Review

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Neuroinflammation in the Post-Ischemic Brain in the Presence of Amyloid and Tau Protein

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Ischemia-induced brain neurodegeneration is a leading cause of mortality and permanent disability worldwide, with no definitive cure. The development of neuroinflammation following ischemic events plays a dual role; it is essential for brain repair and homeostasis and can also exacerbate post-ischemic damage and worsen neurological outcomes. Neuroinflammation represents a complex process involving interactions between infiltrating immune cells from the bloodstream and resident immune cells within the affected brain regions. This inflammatory response begins immediately after ischemia and can persist for years. This review focuses on the intricate relationship between neuroinflammation, amyloid accumulation, tau protein pathology and glial cells in the post-ischemic brain. Notably, it examines whether amyloid and tau protein amplify neuroinflammation and whether neuroinflammatory responses influence the behavior and aggregation of these molecules. Understanding these interactions is critical, as they contribute to the progression of post-ischemic brain neurodegeneration. Additionally, this review highlights the role of neuroinflammation as a functionally complex immune response regulated by transcription factors and mediated by cytokines. It explores how the presence of amyloid and modified tau protein may shape the inflammatory landscape. This review aims to advance our understanding of post-ischemic neuroinflammation and its implications for long-term brain health and neurodegenerative diseases.

Keywords: brain ischemia; neuroinflammation; transcription factors; cytokines; amyloid; tau protein; dementia

Introduction

The global increase in average life expectancy has led to a rising prevalence of age-related diseases, such as brain ischemia and its associated complications [1]. Brain ischemia is now recognized as a critical global health concern, contributing significantly to socioeconomic burdens and ranking among the leading causes of mortality and disability worldwide [2–5]. Among survivors, post-ischemic brain damage is the second most common cause of dementia and the third leading cause of disability, affecting approximately 80% of cases [6–10]. Globally, brain ischemia affects an estimated 17 million individuals annually, of whom 5 million are left with permanent disabilities, and 6 million succumb to the condition [10–12]. Advanced age is a primary risk factor, with approximately 75% of brain ischemic patients being over 65 years [4,12]. Current estimates place the number of post-ischemic patients worldwide at approximately 33 million, with this figure projected to rise to 77 million by 2030 [10,11,13].

Post-ischemic survivors frequently develop a wide range of cognitive impairments, ranging from mild cognitive impairment (affecting 40% of survivors) to advanced dementia [5,14]. Notably, the risk of developing dementia in brain ischemic survivors is twice as high as in individuals without a history of ischemic injury [14]. Evidence also suggests that post-ischemic brain injury accelerates the onset of dementia by approximately 10 years [4,15,16].

Numerous mechanisms contribute to ischemic neuronal death, including excitotoxicity, free radical release, protein misfolding, apoptosis, necrosis, autophagy, mitophagy, and neuroinflammation [17–21]. Recent attention has focused on hallmark pathological features observed after ischemia, such as amyloid plaques and neurofibrillary tangles, primarily in brain regions responsible for learning and memory [22–27]. Under physiological conditions, amyloid is produced in small amounts and effectively cleared from the brain to prevent its deposition [4,28]. This clearance involves multiple mechanisms, including enzymatic metabolism, translocation across the blood-brain barrier (BBB) [29,30], cellular uptake and phagocytosis by neuroglial cells [31]. Low-density lipoprotein receptor-related protein 1 (LRP1) facilitates amyloid efflux across the BBB, a process that is impaired following ischemia [32–34]. In contrast, the receptor for advanced glycation end-products (RAGE) predominates in the post-ischemic brain, promoting amyloid accumulation and the formation of amyloid plaques [33].

Amyloid accumulation also occurs within cerebral blood vessels, a condition known as cerebral amyloid angiopathy (CAA) [35,36]. CAA is associated with neu-

rovascular dysfunction, increased BBB permeability, and chronic neuroinflammation, all of which contribute to neurodegeneration [4,34]. Furthermore, amyloid production induces neuroinflammatory reactions, primarily mediated by astrocytes and microglial cells, which exacerbate secondary neuronal injury and accelerate neurodegeneration [37]. Amyloid production is linked to the phosphorylation and aggregation of tau protein [24–27], neuroinflammatory responses, and the loss of synaptic and neuronal integrity [23,34,38]. Hyperphosphorylated tau protein undergoes abnormal folding, forming neurofibrillary tangles [24,27]. In its soluble form, tau protein acts as a transcellular transmission factor, spreading pathogenic effects between interconnected cells and brain regions [39]. Recent findings reveal that ischemia-induced brain damage is driven by a set of genetic alterations that lead to neuronal death via amyloid- and tau protein-dependent mechanisms [33,40–44]. These processes are compounded by acetylcholine deficiency [45], gradual progressive neuroinflammation [2,4], brain atrophy [19,22,41], and the subsequent development of Alzheimer's disease-like dementia [46–49]. Extended neuroinflammation exacerbates neuronal injury, accelerates the deposition of amyloid plaques, and promotes tau protein pathology [50,51].

Ischemia also triggers the production of reactive oxygen species (ROS) by neuronal and glial cells, depleting glutathione, a critical antioxidant that prevents DNA damage by ROS [52,53]. Post-ischemic oxidative stress and neuroinflammation further damage the BBB, facilitating the infiltration of systemic immune cells, including platelets, neutrophils, and T-lymphocytes, into the post-ischemic brain regions [54–56]. Following the infiltration, necrotic cell membranes release extracellular adenosine triphosphate (ATP), activating microglia and astrocytes [57,58]. Activated glial cells release cytokines, which upregulate adhesion molecules on endothelial cells, further recruiting platelets and leukocytes from the systemic circulation to the ischemic brain regions [54–56]. Neuroinflammation triggers brain tissue injury by inducing the death of surviving ischemic neurons from the primary ischemic episode. However, it also plays a beneficial role in glial scar formation, which aids in the repair and stabilization of damaged tissue [59–61].

A key target of current research into brain ischemia is understanding the neuroinflammatory mechanism(s) that begin within minutes of an acute ischemic brain episode and progress during recirculation [4,23,62]. Therefore, there is rising interest in elucidating the role of inflammation in neurodegenerative processes and diseases, including post-ischemic brain injury. In this review, the author examined the role of neuroinflammation in post-ischemic neurodegeneration, focusing on the cellular processes and interactions involved. Specifically, the author discusses post-ischemic neuroinflammation as a multifaceted immune response regulated by multiple transcription factors and influenced by factors such as amyloid accumulation and altered tau protein. A deeper understanding of the cellular contributors to post-ischemic neurodegeneration and their temporal dynamics could provide insights into strategies for mitigating this damage.

Transcription Factors and Cytokines in Post-Ischemic Neuroinflammation

Neuroinflammation is a critical factor exacerbating neurodegeneration following local and global brain ischemia [4,62,63]. The immune response in ischemic brain tissue begins with the activation of resident microglia and astrocytes, which facilitates the infiltration of peripheral immune cells into the ischemic region [64–69]. Following brain ischemia, the expression of pro- and anti-inflammatory genes is tightly regulated by transcription factors [70,71].

Transcription Factors

The regulation of neuroinflammation in the brain is influenced by gene expression alterations triggered by ischemic injury. Numerous transcription factors are involved in modulating neuroinflammatory responses, including c-Fos protein (c-Fos), p53, interferon regulatory factor-1 (IRF-1), cAMP response element-binding protein (CREB), activating transcription factor-2 (ATF-2), peroxisome proliferator-activated receptor (PPAR) α and γ, nuclear factor kappa B (NF-κB), signal transducer and activator of transcription (STAT) isoforms, cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein (C/EBP)α and β, hypoxia-inducible factor-1 (HIF-1), early growth response-1 (Egr1), transcription factor (Sp3), transcription factor (JunD), and transcription factor AP-2α [72–74]. Among these, NF-κB, IRF-1, STAT3, ATF-2, Egr1, and C/EBPβ are known to amplify neuroinflammation and neuronal loss following ischemic brain injury [65,74]. Conversely, transcription factors such as HIF-1, JunD, c-Fos, STAT5a/b, CREB, p53, and peroxisome proliferator-activated receptor (PPAR)α/γ exhibit anti-inflammatory properties that can mitigate neuronal and brain injury after ischemia [65,75].

Post-ischemic injury activates NF-κB, which promotes the release of chemokines and pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1α (MIP-1α), IL-8, TNF receptor-associated factor (TRAF), monocyte chemotactic protein-1 (MCP-1), and brain cell death-promoting protein B-cell lymphoma 2 (Bcl-2) [65,76]. These factors facilitate the recruitment of peripheral immune cells into the ischemic brain. Additionally, microglial activation by NF-κB leads to the release of neuroinflammatory mediators such as IL-1β, TNF-α, and ROS

[77]. Astrocytic NF-κB, activated by IL-1β, TNF-α, ROS, IL-17, and Toll-like receptor signaling, further promotes the release of chemokines that recruit leukocytes, amplifying neuroinflammation [78].

The activator protein 1 (AP-1) transcription factor, composed of heterodimers of the Fos, activating transcription factor (ATF), and Jun subfamilies of basic-region leucine-zipper (B-ZIP) proteins regulates cell survival, proliferation, and neuroinflammation [65]. AP-1 activation during ischemia stimulates pro-inflammatory gene expression, such as *TNF-α* and *IL-1β*, increasing platelet aggregation through the receptor-interacting protein 1 (RIP1)/RIP3/AKT pathway and exacerbating ischemic brain injury [79,80]. On the other hand, AP-1 can be a double-edged sword by influencing the generation of IL-10 through α-ketoglutarate, which inhibits neuroinflammatory responses through the c-Fos/IL-10/STAT3 way post-ischemia [81]. Moreover, IRF-1, a nuclear transcription factor responsible for regulating the expression of interferon-α (*IFN-α*) and *IFN-β* genes, is also implicated in post-ischemic neuroinflammation [82]. IRF-1 contributes to increased neuroinflammation, apoptosis, and secondary brain damage post-ischemia [83]. Notably, *IRF-1* deletion has been shown to reduce brain injury and enhance neurological outcomes in animal models of focal ischemic brain injury [83].

Neuronal and neuroglial cells possess numerous isoforms of the STAT family of transcription factors, including STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [84]. Animal studies have demonstrated the induction of various STAT isoforms following reversible cerebral ischemia [85,86]. After reversible local brain ischemia, phosphorylated STAT3 (pSTAT3) and phosphorylated Janus kinase 2 (pJAK2) were predominantly observed in macrophages and microglial cells [65]. Notably, the knockdown of *STAT3* or inhibition of JAK2 in ischemic animal models exhibited neuroprotective properties and improved neurological outcomes [65]. Homocysteine-induced *STAT3* activation in microglial cells post-ischemia was associated with increased neuroinflammation [85], while blocking *STAT3* signaling through the nuclear localization of the yes-associated protein (YAP) in astrocytes confers neuroprotection against post-ischemic brain injury [86]. These findings highlight the harmful role of STAT3 in post-ischemic neurodegeneration.

IRF-1 gene expression was significantly upregulated in animal models of ischemia, peaking on the 4th day after reperfusion [83]. Similarly, NF-κB activation occurs following focal brain ischemia, and its inhibition reduces infarct size, suggesting its role in exacerbating neuronal injury [65,87]. *NF-κB* deficient animals exhibited smaller infarcts, further supporting its deleterious effects in ischemic injury [65]. *Egr1*-knockout mice demonstrated reduced infarct sizes, improved neurological outcomes, and decreased expression of inflammatory genes, indicating the role of *Egr1* as a significant activator of inflammation and neuronal injury following cerebral ischemia [87].

Post-ischemic STAT3-JAK2 signaling increases the phosphorylation of these factors in macrophages and microglial cells. Treatment with a JAK2 phosphorylation inhibitor (AG490) or *STAT3* siRNA reduces neuroinflammation and secondary brain tissue injury [65]. Moreover, JAK-STAT pathway stimulation after focal ischemia enhances levels of cytokine signaling-3 suppressor (SOCS3), a negative feedback regulator of IL-6 signaling [65]. In contrast, *C/EBPβ* knockout mice displayed reduced expression of genes associated with neuroinflammation and neuronal damage, indicating a negative role of *C/EBPβ* in ischemic brain injury [65]. Conversely, treatment with the PPARα antagonist WY14643 after transient ischemia reduced oxidative stress, intercellular adhesion molecule 1 (ICAM-1), and inducible nitric oxide synthase (iNOS) levels, suggesting that PPARα has neuroprotective effects [88]. PPARγ agonists further inhibited the expression of inflammatory genes, generated the expression of antioxidant genes, and reduced infarct volume and neurological dysfunction following ischemia [65].

Transcription factors regulate the release of inflammatory mediators and modulate neuroinflammatory mechanisms through the control of non-coding RNAs (ncRNAs) [65]. Numerous transcription factors, such as multifunctional transcription factor (c-Myc), NF-κB, HIF-1α, and p53, are involved in the redox-sensitive regulation of microRNAs (miRNAs) [89]. For instance, p53 influences microglial activity through miR-145 and miR-34a [90]. Similarly, NF-κB modulates the expression of pro-inflammatory genes and miRNAs, such as miR-21, miR-9, miR-155, and miR-146a, which, regulate inflammatory mRNA targets [91–94]. The transcription factor early region 2 binding factor 1 (E2F1) directly regulates the miR-122 expression following ischemic brain injury [95].

Alterations in long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) levels in the post-ischemic brain are controlled by transcription factors [96,97]. Recent studies have revealed that NF-κB worsens ischemic brain injury recovery by upregulating the pro-inflammatory lncRNA FosDT [97,98].

Cytokines

Pro- and anti-inflammatory cytokines are small polypeptides that regulate innate and adaptive immune responses. Under physiological conditions, they are present in the brain at very low concentrations [99]. Following brain ischemia, the release of cytokines is rapidly initiated, leading to increased levels throughout the brain (Fig. 1) [100,101]. Key cytokines involved in post-ischemic responses include IL-10, TNF-α, IL-6, IL-1β, transforming growth factor-β (TGF-β), and IFN-β. These cytokines are key mediators of BBB disruptions and brain tissue injury after brain ischemia [99,102]. Among these, IL-1β and TNF-

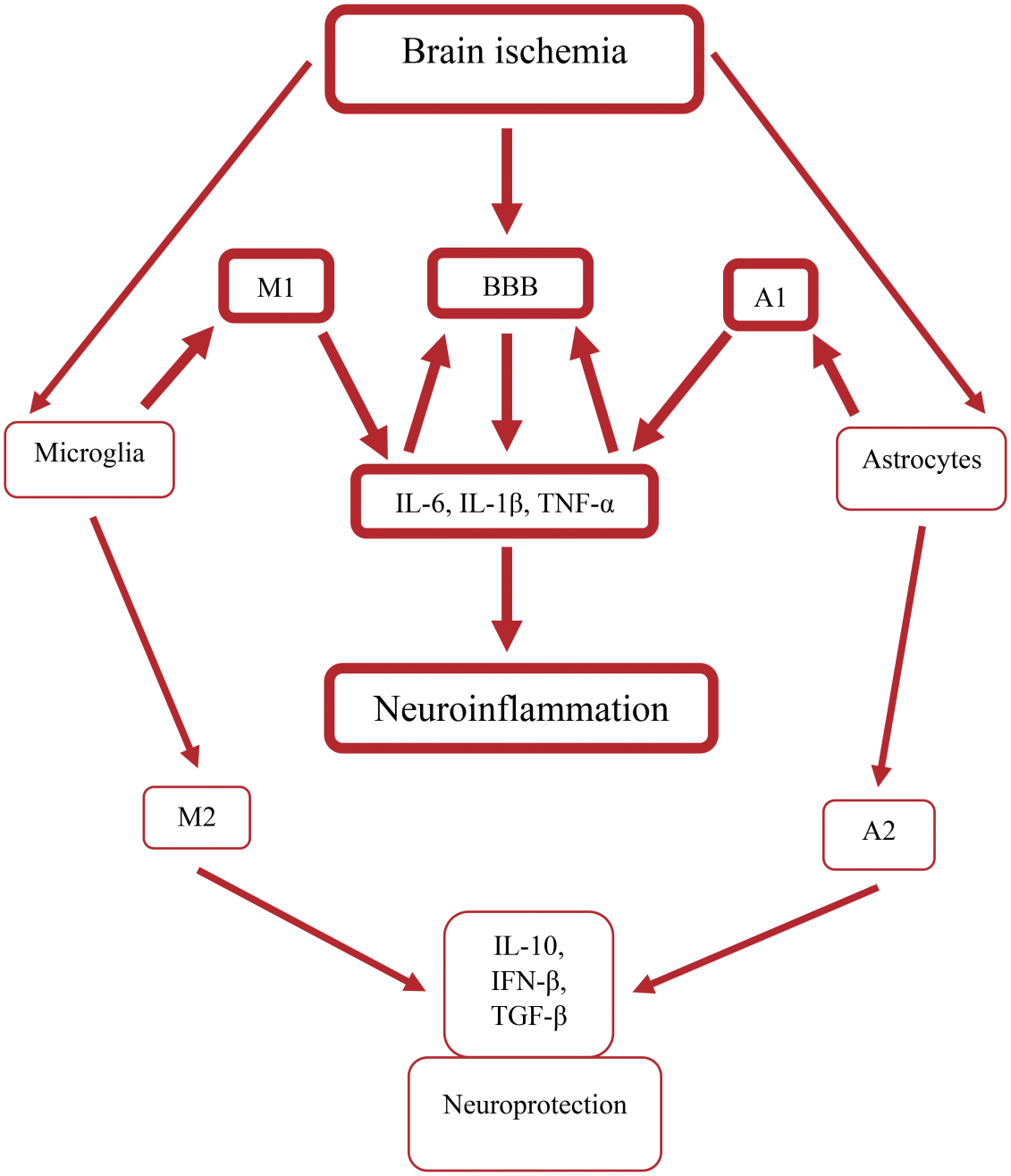

Fig. 1. The role of microglia and astrocytes in post-ischemic neuroinflammation. M1 and M2 types of microglia, A1 and A2 types of astrocytes, blood-brain barrier (BBB). Thicker arrows indicate the dominant mechanism. IL, interleukin; TNF, tumor necrosis factor; IFN-β, interferon-β; TGF-β, transforming growth factor-β. This figure was drawn using Microsoft Word (Microsoft Corporation, Redmond, WA, USA).

α exacerbate post-ischemic brain damage, while TGF-β, IFN-β, and IL-10 exhibit neuroprotective properties [102, 103]. After brain ischemia, activated macrophages and microglial cells are the primary sources of TGF-β1, while astrocytes and neurons primarily produce TGF-β2 [104].

IL-1β, derived from peripheral and central sources, contributes to BBB disruption and brain parenchymal injury following ischemia [99,102,104]. Notably, *IL-1*β and *TNF-*α mRNA levels rise within 3 hours post-ischemia, with TNF-α protein levels peaking between 6 hours to 5 days after the ischemia event [99]. Immunostaining studies of IL-1β and IL-6 in astrocytes within the CA1 hippocampal region, a site highly susceptible to ischemic episodes, revealed significant loss of pyramidal neurons accompanied by extensive gliosis [4,22,63]. The intensity and frequency of astrocytic staining for IL-1β and IL-6 were highest on

day 14 post-ischemia and remained elevated through day 28. These findings suggest that astrocyte-derived IL-6 and IL-1β contribute to the neurodegeneration of CA1 pyramidal neurons.

Targeting pro-inflammatory cytokines has demonstrated therapeutic potential. For example, the inhibition of TNF-α using antibodies significantly reduced the ischemic area following focal brain ischemia [99]. Similarly, IL-10 is protective against ischemic brain damage, as evidenced by increased infarct size and worsened neurological deficits in *IL-10*-deficient mice following focal brain ischemia [105]. Administration of adenoviral vectors encoding the human *IL-10* gene into the lateral ventricle after ischemia significantly reduced infarct size [106]. Interferon-β has also shown neuroprotective properties, reducing infarct size and preventing the infiltration of inflammatory cells into brain tissue post-ischemia [107]. TGF-β1 exerts additional protective effects, including reducing infarct size, improving neurological outcomes, and promoting neurogenesis after focal brain ischemia [108]. These outcomes were further enhanced through adenovirus-mediated *TGF-β1* expression, which significantly decreased inflammatory responses and infarct size [109].

Amyloid and Tau Protein in Post-Ischemic Neuroinflammation

Post-ischemia brain injury is an incurable, chronic, and progressive neurodegenerative condition characterized by gradual neuronal death [4], cognitive decline, and eventual progression to dementia [36,46–49]. A hallmark of this condition is the slow and insidious accumulation of misfolded protein aggregates, notably amyloid plaques and neurofibrillary tangles [20,21,24,27]. These pathological features develop over time, especially in the hippocampus, disrupting its function, damaging neuronal networks, and impairing memory [36,46–49]. The underlying mechanisms of these changes following brain ischemia involve altered gene expression associated with amyloid precursor protein (APP) metabolism. Dysregulation of APP processing results in the accumulation of amyloid oligomers and the formation of amyloid plaques [20,22,30,44].

Microglial cells have been shown capable of binding soluble amyloid through cell surface receptors such as cluster of differentiation 36 (CD36), CD14, CD47, and Toll-like receptors [110]. This binding activates microglia, triggering the production of pro-inflammatory cytokines and chemokines [110]. Pro-inflammatory cytokines secreted by activated microglia, including TNF-α and IL-1β, are elevated in the ischemic brain [4,63]. These cytokines have been shown to increase β-secretase activity, further amplifying amyloid production [110].

The relationship between amyloidogenesis and neuroinflammation is well documented, with evidence linking increased β- and γ-secretase activity to enhanced amyloid deposition [110]. Studies using a lipopolysaccharide (LPS) model have demonstrated reduced microglial amyloid clearance, elevated amyloid levels, and persistent neuroinflammation associated with systemic inflammation [110]. Moreover, pro-inflammatory cytokines in the brain have been shown to elevate the APP levels in neurons [110]. Traditionally, amyloid accumulation and neuroinflammation have been considered independent pathological pathways. However, growing evidence supports a bidirectional interaction between these processes, driving post-ischemic neurodegeneration (Fig. 2) [4,22,110]. This interaction establishes a vicious cycle wherein amyloid accumulation activates glial cells, releasing inflammatory mediators that exacerbate amyloid deposition and perpetuate neuroinflammation [4,22,111,112].

Reactive astrocytes and microglia are frequently observed close to amyloid deposits in neurodegenerative diseases and post-ischemic neurodegeneration [19,111,112]. This phenomenon underscores the pro-inflammatory properties of amyloid, which, in combination with its neurotoxic effects, leads to sustained microglial activation, astrocyte proliferation, and the continuous release of pro-inflammatory factors (Fig. 2) [4,22]. These processes further amplify amyloid production, creating a self-perpetuating cycle of neuroinflammation and neurodegeneration [112].

Amyloid is a critical inducer of microglial and astrocytic activation and neuroinflammation, making it a fundamental and unifying factor in the progression of post-ischemic neurodegeneration (Fig. 2) [4,22]. In addition to its direct neurotoxic effects, amyloid-induced neuroinflammation promotes protein aggregation, a hallmark of neurodegenerative diseases, which also plays a pivotal role in the pathogenesis of post-ischemic neurodegeneration [20,22,111,112].

In addition to amyloid, the accumulation of hyperphosphorylated tau protein is a key contributor to post-ischemic brain neurodegeneration (Fig. 2) [24–27]. Tau protein is located in cells in brain blood vessels, regulating cerebral blood flow and maintaining the integrity of the BBB [39]. Following brain ischemia, pathological changes in tau protein disrupt the blood supply to various brain structures during recirculation, and also affect the state of the blood-brain barrier, leading to progressive neuronal neurodegeneration (Fig. 2).

Emerging evidence suggests that extracellular tau protein significantly contributes to neuroinflammation in neurodegenerative processes (Fig. 2) [39,113]. Tau protein accumulation has been shown to activate microglial cells in transgenic rats and mice [39,113]. It was also presented that in transgenic rats, neurofibrillary tangles are associated with the accumulation of reactive microglial cells and macrophages [39]. Additionally, truncated tau protein has been implicated in the transformation of microglial cells from a resting to a reactive state [39]. This

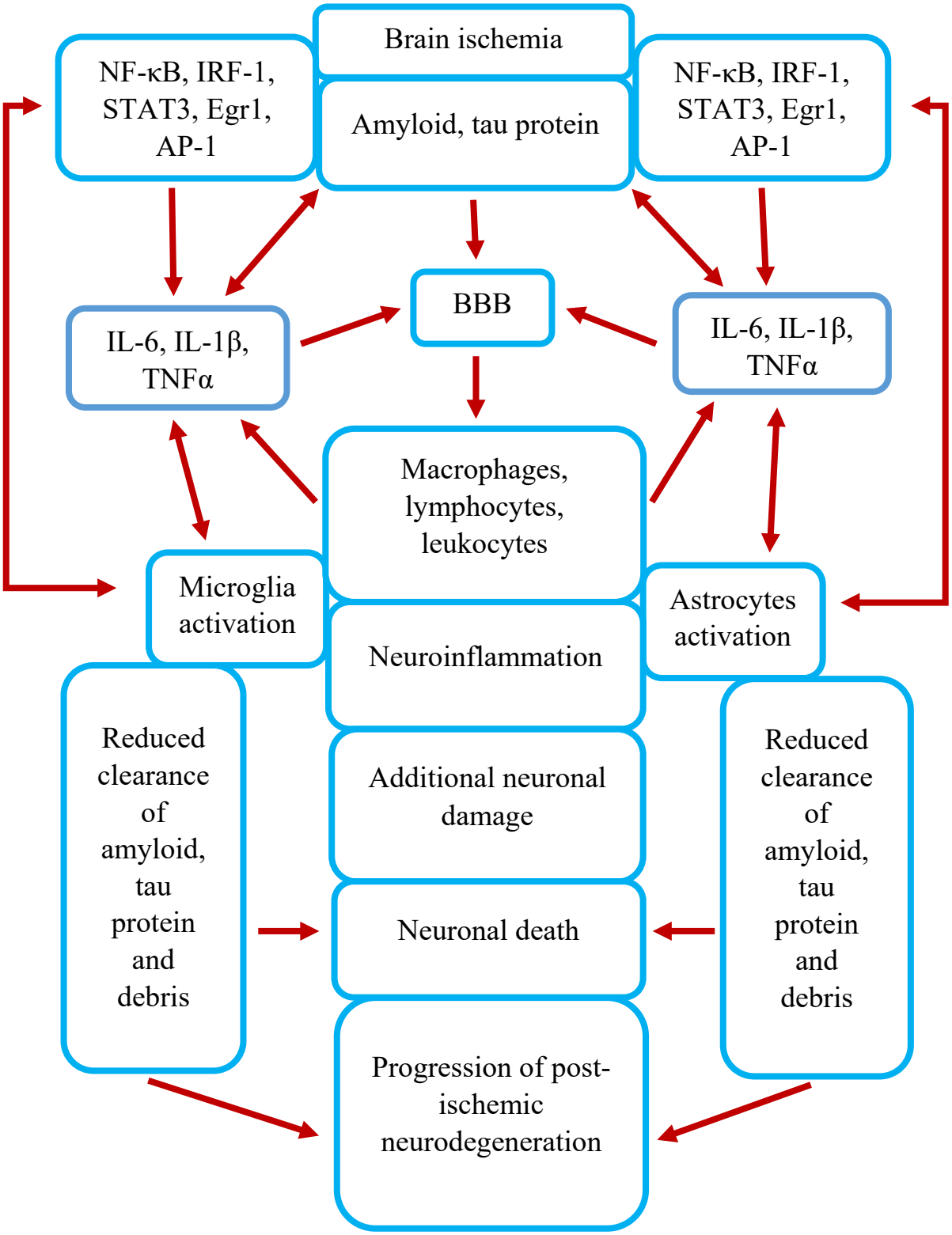

Fig. 2. Mechanisms of neuroinflammation following ischemic brain injury. The figure illustrates the roles of transcription factors (NF-κB, IRF-1, STAT3, Egrl, AP-1), pro-inflammatory cytokines (IL-6, IL-1β, TNF-α), the BBB, microglia, astrocytes, amyloid, tau protein, and peripheral immune cells in mediating post-ischemic neuroinflammation. NF-κB, nuclear factor kappa B; IRF-1, interferon regulatory factor-1; AP-1, activator protein 1; STAT3, signal transducer and activator of transcription; Egr1, early growth response-1. This figure was drawn using Microsoft Word (Microsoft Corporation, Redmond, WA, USA).

transformation triggers the release of nitric oxide (NO) and pro-inflammatory cytokines, including IL-6, TNF-α, IL-1β, and tissue inhibitor of metalloproteinase-1 (TIMP-1) in neuroglial cell cultures [39]. Specifically, stimulation of microglia cultures with truncated tau protein leads to significantly increased production of pro-inflammatory cytokines, underscoring the critical role of microglia in tau protein-induced neuroinflammation [39,113]. Furthermore, truncated tau protein elevates the mRNA expression levels of extracellular signal-regulated kinase 1 (*ERK1*), *p38*β, Jun N-terminal kinase (*JNK*), and transcription factors such as *NF-*κ*B* and *AP-1*. This cascade ultimately results in heightened mRNA expression of *NO*, *IL-1*β, *TNF-*α, and *IL-6* [39]. These findings identify truncated tau protein operates as a powerful innate inflammatory stimulus.

Under physiological conditions, amyloid, tau protein, and the secreted cytokines and chemokines facilitate the activation of microglia and astrocytes to efficiently clear misfolded protein aggregates and debris from degenerating neurons. However, as post-ischemic neurodegeneration progresses, cytokines, chemokines, and transcription factors produced in response to amyloid and tau protein aggregation impair the clearance mechanisms. This dysfunction leads to further amyloid and tau protein accumulation, exacerbating neuroinflammation and advancing the neurodegenerative process (Fig. 2) [4,111].

Cross-Talk between Amyloid and Tau Protein

Amyloid is proposed to initiate a cascade of events that result in tau protein dysfunction [114]. Amyloid promotes tau protein hyperphosphorylation, which destabilizes microtubules, induces neuroinflammation and oxidative stress, and impairs synaptic function [115]. Studies have demonstrated that exposure of neuronal cells to amyloid activates the p38 mitogen-activated protein kinase (p38 MAPK) signaling pathway, resulting in tau protein hyperphosphorylation [116–118]. Activation of the p38 MAPK pathway disrupts tau protein function, contributing to the generation of neurofibrillary tangles and microtubule instability. Although the exact mechanisms by which amyloid activates p38 MAPK action and induces tau protein hyperphosphorylation remain under investigation, it is hypothesized that amyloid activates intracellular signaling processes involving specific receptors and/or oxidative stress, ultimately leading to p38 MAPK activation. Once activated, p38 MAPK directly phosphorylates tau protein or triggers downstream kinases that promote tau protein hyperphosphorylation. Hyperphosphorylated tau protein loses its ability to bind and stabilize microtubules, leading to their destabilization and subsequent neuronal death [119,120].

The above processes drive the transformation of tau protein into neurofibrillary tangles, which compromise the neuronal network through neuronal loss and worsen cognitive decline. Additionally, tau protein has the capacity to propagate through brain tissue, spreading pathological processes from one region to another [121]. This interplay between amyloid and tau protein appears to have synergistic effects, amplifying neuronal death and prolonging neurodegenerative processes in the post-ischemic brain [122].

Cerebral Amyloid Angiopathy

Brain tissue relies on multiple mechanisms for the clearance of waste products, including amyloid and modified tau protein. These cleansing pathways often operate in parallel or synergistically to maintain brain homeostasis. However, impairment in amyloid clearance through one or multiple processes may lead to its accumulation in the brain, especially within cerebral vessels, leading to CAA [3,35,36]. Amyloid deposition in cerebral vessels occurs gradually. Initially, amyloid accumulates in the tunica media and adventitia of the vessels, causing vascular smooth muscle cell damage and eventual cell death [35]. As deposition advances, the tunica media is entirely replaced by amyloid, leading to endothelial cell death and the breakdown of BBB [123]. This pathological process decreases vascular reactivity, reduces vessel diameter, and triggers chronic vascular inflammation [35,124]. Consequently, vascular dysfunction is associated with secondary brain ischemia, exacerbated neuroinflammation, parenchymal deposition of soluble amyloid, formation of neurofibrillary tangles and amyloid plaques, and the progression of neurodegeneration following ischemic events [4,20,24,27,35].

Amyloid transport across endothelial cell membranes after ischemia is regulated by LRP1, which removes amyloid from brain tissue into the systemic circulation [33]. LRP1-mediated endocytosis controls cellular amyloid uptake by binding amyloid directly or via co-receptors or ligands. Conversely, the RAGE, located on the luminal side of endothelial cells in the BBB, facilitates the transport of amyloid from systemic circulation into brain tissue [33,125]. RAGE is a receptor located on the luminal side of endothelial cells of the blood-brain barrier. RAGE-facilitated transport of amyloid through the blood-brain barrier leads to amyloid accumulation in the brain, and further stimulates neuroinflammatory processes [4,125]. The pro-inflammatory effects of the amyloid-RAGE interactions have been demonstrated in numerous animal and cell models [33,123,125,126].

Amyloid, Tau Protein, and Neuroglial Cells

An increasing body of research investigates the relationship between amyloid and neuroglial cells to determine whether inflammation triggers or sustains amyloid dyshomeostasis. *In vivo* and *in vitro* studies have identified neuroinflammation as a significant pathogenic factor in post-ischemic neurodegeneration [2,4,53,65]. In the ischemic brain, there is communication between different amyloid forms and receptors located on microglial cells and astrocytes, initiating an innate immune response. Amy-

loid accumulation in the brain tissue activates a mechanism known as microglia "priming", rendering them more susceptible to secondary neuroinflammation [127]. Consequently, activated microglia become a distinguishing neuropathological element of brain ischemia, surrounding amyloid deposits to form protective barriers and aiding amyloid clearance from the brain [128–130]. However, when microglial function is impaired, pathological substances such as amyloid and tau protein accumulate, intensifying neurodegeneration [130,131].

Amyloid aggregates, including protofibrils, oligomers, and fibrils, promote neuroinflammation [132–134]. Microglial cells, equipped with receptors capable of binding these aggregates, initiate neuroinflammation that contributes to disease progression. Neurotrophic factor TGF-β1 plays a central role in microglial-mediated amyloid clearance by enhancing their phagocytic activity, thereby reducing amyloid levels in the brain tissue and exerting protective effects against neurodegeneration [31,135,136]. Conversely, TNF-α plays a pro-inflammatory role, and elevated TNF-α levels in neurodegenerative brains contribute to chronic neuroinflammation and progressive neuronal damage [4,137–140].

It should be noted that the immune answer and neuroinflammation in neurodegeneration involve cumulated interactions between different elements and cell kinds [141–143]. Microglial activity is modulated by the triggering receptor expressed on myeloid cells 2 (TREM2), which plays a pivotal role in responding to amyloid plaques, a hallmark of post-ischemic brain neurodegeneration [20,21]. Upon recognizing amyloid plaques, TREM2 activation induces the release of inflammatory cytokines. This response is part of the innate immune response against amyloid deposition. The regulation of microglial cell function via the TREM2 and the maintenance of a balanced neuroinflammatory response are critical areas of research for understanding the underlying mechanisms of neurodegeneration [144–146].

In addition to microglial cells, activated astrocytes play a pivotal role in amyloid plaque dynamics. Astrocytes encircle amyloid plaques and reduce the burden of amyloid plaques [31,147]. Upon interaction with amyloid plaques, astrocytes release pro-inflammatory mediators, sustaining a chronic inflammatory environment within the brain tissue [147–149]. As integral components of ischemic brain response to amyloid accumulation in post-ischemic neurodegeneration, astrocytes influence amyloid metabolism through cellular mechanisms, including phagocytosis [4]. This neuroglia can promote and alleviate amyloid neurotoxicity, playing a multifaceted role in post-ischemic brain injury progression [150–152]. Astrocytes contribute to amyloid deposition primarily due to impaired clearance mechanisms. Under physiological conditions, astrocytes express amyloid-degrading enzymes such as neprilysin and α-secretase. However, in post-ischemic neurodegeneration, the expression and activity of these enzymes are often disrupted, resulting in reduced amyloid degradation and subsequent deposition in the intra- and extracellular space [30,37,153]. Furthermore, astrocytes internalize amyloid via the LRP1, but this pathway becomes less efficient in post-ischemic neurodegeneration, further influencing amyloid accumulation [33,154].

Reactive astrocytes that release pro-inflammatory cytokines create a long-term neuroinflammatory state that disrupts physiological amyloid clearance and normal brain function [152,155–157]. Additionally, these astrocytes produce ROS, contributing to oxidative stress and further impairing the metabolism of amyloid precursor protein into amyloid [158,159]. Astrocytes also promote the development of amyloid plaques through scar formation, which acts as a physical barrier that effectively stops the clearance of amyloid from brain tissue [61,160]. Moreover, astrocytes secrete apolipoprotein E (ApoE) after cerebral ischemia, which accelerates amyloid aggregation, stabilizes amyloid plaques, and aggravates amyloid toxicity [161,162].

The interplay between astrocytes and microglial cells is central to the process of amyloid production, accumulation, and the accompanying neuroinflammation in post-ischemic neurodegeneration [4,161]. Astrocytes and microglial cells communicate extensively through chemokines and cytokines, modulating the activity of each other [163]. For example, astrocytes release chemokine CC chemokine ligand 2 (CCL2), which attracts microglial cells to sites of amyloid accumulation. Astrocyte-derived cytokines, such as IL-1β and TNF-α, can activate microglial cells, driving them into a reactive state. Once activated, microglia release their cytokines, establishing a feedback loop that intensifies inflammation. This bidirectional signaling supports a chronic neuroinflammatory environment, which impedes amyloid clearance and stimulates its accumulation [164–166].

Recruitment of Inflammatory Cells in Post-Ischemic Brain

It is established that brain ischemia activates the immune system within damaged brain regions. This neuroinflammatory response represents an intrinsic brain reaction and involves complex interactions between infiltrating immune cells from the bloodstream and resident immune cells in the affected areas. The role of non-neuronal cells in brain neurodegeneration following ischemia has been the subject of numerous studies. Additionally, it is crucial to consider the functional "neurovascular unit", a collective system comprising neuronal, neuroglial, and vascular cells, as a central entity in the pathophysiological response to ischemia.

Initially, brain ischemia triggers the activation of neuroglial cells within the brain tissue. Subsequently, leukocytes infiltrate the brain parenchyma, followed by mono-

cytes and other immune cells. This immune cell recruitment contributes to ischemic brain neurodegeneration, which is characterized by cerebral edema, progressive neuronal cell death, and brain atrophy. Numerous clinical and experimental investigations have demonstrated the participation of non-neuronal cells in the progression of post-ischemic neurodegeneration [4,93,167]. Neuroinflammation following cerebral ischemia engages various cell types, including neuroglial cells, leukocytes, lymphocytes, macrophages, and monocytes [2,4,53,65]. The specific role of these cells in neurodegeneration is stage-dependent, with their effects being beneficial or detrimental depending on whether they act during the acute or chronic phase of post-ischemia [2,4]. To develop effective therapeutic strategies, it is imperative to identify the cell types that contribute most significantly to post-ischemic neurodegeneration and to determine the time and mechanisms of their involvement.

Astrocytes

Astrocytes are vital in maintaining normal brain function and undergoing significant phenotypic changes post-ischemia. These glial cells are a key component in the structural integrity of the brain, BBB function, and homeostatic regulation. Astrocytes maintain water balance, secrete neurotrophic mediators, clear excess neurotransmitters and cellular debris, remove metabolic waste, and transport nutrients to neurons. Under physiological conditions, astrocytes take up excess glutamate from the extracellular space, converting it into glutamine for neuronal reuse. However, during post-ischemic brain injury, astrocytic damage impairs their glutamate uptake capacity and exacerbates excitotoxicity [2,17].

Cytokines from neuronal cells and neuroglia drive gliosis and glial scar formation during post-ischemic neurodegeneration [59–61,146]. Following ischemia, dysfunction of the sodium-potassium pump in astrocytes causes cell swelling, leading to brain edema. This edema further reduces cerebral blood flow during the reperfusion period, worsening tissue injury [168,169]. In rat models of local brain ischemia, astrocyte activation occurs prominently in the injury core within 4–24 hours, peaks around day 4, and persists for up to 28 days [170]. Similarly, in global brain ischemia models, astrocyte activation peaks at day 14 and remains elevated for 28 days in hippocampal regions [63]. In long-term studies, rats surviving 2 years after global ischemia demonstrated robust astrocyte activation in the CA1 and CA3 regions of the hippocampus, dentate gyrus, somatosensory and motor cortex, thalamus, and striatum [4].

After 3 days following transient complete cerebral ischemia, hippocampal astrocytes show increased expression of glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS), and nicotinamide adenine dinucleotide phosphate (NADPH) diaphorase [28]. An autopsy study of individuals who succumbed seven days after stroke revealed elevated IL-15 levels in astrocytes [2]. The experimental study has highlighted the dual role of IL-15 in ischemic pathology. Knockdown of *IL-15* in astrocytes reduced infarct size in reversible focal brain ischemia models [32], while transgenic mice overexpressing *IL-15* revealed enlarged infarct size and more severe neurological deficits [2]. Furthermore, GFAP and vimentin are crucial for astrocytic responses to ischemic injury. Double-knockout mice lacking GFAP presented cortical hypoperfusion in the brain and larger infarct sizes after focal ischemia, underscoring the protective role of these intermediate filaments in maintaining astrocytic integrity during ischemic events [171].

Microglial Cells

Microglial cells, comprising approximately 20% of the glial cell population in the brain, undergo significant phenotypic changes following ischemia [2]. Upon activation, microglia acquire macrophage-like functions, including the ability to eliminate pathogens and clear cellular debris. Microglial cells are activated during ischemic events, undergoing morphological and behavioral changes [167,172–174]. In animal models of reversible local brain ischemia, microglial activation has been observed in the brain cortex of the ischemic hemisphere [175]. Activated microglia migrate toward the injury site and form close associations with the neuronal cells through a process called “capping”. This process facilitates the early recognition and rapid phagocytic removal of neuronal cell debris following cell death [176,177].

Microglial activation begins within minutes of an ischemic episode and increases over the following days, peaking around the 10th day post-ischemic brain injury [178]. In models of global cerebral ischemia, microglial cells activation has been identified in regions such as the hippocampus, striatum, lateral dorsal nuclei of the thalamus, and the subventricular zone, with inflammatory processes in these areas persisting for up to one year post-ischemia [4]. Interestingly, this prolonged activation was also associated with increased neurogenesis markers and neuroblast migration in the subventricular zone [4]. In another study, significant microglial cell activation was observed in the CA1 and CA3 hippocampal regions and motor cortex of rats even two years after ischemia [22].

Upon activation, microglia release cytokines and matrix metalloproteinases, which increase the leakage of BBB, promoting early leukocyte infiltration from the systemic circulation into the ischemic brain tissue. Once activated, microglia can adopt two primary phenotypes: the pro-inflammatory (M1) phenotype, which secretes cytokines such as IL-6, TNF-α, IL-1β, and nitric oxide; and the anti-inflammatory (M2) phenotype, which produces neuroprotective factors such as IL-10 and IL-4 and supports tissue repair [179]. The M2 phenotype is crucial in mitigating ischemic damage and promoting recovery. Recent studies highlight the critical roles of microglia in ischemic pathology [4,22,63]. For example, depletion of mi-

croglial cells the dual colony-stimulating factor 1 inhibitor PLX3397 worsened infarct size and neurological outcomes, as well as increased leukocyte infiltration, astrocytic inflammatory mediator release, and neuronal death following reversible cerebral ischemia [69]. These findings suggest that microglia play a protective role by modulating astrocytic inflammatory responses post-ischemia [69]. Additionally, microglia secrete neurotrophic mediators that stimulate plasticity and neurogenesis, further underscoring their multifaceted role in the post-ischemic brain [65]. These findings demonstrate that different microglia subsets perform distinct functions after ischemic brain injury.

Macrophages

Blood-borne macrophages play a pivotal role in the development of neuroinflammation after brain ischemia. Activated macrophages can be detected in brain tissue as early as two hours post-ischemia [4]. Between 22 and 46 hours post-ischemia, systemic circulation-derived and brain-resident macrophages infiltrate ischemic brain regions and remain evident for up to one week in animals [4]. Another study noted the presence of macrophages in the brain four days post-ischemia, peaking around seven days before gradually declining [4]. These findings align with evidence that macrophages heavily infiltrate the injured brain within 3–7 days post-ischemia, a period coinciding with the chronic phase of post-ischemic neurodegeneration [4].

Lymphocytes

T lymphocytes contribute to the late stages of ischemia-induced neurodegeneration. After focal brain ischemia, infiltrating lymphocytes encircle the ischemic area, with their numbers increasing by day three, peaking around one week post-ischemia, and subsequently declining [180]. Depletion of $CD4^+$ lymphocytes in animal models exacerbated neuronal death and neurological dysfunction seven days after acute focal cerebral ischemia [181]. Similarly, the absence of $\gamma\delta$ T lymphocytes or administration of antibodies targeting their receptors reduced infarct size in ischemic models [182].

Another investigation identified an increase in $CD4^+CD28$null lymphocytes in individuals who survived cerebral ischemia or succumbed to it [183]. Clinical investigations have also shown a significant elevation in peripheral $CD4^+$ lymphocytes and $CD4^+CD28$null lymphocytes in patients after acute stroke [56]. Additionally, increased expression of killer cell *immunoglobulin-like receptor* genes was observed in patients following local ischemic infarction, likely contributing to the amplification of neuroinflammation during the acute phase post-stroke [184]. T lymphocytes infiltrating the ischemic brain can persist for extended periods. Studies have shown that these cells remain in the brain for years after acute stroke [185]. Within one month of the local ischemic event, a notable increase in various T lymphocyte subtypes was observed in the peri-infarct area [185]. Immunohistochemical analyses of brain tissues one year post-ischemia revealed that T helper ($CD4^+$) cells predominantly localized to the hippocampus and striatum [4].

Leukocytes

Leukocytosis serves as a biomarker of neuroinflammation in response to brain ischemia. Elevated white blood cell counts are predictors of ischemic stroke severity, poorer neurological outcomes, and higher mortality rates [186]. Neutrophils are the primary leucocytes to infiltrate the post-ischemic brain. Once in the brain, they are recruited to ischemic regions via chemokines, where they increase secondary injury by releasing pro-inflammatory factors [187]. These factors damage endothelial membranes and the basal lamina, leading to leakage of BBB and the development of brain edema following ischemia [34]. This pathological process unfolds rapidly, beginning within 30 minutes post-ischemia, peaking within three days, and gradually resolving over the next five days [100,188,189]. Within 15 minutes of ischemia, neutrophils and macrophages activate molecules that allow interaction with endothelial cells. By 6–8 hours post-ischemia, neutrophils accumulate within vessel walls and surrounding the blood vessels, eventually spreading throughout brain tissue [190–192]. Monocytes follow neutrophil infiltration, migrating to the post-ischemic region with peak activity between days three and seven post-ischemia [189]. Infiltrating neutrophils can persist in the ischemic zones for over a month, though their presence is often overshadowed after three days due to macrophages and microglial activation at the site of neuroinflammation [193]. Neutrophils contribute to cerebral microcirculatory dysfunction through mechanical obstruction and the secretion of vasoconstrictor substances, pro-inflammatory factors, and hydrolytic enzymes, leading to the "no reflow phenomenon" post-ischemia [124,194–196]. This phenomenon results in vasoconstriction and accumulation of platelets within and around cerebral vessels [54,124].

The extent of post-ischemic infarction and the severity of neurological deficits correlates strongly with elevated neutrophil levels and activity, which significantly increase the risk of mortality [189,197]. In contrast to neutrophils, lymphocyte levels decrease following cerebral ischemia, leading to an elevated neutrophil-to-lymphocyte ratio (NLR), and high NLR is directly associated with larger infarct volumes and increased patient mortality [197]. Finally, infiltrating leukocytes further intensify neuronal injury in the ischemic penumbra and infarct core by releasing pro-inflammatory factors, intensifying the damage caused by ischemia [198].

Innovations and Future Directions

Post-ischemic neuroinflammation, while essential for the removal of amyloid, tau protein, and cellular debris to prepare the brain for repair and plasticity, can be deleterious when prolonged. Chronic neuroinflammation exacerbates secondary brain damage, impairs tissue repair, and contributes to post-ischemic neurodegeneration. Following cerebral ischemia, activated endothelial cells release molecules that promote the adhesion and transmigration of peripheral immune cells across the BBB into the brain parenchyma. Furthermore, the immune response in ischemic tissue is initiated by immune effectors present in the brain, such as glial cells. In addition, amyloid and tau protein are involved in the above phenomena, which enhance the process of neuroinflammation after ischemia. This represents a novel finding, highlighting the interplay between amyloid-tau protein pathways and neuroinflammation in promoting the pathology of post-ischemic neurodegeneration [10,22,41]. The resulting cascade of events activates transcription factors, including AP-1, IRFs, NF-κB, and STATs, which regulate gene expression, cytokine production, neuronal survival and death, and neurological outcomes. However, the activity of these factors in the brain is modulated by their interactions with each other, accessibility to DNA binding sites, and the influence of ncRNAs and other epigenetic regulators. ncRNAs, including miRNAs, lncRNAs, and circRNAs, have emerged as essential regulators of gene expression in post-ischemic neuroinflammation.

Biochemical modifications of RNA, collectively referred to as the epitranscriptome, impact gene expression and protein synthesis following ischemia, thereby influencing neuroinflammation. For example, N6-methyladenosine, the most common RNA modification, affects RNA stability, splicing, biogenesis, and translation while modulating neuroinflammation by influencing microglial and astrocytic polarization. Targeting the epitranscriptome holds promise for regulating neuroinflammatory responses, clearing amyloid and tau protein, promoting tissue repair, and improving neurological outcomes following cerebral ischemia.

In addition, differential DNA methylation, hydroxymethylation, and histone modification are pivotal in regulating the expression of genes involved in post-ischemic neuroinflammation and injury. Modulating transcription factors, ncRNAs, and epitranscriptomic or epigenetic pathways offer potential therapeutic targets for post-ischemic neurodegeneration. Epigenetic reprogramming represents an innovative approach to mitigate ischemic damage. Activators and/or inhibitors of transcription factors, epigenetic modulators, and RNA-based drugs should also be considered.

Efforts to develop RNA-based therapies have shown promise over the past decade. For instance, targeting ncRNAs such as miRNA, miR-7, and lncRNA FosDT has demonstrated improved outcomes in experimental models, offering a promising direction for future treatments [65,70]. However, RNA-based therapies remain in their infancy, facing delivery, specificity, and tolerability challenges. Moreover, further experimental studies are needed to elucidate the role of RNA modification, RNA processing, RNA-RNA, and RNA-protein interactions in post-ischemic neuroinflammation, paving the way for novel therapeutic strategies.

Epigenetic DNA and epitranscriptomic RNA modifications respond to ischemia and thus influence functional outcomes. Precise manipulation of these processes will be critical in the development of effective therapies. In summary, the interplay between transcription factors, ncRNAs, and epitranscriptomic and epigenetic changes underlies post-ischemic neuroinflammation, contributing to secondary ischemia-induced brain injury.

Considering the pivotal role of stem cells in brain function, the stimulation or modulation of their behavior presents a promising avenue for intervention in the brain-immune axis following ischemia. Although consensus on the exact mechanisms through which stem cells or their signaling pathways influence neuroimmunology remains elusive, advancing research in this segment could yield innovative therapies and improve post-ischemic therapeutic monitoring. Promoting the integration of stem cell research into brain ischemia projects is imperative to mitigate neuroinflammation and prevent the progression of neurodegeneration and dementia. Gaining deeper insights into the underlying mechanisms governing stem cell behavior and neuroinflammatory responses will be crucial for identifying novel therapeutic targets and developing strategies to enhance post-ischemic neurological recovery and functional outcomes.

Conclusions

Neuroinflammation is a key driver of post-ischemic brain neurodegeneration. Chronic neuroinflammation increases neuronal damage, promotes the formation of amyloid plaques and tau protein dysfunction, and contributes to cognitive impairment and dementia development. Targeting neuroinflammation offers a compelling opportunity for medical intervention. However, translating findings from preclinical animals into effective clinical therapies has been challenging [199].

Current strategies focus on modulating the inflammatory response to shift immune and glial cells towards an anti-inflammatory phenotype, thereby promoting the survival of ischemic neurons [62,65]. This approach shows promise as a therapeutic avenue for mitigating ischemia-induced damage. A comprehensive understanding of the role of neuroinflammation in experimental brain ischemia is critical for identifying new treatment strategies. Such ad-

vancements will enhance our ability to mitigate neuroinflammation and also alleviate the global burden of post-ischemic brain neurodegeneration.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization, methodology, investigation, formal analysis, writing, editing, visualization, supervision: RP. The author contributed significantly to editorial changes of important content. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The author declares no conflict of interest.

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