of lymphocyte infiltration depends on changes in BBB permeability [64]. Immune system activation mediated by lymphocyte infiltration can have both harmful antigen-specific autoreactive responses and cellular protection in IS [65]. During this process, helper T cells are divided into Th1 cells secreting proinflammatory cytokines (such as IFN-γ, TNF-α, and lymphotoxin alpha (LT-α)), Th2 cells secreting anti-inflammatory cytokines (such as IL-4 and IL-10), and TH17 cells secreting IL-17, IL-21, and IL-22 cytokines [66]. $\gamma\delta$ T cells, associated with post-stroke neurotoxicity, are induced by macrophage-secreted IL-23 and DAMPs-activated surface TLRs [67]. Activated $\gamma\delta$ T cells migrate to the ischemic tissue and produce IFN-γ and IL-17 [68]. IFN-γ, mainly secreted by T cells, mediates delayed neurotoxic effects in IS [69,70]. Regulatory T cells (Treg cells) exhibit stronger anti-apoptotic properties compared to other cells [71] and secrete cytokines such as IL-10, which have protective effects after cerebral ischemia. Treg cells reduce the early invasion and activation of neutrophils and T cells. When Treg cells are depleted, the expressions of TNF-α, IL-1β, IFN-γ, and other proinflammatory cytokines increase in the brain [72]. Regulatory B cells also have beneficial effects on the ischemic brain by secreting IL-10 [73]. Studies have shown that lack of B cells increases migration cross the BBB and decreases IL-10 production. Conversely, infiltration of B cells into the brain reduces brain infarct size and peripheral T cell activation [73].

2.2 Inflammatory Action of Cytokines and Chemicals

Brain ischemia triggers a surge in inflammatory cytokine production by various cell types, including microglia, astrocytes, endothelial cells, and neurons, with contrasting outcomes. Proinflammatory cytokines (such as TNF-α and IL-1) exacerbate stroke-related brain injury, while anti-inflammatory cytokines (such as IL-10 and TGF-β) alleviate cerebral ischemia injury [23,55,74]. Table 1 (Ref. [8,22,55,69,75–124]) outlines the role of inflammatory mediators.

Previous studies have associated differences in the production of inflammatory to infarct size following cerebral ischemia. Proinflammatory factors can increase cell edema and death, while the expression of anti-inflammatory factors can partially alleviate nerve damage [125,126]. IL-1 is widely produced in nerve cells, microglia, and astrocytes after brain tissue ischemia. It is an important proinflammatory cytokine in the inflammatory response [55]. IL-1 can promote neuronal death by inducing calcium ions to enter cells by acting on N-Methyl-D-aspartic acid receptors (NMDARs) [78]. IL-1 also activates phospholipase A2, disrupting cell phospholipase bilayers, inducing apoptosis, and promoting the release of metabolites such as prostaglandins and leukotrienes, which can induce BBB breakdown and promote inflammatory response [93,127]. Furthermore, IL-1 induces BBB breakdown and promotes leukocyte infiltration through adhesion molecules on endothelial cells [55,128–130]. Adhesion molecules act as ligands involved in leukocyte chemotaxis and inflammatory responses by binding to leukocyte integrin receptors attached to endothelial cells [20]. Moreover, inflammatory stimulation results in a significant upregulation of ICAM-1 and animal studies have shown that artificial intervention with IL-1 receptor antagonists can reduce cerebral infarct size [131–133].

IL-6 is a proinflammatory cytokine that is highly expressed after a stroke event [134] and is associated with brain tissue necrosis and poor clinical prognosis [55,94,135]. However, there is another view that IL-6 has an anti-

Table 1. The inflammatory action of cytokines and chemicals after ischemic stroke.

Classification	Designation	Produced by	Roles in inflammatory response	References
Pro-inflammatory cytokines	TNF-α	Neurons, microglia, astrocytes, monocytes, Th1 cells, and endothelial cells	Combine TNF receptors, form complex1, active caspase, and induce apoptosis Upregulate nuclear factor kappa-B (NF-κB) activation, increase glutamate, NO, MMPs, and ROS Activate microglia and astrocytes and increase infarct volume Increase chemokines and adhesion molecules (ICAM and VCAM), promote coagulation and BBB breakdown, promote neutrophil infiltration Enhance the toxic effects of IL-1	[22,75–77]
	IL-1α/β	Neurons, microglia, astrocytes, monocytes, and endothelial cells	Increase NMDAR function and Ca^{2+} concentration and lead to neurogenic death Promote the expression of adhesion molecules (ICAM-1, ICAM-2, P-selectin, E-selectin, and VCAM-1) and induce BBB breakdown Activate lipoprotein-associated phospholipase 2 (LP-A2), induce apoptosis, release metabolites (such as prostaglandins and leukotrienes), induce BBB breakdown, and promote leukocyte infiltration Activate microglia and astrocytes and increase IL-1, IL-6, TNF-α, NO, iNOS, and MMP levels Upregulate NF-κB activation	[55,78–81]
	IL-12	Microglia, monocytes, NK cells, and T cells	Induce inflammatory T cell and increase infarct volume	[8,82]
	IL-15	Neurons, microglia, macrophages, astrocytes, and endothelial cells	Promote the migration of T cells Activate NK cells and increase infarct volumes	[83–85]
	IL-17	Neurons, microglia, astrocytes, monocytes, endothelial cells, Th17 cells, $\gamma\delta$ T cells, and NK cells	Upregulate NF-κB activation, induce BBB breakdown, and promote neutrophil infiltration	[86]
	IL-21	Th17 cells, B cells, and NK cells	Activate the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway Increase infarct size and lymphocyte accumulation	[87,88]
	IL-23	Monocytes, microglia, and astrocytes	Promote T-cell activation to produce IL-17	[89]
	IFN-γ	Astrocyte, ($\gamma\delta$) T cells, NK cells, microglia, and macrophages	Increase the expression of IP-10 and infarct size	[69,90]
Anti-inflammatory cytokines	IL-4	Th2 cells, microglia, and monocytes	Polarize microglia, promote angiogenesis, alleviate ischemic stroke Downregulate the expression of TNF-α and IL-1β	[91,92]
	IL-6	Neurons, microglia, astrocytes, monocytes, endothelial cells, lymphocytes, T cells, B cells, and neutrophils	Promote tissue recovery, reduce infarct severity, induce neutrophil apoptosis, inhibit the expression of TNF-α, and induce the synthesis of IL-1 receptor antagonists	[93–96]
	IL-10	Neurons, microglia, astrocytes, monocytes, endothelial cells, Th cells, Treg cells, and B cells	Reduce infarct size and inhibit cell apoptosis Increase nerve growth factor (NGF) and l-glutathione (GSH) and decrease IL-1β, TNF-α, IFN-γ levels	[97,98]
	IL-22	Th17 cells	Activate the JAK2/STAT3 pathway Reduce infarct size and inhibit cell apoptosis Decrease IL-1β, TNF-α, and MCP-1 levels	[99]
	TGF-β	Microglia, astrocytes, and macrophages	Promote glial scar formation and microglia polarizing Inhibit apoptosis, counteract excitotoxic neuronal loss, and reduce infarct size and neuroinflammation	[100,101]
	IGF-1	Neurons, astrocytes, endothelial cells, and macrophages	Promote microglia polarizing and decrease IL-1β, TNF-α, iNOS, and ROS levels Maintain astrocyte glutamate uptake and glucose homeostasis Reduce neurogenic death	[102]

Table 1. Continued.

Classification	Designation	Produced by	Roles in inflammatory response	References
Chemokines	IL-8	Microglia, monocytes, endothelial cells, and T cells	Induce neutrophil adhesion and migration	[103,104]
	MIF	Astrocyte	Promote leukocyte recruitment and thrombus formation	[105]
	MIP-1α/β	Microglia	Promote macrophage and neutrophil migration, increase inflammatory mediators, and increase infarct size	[106]
	MCP-1	Neurons, microglia, macrophages, astrocytes, and endothelial cells	Induce BBB breakdown, promote macrophage migration Increase infarct size	[106]
	IP-10	Neurons, microglia, astrocytes, monocytes, endothelial cells, and NK cells	Induce NK cell accumulation and BBB breakdown	[107]
Free oxygen radicals	ROS	Neurons, microglia, neutrophil, and astrocytes	Activate the NF-κβ pathway, cause inflammatory cascades, damage mitochondria, and induce autophagy	[108,109]
	NO	Neurons, macrophages, astrocytes, microglia, and endothelial cells	Induce mitochondrial dysfunction and energy depletion, promote angiogenesis, and increase infarct size Produce neurotoxic effect and promote inflammation, cell death, and BBB damage	[110–112]
	iNOS	Endothelial cells, astrocytes, microglia, and neutrophils	Promote NO production and vasodilation, and increase infarct volume	[113,114]
Protease	MMPs (MMP-3/9)	Neurons, microglia, astrocytes, neutrophil, endothelial cells, and macrophages	Induce BBB breakdown and neuronal apoptosis Promote leukocyte adherence and transmigration Induce cerebral edema and hemorrhagic complications Increase infarct size	[115,116]
Adhesion molecules	ICAMs (ICAM-1, ICAM-4)	Microglia, astrocytes, macrophages, endothelial cells, and leukocytes	Promote neutrophils' entry into the BBB	[117,118]
	VCAM-1	Microglia, astrocytes, macrophages, endothelial cells, and leukocytes	Promote macrophages' entry into the BBB and neovascularization	[119,120]
	P-selectin	Microglia, astrocytes, macrophages, endothelial cells, and leukocytes	Promote leukocyte adhesion and migration	[121]
	E-selectin	Microglia, astrocytes, macrophages, endothelial cells, and leukocytes	Induce upregulation of endothelial cell adhesion molecules Promote leukocyte adhesion and migration	[122–124]

TNF-α, tumor necrosis factor-α; IL, interleukin; IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; IGF-1, insulin-like growth factor 1; MIF, migration inhibitory factor; MIP-1α/β, macrophage inflammatory protein-1α/β; MCP-1, monocyte chemoattractant protein-1; IP-10, Interferon-γ (IFN-γ)-induced protein 10; ROS, reactive oxygen species; NO, nitric oxide; iNOS, inducible nitric oxide synthase; MMPs, matrix metalloproteinases; ICAMs, intercellular cell adhesion molecules; VCAM-1, vascular endothelial cell adhesion molecule-1; NF-κB, nuclear factor kappa-B; NMDAR, N-Methyl-D-aspartic acid receptor; BBB, blood-brain barrier; JAK/STAT, janus kinase/signal transducer and activator of transcription; NK cells, natural killer cells; NGF, nerve growth factor; GSH, glutathione.

inflammatory effect by promoting tissue recovery and reducing infarct severity [136–138]. Currently, the known anti-inflammatory action mechanisms include inhibiting inflammatory factors, inhibiting TNF-α expression, inducing the production of IL-1 receptor antagonists, and inducing neutrophil apoptosis [95,139]. Therefore, the role of IL-6 in the neuroinflammatory pathophysiological of IS is complex.

TNF-α is an important proinflammatory cytokine produced by microglia, monocytes, and other immune cells during acute inflammation, resulting in cell necrosis or apoptosis through intracellular signaling pathways [140]. TNF-α level was positively correlated with cerebral infarction volume [141,142]. Artificial use of anti-TNF-α and TNF-α binding protein could decrease tissue necrosis and infarct size [143–146]. TNF-α can activate microglia and astrocytes, induce the expression of adhesion molecules in brain endothelial cells, destroy the BBB, promote leukocyte infiltration, and affect glutamate transfer and synaptic plasticity [22,75].

IL-10 is an anti-inflammatory cytokine widely present in astrocytes, mononuclear macrophages, Th cells, and B cells, and animal experiments have demonstrated that mice with IL-10 overexpression have smaller infarct size and limited apoptosis [97]. Previous research showed that IL-10 can reduce infarct size after focal ischemia, reduce leukocyte and monocyte/macrophage infiltration, and mitigate nerve damage caused by inflammatory cytokines [72,147,148].

TGF-β, a neuroprotective factor, promotes tissue regeneration and neurological recovery [55,149,150]. Experimental results showed that TGF-β can promote endothelial cell angiogenesis, stimulate M2 polarization of microglia cells, and inhibit neuron damage [151]. Moreover, TGF-β stabilizes the BBB during early stroke [152,153].

Nuclear factor kappa-B (NF-κB), a heterogeneous transcription factor activated after cerebral ischemia, induces inflammation [154–156]. Studies have shown that NF-κB influences microglia activation and polarization [157] while promoting the expression of inflammatory cytokines, MMPs, and adhesion molecules in inflammatory response [158–160]. Multiple pathways, including the suppressor of cytokine signaling 1/janus kinase/signal transducer and activator of transcription (SOCS-1/Janus/STAT) signaling pathway, are involved [161].

MMPs are a family of proteolytic enzymes which can induce BBB breakdown [162]. During the acute phase of IS, MMP expression increases [163,164]. MMPs are found in microglia, astrocytes, and endothelial cells. Moreover, MMPs activate microglia, macrophages, and neutrophils, further promoting MMP secretion and leading to vascular and BBB damage [165]. Experimental studies have shown that silencing *MMP-IX* and *MMP-III* gene expression significantly alleviated BBB damage and edema [166,167].

3. Features of circRNA

Discovery, Functions, Biogenesis and Classification of circRNAs

CircRNAs are non-coding RNA molecules that form covalent ring structures without 5′ terminal cap or 3′ terminal poly (A) tails [168]. CircRNAs were first discovered in plant viroids in 1976 and were widespread in the cytoplasm of eukaryotes [169–175]. Initially considered as by-products of mis-splicing [176], circRNAs currently have various functions (Fig. 2), including (i) acting as microRNA (miRNA) sponges: circRNAs contain miRNA binding sites, competitively binding miRNAs to indirectly regulate their transcription and translation [177]; (ii) impacting RNA polymerase II transcription: circRNAs can form R-loops with their producing locus or coactivate transcription factors (TFs) to modulate transcription [178,179]; (iii) regulating splicing: circRNA back-splicing sites can compete with pre-mRNA splicing, influencing mRNA synthesis [180,181]; (iv) absorbing or combining proteins: circRNAs containing protein-binding sites can bind to proteins, influencing their participation in other neuronal functions [180,182–184]; (v) forming functional circRNA-protein (circRNP) complexes: several circRNAs can form circRNP complexes with RNA binding proteins (RBPs), thereby modulating signaling pathways [185–187]; (vi) affecting mRNA expression: partial circRNAs can impact mRNAs' stability and translation by directly binding to mRNAs [188,189]; and (vii) protein translation: some circRNAs through splicing-dependent and cap-independent mechanisms, can be translated into proteins [190–192].

CircRNAs can be categorized into four groups based on their biogenesis: exonic circRNAs (ecircRNAs), synthesized from only the exon sequence, circular intronic RNAs (ciRNAs) containing introns, exon-intron circRNAs (EIciRNAs) containing both exon and intron sequences, and tRNA intronic circular RNAs (tricRNAs) [10,173,193–195]. The biogenesis of circRNAs is illustrated in Fig. 2.

4. Role of circRNAs in IS

4.1 Initiative circRNAs were Involved in the Inflammatory Process of IS

4.1.1 CircRNAs were Abnormally Expressed in Brain Tissue and Peripheral Blood in Different Animal Models

The earliest study on circRNA expression profiles was published in STROKE in 2017 by Mehta *et al.* [196]. Using a transient middle cerebral artery occlusion (tMCAO) mice model, they detected 1320 circRNAs from exonic gene regions in the ischemic penumbral cortex. Among these, 283 were significantly altered after tMCAO compared to controls. This abnormal circRNA expression may play a potential pathophysiological role in the ischemic brain tissues of mice with tMCAO. In another study, Duan *et al.* [197] identified 14,694 differentially expressed circRNAs in MCAO rat brain tissues through high-throughput sequencing and quantitative reverse transcription-polymerase chain reac-

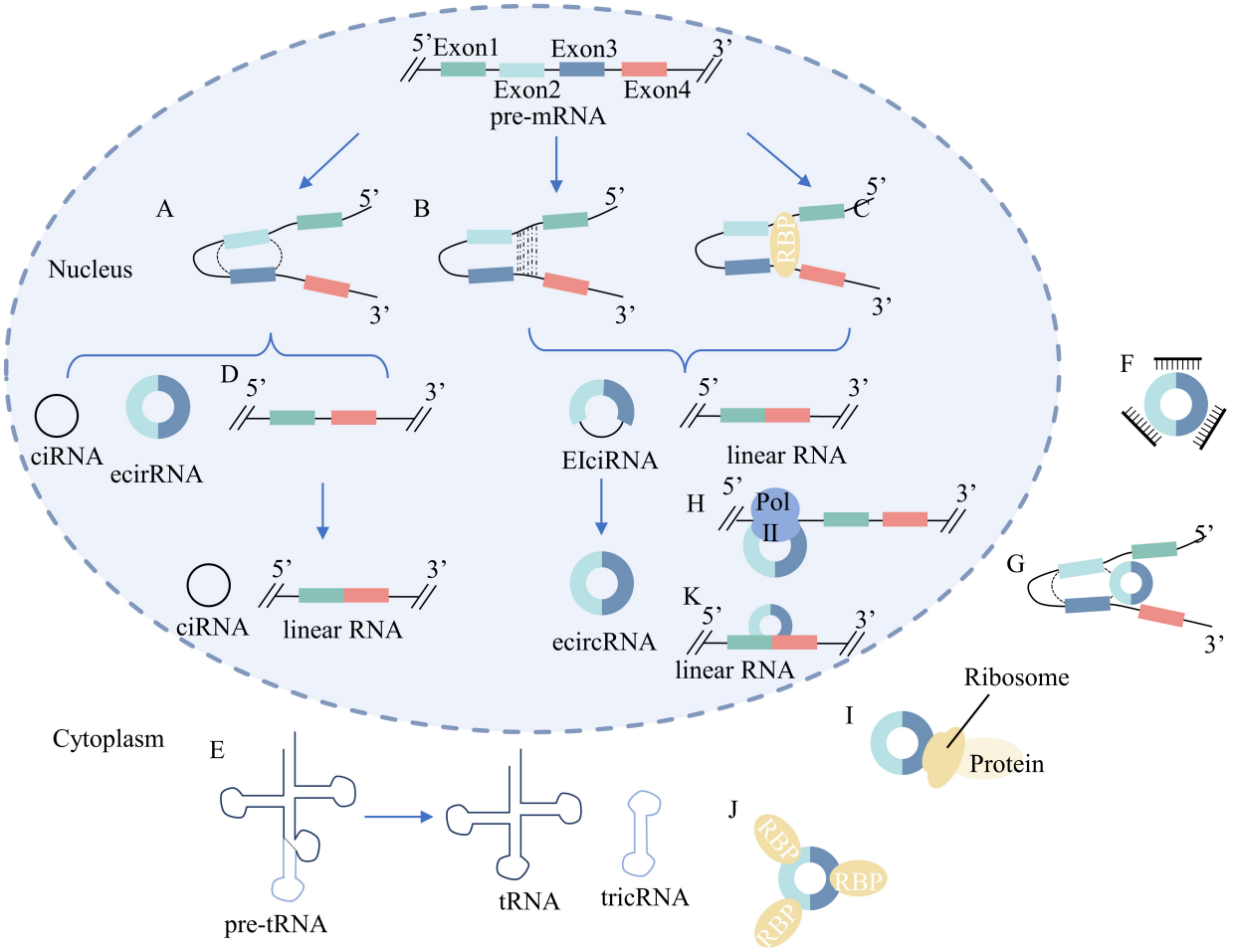

Fig. 2. Biogenesis and function of circRNAs. (A) Lariat-driven circularization model: the 3′ splice donor of exon 1 and the 5′ splice acceptor of exon 4 links up end-to-end by exon skipping and form an exon-containing lariat structure. Finally, the ecircRNA forms after intron removal. (B) Intron pairing-driven circularization model: direct base pairing of introns forms a circulation structure, thereby forming ecircRNA or EIciRNA after intron removal. (C) RBP-dependent cyclization model: RBPs bridge two flanking introns close together and then remove introns to form circRNAs. (D) ciRNA formation model: the elements near the splice site escape debranching stably to form the intron lariat from the splicing reaction. (E) tRNA intronic circRNA: tricRNAs derived from introns removed during precursor-tRNA (pre-tRNA) splicing. (F) Act as microRNA (miRNA) sponges. (G) Impact RNA Pol II transcription. (H) Regulate splicing. (I) Absorb or combine proteins. (J) Form functional circRNP complexes. (K) Interact with mRNAs to affect their expression. circRNAs, Circular RNAs; ecircRNAs, exonic circRNAs; EIciRNAs, exon-intron circRNAs; RBP, RNA binding protein; ciRNAs, circular intronic RNAs; tricRNAs, tRNA intronic circular RNAs.

tion (RT-PCR), with 87 differentially expressed circRNAs displaying significant fold changes. Moreover, Liu *et al.* [198] used RNA extraction and microarray assays to analyze circRNA expression in reperfused mice brain tissues after transient ischemia, revealing differential regulation of 1027 circRNAs, with 914 upregulated and 113 downregulated. These studies suggest the presence of abnormal circRNA expression in ischemic brain tissue, with potential pathophysiological implications after MCAO.

In addition to the ischemic core and penumbra, significantly expressed circRNAs were also identified in non-ischemic areas and peripheral blood from an MCAO mouse model. In one experiment, focal cortical ischemia was induced in adult male distal MCAO mice, and circRNA expression in the ipsilateral non-ischemic thalamic regions was measured using high throughput sequencing. The results revealed 2659 circRNAs with significant alterations in the non-infarct area of the ipsilateral hemisphere [199]. Another experiment validated the differential expression of blood circRNAs in tMCAO mice, confirming their role after IS. The result showed 10739 highly expressed circRNAs, and their expression across different time points showed no significant difference, indicating the non-random nature of circRNA alterations. Most circRNAs detected in blood were also present in the brain. Therefore, circRNAs may play potential functional roles after IS, and

circRNAs in the blood may have the same origin as circRNAs in the ischemic brain [200]. Peripheral inflammatory cells possibly pass the BBB through chemotaxis and reach the brain tissue at the ischemic penumbra to exert an inflammatory response.

4.1.2 Peripheral Blood Immune Cells Participate in the Inflammatory Response after Stroke through the Function of circRNAs

Recently, with advances in clinical trials, the relationship between circRNAs and IS has become increasingly evident. Clinical trial results are highly consistent with those of animal trials.

In a study by Dong Z *et al*. [201] in 2020 examining circRNA expression in stroke, the expression profile of 164532 circRNAs was generated in peripheral blood mononuclear cells (PBMCs) from patients with acute ischemic stroke (AIS) and controls using high-throughput sequencing technology. Among these, 521 circRNAs were differentially expressed, with 373 upregulated and 148 downregulated. The study demonstrated significant differences in circRNAs in PBMCs between patients with AIS and controls. Additionally, this study indicated that circRNAs participated in the inflammatory pathways (such as the NF-κB, the TNF, and the chemokine signaling pathways) by acting as miRNA sponges [201]. However, the specific pathways of circRNA action were not studied in more detail in this paper. Table 2 (Ref. [202–219]) outlines the role of circRNAs in modulating inflammation.

4.1.2.1 CircFUNDC1, circPDS5B, and circCDC14A.

Another study exploring the role of peripheral blood circRNAs in IS found that among the 10798 circRNAs analyzed in human blood, 68 downregulated and 10 upregulated circRNAs differed significantly between groups. Moreover, hsa_circ_0007290 (circFUNDC1), hsa_circ_0004494 (circPDS5B), and hsa_circ_0000097 (circCDC14A) levels were positively correlated with cerebral infarct volume. circPDS5B levels showed significantly higher expression in peripheral blood lymphocytes, granulocytes, and plasma in patients with stroke, whereas circCDC14A was significantly upregulated in granulocytes [220]. Bai *et al*. [202] demonstrated the role of circFUNDC1 in human IS and oxygen-glucose deprivation (OGD)-treated cell models. In both model types, circFUNDC1 was upregulated, resulting in low miR-375 levels. CircFUNDC1 knockdown and miR-375 overexpression enhanced the angiogenesis ability of human brain microvascular endothelial cells (HBMECs) by regulating phosphatase and tensin homolog (PTEN) expression. Previous research has shown that PTEN can regulate BBB permeability and neurogenesis [219,221]. Jiang *et al*. [203] found that circPDSB5 was also upregulated in the serum of patients with IS and tMCAO mice. Moreover, circPDS5B knockdown alleviated cell necrosis and provided cerebrovascular protection via the heterogenous nuclear ribonucleoprotein L/vascular endothelial growth factor-A (hnRNPL/VEGFA) pathway. Zuo *et al*. [205] noted the high expression of circCDC14A in peripheral plasma, neutrophils, pericerebral infarction cortex, and astrocytes. Reducing circCDC14A levels in peripheral blood immune cells alleviated astrocyte activation in the periinfarction cortex, thus alleviating brain injury in AIS. This may be because peripheral neutrophils infiltrated ischemic brain tissue through the BBB. Additionally, Huo *et al*. [206] observed that circCDC14A positively modulated C-X-C motif chemokine ligand-12 (CXCL12), inducing neuronal damage and apoptosis via miR-23a-3p in tMCAO mice.

4.1.2.2 CircDLGAP4.

In 2019, Zhu *et al*. [222] identified a correlation between has_circ_0060180 (circDLGAP4) expression and the inflammatory cascade level in patients with AIS. CircDLGAP4 was down-regulated in PBMCs in patients with AIS and negatively associated with miR-143 expression. circDLGAP4 downregulation and miR-143 upregulation increased serum inflammatory cytokines including IL-6, IL-8, IL-22, and TNF-α. However, the relevance of miR-143 in acute stroke remains unclear and may be related to BBB breakdown and PBMC activation [222]. Similarly, Bai *et al*. [204] observed abnormal circDLGAP4 expression in PBMCs and found that circDLGAP4 acts as a miR-143 sponge to reduce miR-143 level, causing downregulation of homologous to the E6-AP C-terminal domain E3 ubiquitin protein ligase 1 (HECTD1) expression in the ischemic brain. CircDLGAP4 overexpression significantly inhibited endothelial-mesenchymal transition to decrease BBB damage and infarct areas by modulating the expression of tight junction protein and mesenchymal cell marker in the tMCAO mouse stroke model. In another cell experiment, Qiu *et al*. [218] confirmed that circDLGAP4 functions as a miR-503-3p sponge to elevate neuronal growth regulator 1 (NEGR1) expression and influence the level of the proinflammatory cytokine, thereby attenuating inflammatory reaction and neuronal impairments during IS.

4.2 CircRNAs Affect Microglia and Astrocytes through the Inflammatory Processes

4.2.1 CircPUM1

Hu *et al*. [209] observed significant upregulation of hsa_circ_0000043 (circPUM1) and DEAD-box helicase 5 (DDX5) and notable miR-340-5p downregulation in a tMCAO mouse model [209]. Abnormally low circPUM1 expression promoted the secretion of inflammatory factors and induced apoptosis by activating microglia and astrocytes through the miR-340-5p/DDX5/ NF-κB pathway, ultimately causing ischemic injury in circPUM1 knockout mice. circPUM1 overexpression acted as miR-340-3p sponge, upregulating DDX5 and reducing the content of pro-inflammatory factors (IL-1β, IL-6, TNF-α), and the NF-κB (p-p65, cleaved caspase-3, and Bax) expression

Table 2. The evidence of circRNAs regulatory roles in the pathophysiological changes of ischemic stroke.

Pathological process	Cell line/treatment	Animal/disease model	CircRNAs and expression		Regulating axis	Overexpression role	References
Angiogenesis	HBMECs OGD-treated	/	CircFUNDC1	UP	miR-375/PTEN	Inhibit angiogenesis Detrimental	[202]
	HBMECs/ OGD-treated	tMCAO Mouse	CircPDS5B	UP	hnRNPL/VEGFA	Inhibit angiogenesis Detrimental	[203]
	/	tMCAO Mouse	Circ-DLGAP4	DOWN	miR-143/hectord1/EndoMT	Decrease BBB damage Protective	[204]
Apoptosis	HT22 OGD/R	tMCAO Mice	CircCDC14A	UP	miR-23a-3p/CXCL12	Induce apoptosis Detrimental	[205,206]
	astrocyte OGD/R	tMCAO Mouse	Circ-CELF1	UP	DDX54/NFAT5	Induce apoptosis Detrimental	[207]
	HT22 OGD	MCAO Mice	Circ-HECTD1	DOWN	miR-125b-5p/GDF11	Inhibit apoptosis Protective	[208]
Inflammation	/	tMCAO Mouse	CircPUM1	UP	miR-340-5p/DDX5/NF-κB	Inhibit inflammation Protective	[209]
	microglia OGD	/	CircPTK2	UP	miR-29b-SOCS-1-JAK2/STAT3-IL-1β	Induce inflammation Detrimental	[210]
	microglia OGD	tMCAO Mice	Circ-0000831	UP	miR-16-5p/AdipoR2	Induce inflammation Detrimental	[211]
	HCN-2 OGD	/	Circ-0007290	UP	miR-496/PDCD4	Induce inflammation Detrimental	[212]
	HBMVECs H/R	/	Circ-Memo1	UP	miR-17-5p/SOS1	Induce inflammation Detrimental	[213]
	HBMECs OGD	/	Circ-0006459	UP	miR-940/FOXJ2	Induce inflammation Detrimental	[214]
	HBMECs OGD/R	/	Circ-0000566	UP	miR-18a-5p/ACVR2B	Induce inflammation Detrimental	[215]
	SK-N-SH OGD/R	/	Circ-0000647	UP	miR-126-5p/TRAF3	Induce inflammation Detrimental	[216]
	SK-N-SH OGD	tMCAO Mice	Circ-0101874	UP	miR-335-5p/PDE4D	Induce inflammation Detrimental	[217]
	HT22 OGD/R	MCAO Mouse	Circ-HECTD1	UP	miR-133b/TRAF3	Induce inflammation Detrimental	[208]
	HCN-2 OGD	/	Circ-DLGAP4	DOWN	miR-503-3p/NEGR1	Inhibit inflammation Protective	[218]
	astrocyte OGD/R	MCAO Mouse	Circ-CTNNB1	DOWN	miR-96-5p/SRB1	Inhibit inflammation Protective	[219]

HBMECs, human brain microvascular endothelial cells; OGD, oxygen-glucose deprivation; HT22, hippocampal neuronal cell line; HCN-2, cortical neuron cell line; HBMVECs, human brain microvascular endothelial cells; H/R, hypoxia/reoxygenation; SK-N-SH, human neuroblastoma cell line; tMCAO, transient middle cerebral artery occlusion; PTEN, phosphatase and tensin homolog; hnRNPL/VEGFA, heterogenous nuclear ribonucleoprotein L /vascular endothelial growth factor-A; EndoMT, endothelial-mesenchymal transition; CXCL12, C-X-C motif chemokine ligand-12; DDX54, DEAD-box helicase 54; NFAT5, nuclear factor of activated T cell 5; GDF11, growth differentiation factor 11; NF-κB, nuclear factor kappa-B; miR-29b-SOCS-1-JAK2/STAT3-IL-1β, suppressor of cytokine signaling 1-Janus kinase2/signal transducer and activator of transcription 3-interleukin-1β; PDCD4, programmed cell death protein 4; SOS1, Son of Sevenless 1; FOXJ2, forkhead box J2; ACVR2B, activin receptor type 2B; TRAF3, TNF receptor associated factor 3; PDE4D, phosphodiesterase 4D; NEGR1, neuronal growth regulator 1; SRB1, scavenger receptor class B type 1; OGD/R, oxygen-glucose deprivation/reoxygenation.

[209,223]. Moreover, miR-340 has been implicated in various diseases, such as multiple myeloma, pulmonary sarcoidosis, heart failure, lung adenocarcinoma, colorectal cancer, and osteoporosis [224–229].

4.2.2 CircPTK2

In 2019, Wang *et al.* [210] found that hsa_circ_0005273 (circPTK2) regulates neuronal apoptosis by activating microglia via miR-29b-suppressor of cytokine signaling 1-Janus kinase 2/signal transducer and activator of transcription 3-interleukin-1β (SOCS-1-JAK2/STAT3-IL-1β) signaling. circPTK2 inhibits miR-29b activity by acting as a miRNA sponge, thus downregulating the suppressor of cytokine signaling 1 (SOCS-1) in microglia. SOCS-1 targets Janus kinase 2 (JAK2) and inhibits the activation of the JAK2/STAT3 pathway [230,231]. STAT3 tyrosine phosphorylation induced IL-1β and IL-6 production in the inflammation response [232]. Therefore, circPTK2 promotes neuronal inflammation and apoptosis by regulating microglia [210].

4.2.3 Circ-0000831

It has been reported that circ-0000831 mitigated inflammatory and apoptotic responses in MCAO mice models, and circ-0000831 was upregulated in microglia after OGD. circ-0000831 acted as a sponge for miR-16-5p, causing its downregulation. Adiponectin receptor 2 (AdipoR2), a target for miR-16-5p, was upregulated and increased peroxisome proliferator-activated receptor γ (PPARγ) expression in microglia in animal models [211]. AdipoR2 has been reported to activate PPARγ pathways to modify inflammatory processes, and PPARγ overexpression alleviated the inflammation response [233,234]. Moreover, AdipoR2 activated the PPARα pathway to inhibit inflammation [235]. Therefore, circ-0000831 can alleviate neuroinflammation and cell apoptosis in MCAO mice via the miR-15-5p-AdipoR2-PPARγ pathway [211].

4.2.4 CircCELF1

Li *et al.* [207] observed that highly expressed circCELF1 in oxygen-glucose deprivation/reoxygenation (OGD/R) astrocytes could exacerbate astrocyte damage, and its expression is associated with inflammatory response. CircRNA hsa_circ_0000304 (circCELF1) knockdown decreased the expression of proinflammatory cytokines in astrocytes after OGD/R. By binding to the RNA binding protein DEAD-box helicase 54 (DDX54), circCELF1 enhances the stability of the nuclear factor of activated T cell 5 (NFAT5) mRNA. In another study, increased NFAT5 expression induced neuroinflammation after IS [236]. NFAT5 overexpression can restore the decline in inflammatory factor levels caused by circCELF1 knockdown [207].

4.2.5 CircCTNNB1

Recently, circRNA catenin beta 1 (circCTNNB1) was found to play a role in the inflammatory response in astrocytes. CircCTNNB1 and IL-10 levels were downregulated, whereas the expression of proinflammatory factors, including IL-1β, IL-6, and TNF-α, was upregulated when mouse astrocytes treated with OGD/R treatment. By sponging miR-96-5p, circCTNNB1 upregulation increased scavenger receptor class B type 1 (SRB1) levels to protect against brain injury [237]. SRB1 is involved in cerebrovascular diseases. However, there is no evidence proving the correlation between SRB1 and the BBB, necessitating further research.

4.3 CircRNAs Affect other Cells through the Inflammatory Processes

4.3.1 CircMemo1

Vascular endothelial cells, an important part of the BBB, were widely implicated in the inflammatory response after IS. Ren *et al.* [213] found that circ-Memo1 and Son of Sevenless 1 (SOS1) levels were highly expressed; however, miR-17-5p expression was low in the peripheral blood of patients with IS. After circMemo1 knockdown, the expression of proinflammatory cytokines was low in the human brain microvascular endothelial cell (HBMVEC) model. CircMemo1 can directly bind with miR-17-5p, negatively regulating miR-17-5p levels, which could inhibit SOS1 expression. Cerebral ischemia stimulates SOS1 activity and disrupts Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) phosphorylation downstream of SOS1 [238]. Moreover, SOS1 can activate the NF-κB pathway by regulating epidermal growth factor (EGF) levels [239]. Inhibiting the ERK1/2 pathway could enhance NF-κB phosphorylation and activity and reduce brain injury. However, ERK1/2 pathway activation promotes inflammation after cerebral ischemia [240,241].

4.3.2 Circ-0006459

Li *et al.* [214] investigated the inflammatory response of circ-0006459 in OGD-induced HBMEC cell models. By sponging miR-940, circ-0006459 overexpression promoted proinflammatory factor levels (including IL-1β, IL-8, IL-18, and TNF-α) and induced forkhead box J2 (FOXJ2) upregulation in HBMEC injury after OGD. FOXJ2 has DNA-binding specificity and is involved in neuroinflammatory responses as a transcription factor [242,243]. This pathway inhibits HBMEC proliferation and promotes inflammatory responses.

4.3.3 Circ-0000566

In a HBMECs model article, it has been discovered that circ-0000566 was highly expressed after OGD [244]. Another study found that circ-0000566 was upregulated after OGD/R, while miR-18a-5p was significantly downregulated. Moreover, Circ-0000566 acted as a miR-18a-

5p sponge, contributing to HBMEC injury and proinflammatory cytokine release [215]. Activin receptor type IIB (ACVR2B) directly targeted miR-18a-5p, causing its upregulation and involvement in the smad2/c-jun axis in neuronal damage after cerebral ischemia in mice [245].

4.3.4 Circ-0000647

In 2022, Dai *et al*. [216] used human neuroblastoma cell line (SK-N-SH) cells to simulate the cerebral ischemia environment and found elevated circ-0000647 levels, with circ-0000647 acting as a miRNA sponge to bind miR-126-5p and decrease miR-126-5p expression [216]. Circ-0000647 upregulation and miR-126-5pc downregulation reduced the expression of TNF-α and IL-6. Mechanistically, TNF receptor-associated factor 3 directly targeted miR-126-5p and reduced TNF-α and IL-6 expressions. Therefore, circ-0000647 can promote inflammation via the miR-126-5p-TRAF3 (TNF receptor associated factor 3) pathway [216].

4.3.5 Circ-0101874

In this review, the involvement of circRNA in IS by influencing inflammatory factors has been summarized. Pei *et al*. [217] observed that circ-0101874 was upregulated in both MCAO mice and OGD-induced cell models. Circ-0101874 knockdown suppressed TNF-α and IL-6 expression in OGD cells. Therefore, miR-335-5p acts as the target of circ-0101864 and deactivates the gene called phosphodiesterase 4D to abate the inflammatory response.

4.3.6 CircHECTD1

The role of circular RNA HECT domain E3 ubiquitin-protein ligase 1 (circHECTD1) in mouse MCAO and OGD cell models has been found in 2021. CircHECTD1 expression was upregulated, and its interaction with miR-133b reduced its expression. TNF receptor-associated factor 3, the target for miR-133b, was highly expressed and promoted the expression of inflammatory cytokines such as NF-κB [208].

4.3.7 CircUCK2

In another cell model, hsa_circ_001,357 (circUCK2) inhibited miR-125b-5p expression by acting as a miRNA sponge and increased the expression of growth differentiation factor 11 (GDF11) [246]. GDF11 is a member of the TGF-β superfamily and binds with TGF-β type I and II receptors to activate the mothers against the decapentaplegic homolog 3 (Smad3) signaling pathway [247]. Smad3 overexpression inhibits inflammation and reduces cell damage after ischemic cerebral infarction [248].

4.3.8 Circ-0007290

Wang *et al*. [212] identified the inflammatory effects of circ-0007290 expression in both *in vitro* and *in vivo* models. Circ-0007290 expression was elevated, and knockdown circ-0007290 knockdown reduced the inflammatory response after OGD. Circ-0007290 acted as a sponge to mitigate miR-496 inhibition of its target, programmed cell death protein 4. Moreover, circ-0007290 inhibition, miR-496 overexpression, or programmed cell death protein 4 upregulation induced proinflammatory factor (such as TNF-α and IL-1β) release.

5. Discussion

IS, a condition causing cerebral tissue death and neuronal damage, still has a high morbidity and mortality rate [249]. Inflammation is an important pathological reaction in AIS, and circRNAs may play critical roles in it [250,251]. CircRNAs are not only potential novel biomarkers but also vital for therapeutic targets for the diagnosis and treatment of IS [252]. After IS, circRNAs are differentially expressed in neurons and inflammatory cells affecting the release of inflammatory mediators. Among them, circRNAs mainly act as sponges to combined with miRNAs so that inhibit the effect of miRNA and increase the expression level of target genes. However, only once study has focused on the function of forming circRNP complexes. Furthermore, circRNAs exhibit diverse functions through multiple pathways. As research progresses, the distinct mechanisms of regulation can be better elucidated, thereby enhancing our understanding of the inflammatory regulatory network involving circRNAs.

Currently, the potential of utilizing circRNAs as targets for early diagnosis and post-treatment analysis is yet to be determined. However, it can be concluded that circRNA is widely involved in the activation of various inflammatory cells, the secretion of inflammatory mediators, and the destruction of the BBB. By modulating circRNAs, it is possible to change the extent of inflammatory response. The regulatory mechanisms of inflammation are incredibly intricate, and the clinical application still needs to face many challenges. Moreover, because of the different etiology of the IS subtypes (such as atherothrombotic IS, cardiac cerebral embolism and so on), it's difficult to explain the inflammatory response in the development of IS [253]. However, the ultimate result of various etiological subtypes is to lead to vascular occlusion, and the inflammatory factors and inflammatory cells involved in the process are the same. Therefore, it is meaningful to use the cell model of oxygen-glucose deprivation and the mouse model of MCAO to study the inflammatory response after IS.

Due to the complexity of etiological subtypes and the difficulty of model building, there are few studies on the involvement of circRNA in etiology. It is great significance to explore the role of circRNA in the pathogenesis of different subtypes of IS. With the advancement of technology, the establishment of more appropriate and realistic models should lead to more perfect results.

6. Conclusion

In this review, we described the inflammatory response after IS and summerized the roles of circRNAs in IS. In all, the immune response in IS is quite complex and circRNAs show dual roles to regulate the neuro-inflammation. Restricting the dentrimental neuroinflammation might be helpful to decrease ischemic volume. CircRNA light a new potential treatment target for IS. In order to determine the effective therapeutic strategy, is important to investigate the mechanisms between circRNA and other inflammatory factors.

Abbreviations

BBB, Blood-brain barrier; circRNA, circular RNA; DAMPs, damage associated molecular patterns; HMGB1, high-mobility group box 1 protein; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-α; IL, interleukin; TGF-β, transforming growth factor-β; MIP-1, macrophage inflammatory protein-1; MCP-1, monocyte chemoattractant protein-1; IP-10 (CXCL10), chemokines interferon-γ-inducible protein 10; MMP, matrix metalloproteinase; IFN-γ, interferon-γ; ICAM-1, intercellular cell adhesion molecule-1; VCAM-1, vascular endothelial cell adhesion molecule-1; MIF, macrophage migration inhibitory factor; NK cells, Natural killer cells; Treg cells, regulatory T cells; NMDARs, N-Methyl-D-aspartic acid receptors; RNA Pol II, RNA polymerase II; TFs, transcription factors; RBPs, RNA binding proteins; ecircRNAs, exonic circRNAs; ciRNAs, circular intronic RNAs; EIciRNAs, exon-intron circRNAs; tricRNAs, tRNA intronic circular RNAs; MCAO, middle cerebral artery occlusion; PBICs, Peripheral blood immune cells; AIS, acute ischemic stroke; PBMCs, peripheral blood mononuclear cells; NF-κB, nuclear factor kappa-B; tMCAO, transient middle cerebral artery occlusion; PTEN, phosphatase and tensin homolog; CXCL12, C-X-C motif chemokine ligand-12; HECTD1, homologous to the E6-AP C-terminal domain E3 ubiquitin protein ligase 1; NEGR1, neuronal growth regulator 1; DDX5, DEAD-box helicase 5; PPARγ, peroxisome proliferator-activated receptor γ; NFAT-5, nuclear factor of activated T cells 5; FOXJ2, forkhead box J2; ACVR2B, Activin receptor type IIB; TRAF3, TNF receptor associated factor 3; PDE4D, phosphodiesterase 4D; GDF11, growth differentiation factor 11; Smad3, mothers against decapentaplegic homolog 3; OGD/R, oxygen-glucose deprivation/reoxygenation; circRNP, circRNA-protein.

Author Contributions

LJ, AWS and CGY proposed this research direction. XG, BC, YYZ, XQL, HQS and ZZ conceptualized, wrote, and edited the manuscript. XG, YJZ, KQL, WQX, LFL, JYH and BBG designed the figures and tables, drafted and edited the manuscript. LFL, KQL, JYH, BBG and CGY helped in revision and edited the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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