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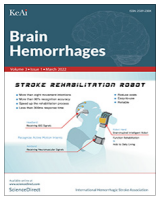

Review article

The function of astrocytes in cerebral infarction and potential therapeutic approaches

Ozal Beylerli [a], Ilgiz Gareev [a], Aferin Beilerli [b], Tatiana Ilyasova [c], Huaizhang Shi [d], Albert Sufianov [e,f,*]

[a] Central Research Laboratory, Bashkir State Medical University, Ufa, Republic of Bashkortostan, 3 Lenin Street, 450008, Russia
[b] Department of Obstetrics and Gynecology, Tyumen State Medical University, 54 Odesskaya Street, 625023 Tyumen, Russia
[c] Department of Internal Diseases, Bashkir State Medical University, Ufa, Republic of Bashkortostan, 450008, Russia
[d] Department of Neurosurgery, First Affiliated Hospital of Harbin Medical University, Harbin, Heilongjiang, China
[e] Educational and Scientific Institute of Neurosurgery, Peoples' Friendship University of Russia (RUDN University), Moscow, Russia
[f] Department of Neurosurgery, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

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ABSTRACT

Astrocytes, the most prevalent cells in the central nervous system, significantly contribute to the normal physiological functions of the brain. Following cerebral infarction, these astrocytes undergo activation, transforming into reactive astrocytes, ultimately leading to the formation of glial scars. These scars play a crucial role in the intricate process of brain injury. Given their involvement in neuroprotection, regulation of scarring, facilitation of nerve regeneration, preservation of the blood–brain barrier, promotion of angiogenesis, and modulation of the immune response post-cerebral infarction, researchers have proposed an array of therapeutic strategies directed towards targeting astrocytes. This review delves into the beneficial functions of reactive astrocytes in the context of cerebral infarction, exploring corresponding treatment strategies that capitalize on these insights.

Introduction

Cerebral infarction, commonly known as ischemic stroke, exerts its impact on various cells within the brain, including neurons and astrocytes, and the intricate signaling interactions among these cells significantly influence the progression of the disease. Astrocytes, being pivotal components in the central nervous system, contribute to various physiological functions such as the regulation of central nervous system development, maintenance of neural network homeostasis, neurovascular coupling, and synaptic transmission [1]. They engage in close interactions with all parenchymal cells. Upon encountering diverse injuries to the central nervous system, such as trauma or ischemia, astrocytes undergo activation, transforming into reactive astrocytes characterized by hypertrophy. This activation process involves the upregulation of glial fibrillary acidic protein, vimentin, and nestin, influenced by signaling pathways like ErbB and Notch1-STAT3-ETB [2–3]. Li et al. identified two distinct reactive astrocyte types induced by ischemic injury: the neurotoxic type A1 and the protective type A2 [4]. Type A1 astrocytes exhibit a significant upregulation of classical complement cascade genes associated with synapse damage, whereas type A2 astrocytes enhance the expression of numerous neurotrophic factors.

An accumulating body of research underscores the active role of reactive astrocytes in promoting neuroprotection, facilitating nerve regeneration, maintaining the blood–brain barrier, fostering angiogenesis, and regulating the immune response. This article provides a comprehensive review of the beneficial contributions of reactive astrocytes in the context of cerebral infarction, along with the corresponding therapeutic strategies.

Neuroprotective effects and responses of reactive astrocytes

Following cerebral infarction, astrocytes demonstrate the capability to provide neuroprotective effects by engaging in metabolic support, acting as antioxidants, and secreting substances with neuroprotective properties. These multifaceted actions contribute to enhancing the survival rates of neurons (Fig. 1) [5].

Metabolic support

In the study by Liu et al., it was revealed that during episodes of transient regional ischemia, astrocytes undergo a fascinating

* Corresponding author at: Department of Neurosurgery, Sechenov First Moscow State Medical University (Sechenov University), Moscow 119992, Russia.
E-mail address: sufianov@gmail.com (A. Sufianov).

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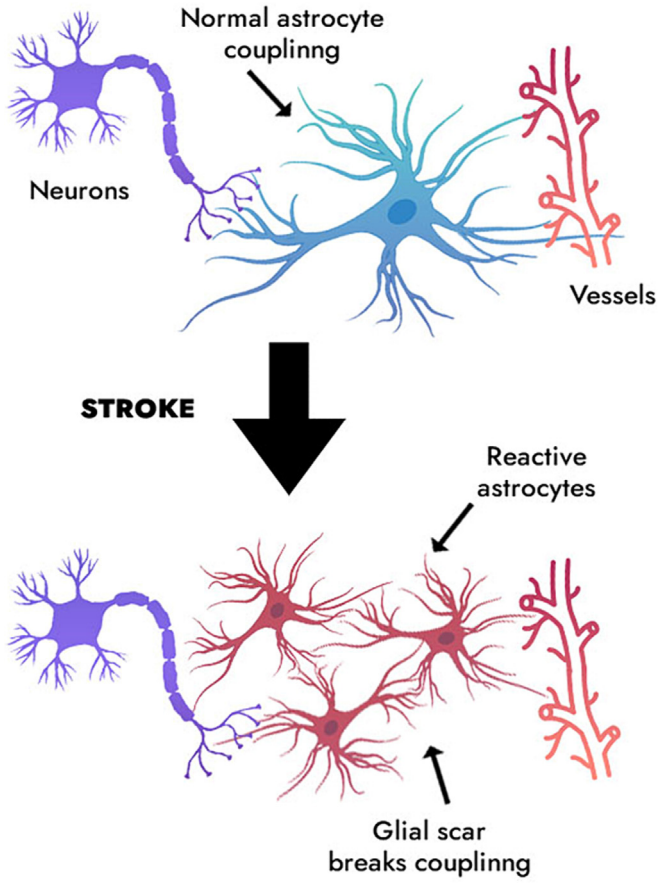

Fig. 1. Excessive activation of astrocytes near the stroke site disrupts the connection between neurons and blood vessels in unaffected areas: In a healthy state, astrocytes form supportive connections between blood vessels and neurons (depicted by long black arrows). However, after a stroke (illustrated by blue arrows), reactive astrocytes retract these connections, leading to a breakdown in coupling (indicated by short black arrows) and the formation of a glial scar. A novel approach to rescuing the brain involves targeting astrocytes to reduce the formation of the glial scar while maintaining their supportive role in providing nutrients and support to neurons. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

response by releasing mitochondria into the extracellular environment [6]. This intriguing phenomenon is orchestrated by the mediation of calcium ions, creating a cascade of events that sees extracellular mitochondria entering neighboring neurons, ultimately enhancing neuronal survival. The intricate signaling pathway involved in this process is governed by the CD38/cyclic ADP ribose pathway. Additionally, the activation of neurons plays a crucial role in the dilation of nearby capillaries and the augmentation of energy supply through astrocytes, with calcium ions again serving as key mediators [7]. Moreover, the neuroprotective capabilities of astrocytes were underscored by their ability to uptake excessive glutamate present in the synaptic cleft through specialized glutamate transporters [8]. Therefore, ensuring the maintenance or enhancement of these glutamate transporters within astrocytes emerges as a critical strategy to counteract the excitotoxic effects triggered by glutamate. In the research conducted by Lu et al., the focus shifted towards the manipulation of gap junctions, revealing that inhibitors such as octanol and gampuric acid could upregulate the expression of glutamate aspartate transporters on astrocyte membranes [9]. This upregulation, in turn, significantly amplifies the capacity for glutamate transport, providing a robust protective mechanism for neurons. Furthermore, astrocytes were found to express a high concentration of ATP receptors (P2 receptors). Under conditions of ischemia and hypoxia, the extracellular ATP levels in astrocytes surge, contributing to excitotoxicity through the activation of ATP receptors and subsequent glutamate release. Employing lower concentrations of P2 receptor antagonists emerges as an effective strategy to prevent neuronal damage in such scenarios. Notably, a combined antagonistic approach targeting both ATP receptors and glutamate receptors has demonstrated remarkable efficacy in preventing the acute ischemic demise of both nerve cells and astrocytes [10].

Anti-oxidation

During episodes of cerebral infarction, the heightened oxidative metabolism characterized by an abundance of reactive oxygen species (ROS) and elevated levels of unsaturated fatty acids, leading to lipid peroxidation, renders the brain particularly vulnerable to oxidative stress. In response, reactive astrocytes emerge as key players in exerting antioxidant effects through the release of ascorbic acid or the upregulation of kynurulineic acid [11–12]. In a study by Kaarniranta et al., the therapeutic potential of the AMPK-PGC-1α signaling pathway in mitigating oxidative damage was explored [13]. Activation of this pathway, facilitated by the ATP analogue accadicin (AICAR), was shown to regulate glutathione production in astrocytes. This regulation not only prevented oxidative damage but also demonstrated promising therapeutic effects in the context of ischemia–reperfusion injury in retinal cells. The findings suggest that targeting the AMPK-PGC-1α signaling pathway could represent a novel and effective strategy for managing reactive astrocytes in the treatment of cerebral infarction. Furthermore, prion proteins were identified as valuable components in aiding nerve cells in coping with the oxidative stress, hypoxia, and ischemia that ensue post-cerebral infarction. Under hypoxic or ischemic conditions, astrocytes release exosomes enriched with high levels of prion proteins. In a remarkable protective role, these prion proteins contribute to shielding neurons from the adverse effects, as neurons absorb the released exosomes [14]. This intricate mechanism highlights the potential therapeutic implications of leveraging prion proteins to mitigate the consequences of cerebral infarction-induced stress on nerve cells.

Secrete neuroprotective substances

Reactive astrocytes exhibit a multifaceted capability in producing various neurotrophic factors, including fundamental players like basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF), which play pivotal protective roles in preserving neuronal health [15]. Notably, bFGF stands out for its ability to modulate the expression of glial fibrillary acidic protein and other markers, thereby mitigating the activation of astrocytes. This intricate modulation extends to the upstream TLR4/NFκB signaling pathway, resulting in a reduction of pro-inflammatory cytokines such as IL-6 and TNF-α. The overall outcome is a neuroprotective effect exerted by bFGF [16]. VEGF, recognized as a significant therapeutic target, is subject to modulation by dexmedetomidine. This modulation proves instrumental in reducing the apoptosis rate of neurons in the hippocampus by promoting VEGF expression in astrocytes, ultimately alleviating hypoxia, and ischemic injury across the entire brain [17]. Furthermore, research by Kuo et al. highlights the role of epoxy hydrolase enzymes in augmenting VEGF secretion, where VEGF, in turn, acts as a potent reducer of neuronal apoptosis by activating VEGF receptor [18]. Recent investigations into mesencephalic astrocyte-derived neurotrophic factor (MANF) have uncovered its remarkable potential in diminishing neuronal cell death. This effect is achieved through the upregulation of heat shock protein 70 expression [19]. Dynamic assessments utilizing MRI technology have demonstrated the

therapeutic efficacy of early MANF administration post-ischemia/reperfusion injury. This intervention showcases notable benefits, including the reduction of cell mortality, improvement in neurological function, diminished cerebral infarction volume, and alleviation of brain tissue damage [20]. The evolving understanding of these intricate astrocyte-mediated processes underscores the potential for targeted therapeutic strategies in the realm of cerebral infarction.

In clinical applications, reactive astrocytes have emerged as a promising avenue for the treatment of cerebral infarction. Notably, the utilization of astrocyte-mediated cell therapy has demonstrated its potential to enhance the secretion of neuroprotective factors, thereby contributing to improved neurological recovery following cerebral infarction [8]. Furthermore, the transplantation of bone marrow stromal cells has been shown to induce astrocytes to increase the production of neurotrophic factors. This, in turn, leads to a reduction in the number of apoptotic neurons and facilitates enhanced regeneration of peripheral nerves and vasculature in ischemic regions. Combining simvastatin with bone marrow stromal cells takes this approach a step further, synergistically inducing astrocytes to upregulate the expression of critical factors such as stromal cell-derived factor 1α, vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and glial cell-derived neurotrophic factor. This combined intervention significantly enhances neuronal function compared to bone marrow stromal cell transplantation alone, showcasing a promising avenue for comprehensive therapeutic enhancement [21]. Innovative strategies, such as the combination of sodium feruloate and butenylphthalide from Angelica sinensis with bone marrow mesenchymal stem cells, have demonstrated remarkable potential in reducing nerve damage post-cerebral infarction. This combination not only mitigates neural injury but also amplifies the expression of crucial factors like VEGF and BDNF within astrocytes. This novel approach provides a fresh perspective for advancing the treatment of cerebral infarction, offering a potential breakthrough in therapeutic efficacy [22]. The exploration of these multifaceted interventions underscores the evolving landscape of cerebral infarction treatment, with astrocyte-based strategies holding significant promise in clinical applications.

Reactive astrocytes regulate scar formation

Following cerebral infarction, reactive astrocytes situated around the infarct region, along with their secreted extracellular matrix components—especially chondroitin sulfate—tend to combine with microglia, forming scar tissue [23]. While a small portion of this scarring gradually diminishes over time, more severe cases often result in irreversible scarring. Functioning as both physical and chemical barriers, glial scars play a crucial role in localizing the damaged area, thereby exerting a protective effect. However, research by Zbesko et al. [24] has shed light on the fact that certain detrimental molecules within the damaged area can still permeate the glial scar. This penetration contributes to the emergence of neurodegeneration in the later stages of cerebral infarction. Moreover, unlike scarring observed in other tissues, scars formed within the central nervous system undergo a significant "softening" process, hindering nerve regeneration. This phenomenon is closely associated with the expression levels of glial intermediate filaments, including glial fibrillary acidic protein and vimentin, as well as extracellular matrix components like laminin and type IV collagen [25]. The unique characteristics of scarring within the central nervous system underscore its complex role, serving as both a protective barrier and a potential impediment to effective nerve regeneration after cerebral infarction.

In the context of treating cerebral infarction, achieving a time-course-dependent balance in the regulation of glial scars becomes crucial. Studies indicate that post-cerebral infarction, the Rho/ROCK signaling pathway undergoes regulation, promoting the activation of reactive astrocytes and the formation of scars, consequently inhibiting the regeneration of damaged neurons [26]. Therefore, intervening in this pathway holds the potential to mitigate the impact of scar-related molecules on nerve regeneration. Li et al. discovered that apoptosis signal-regulating kinase 1 (ASK1) plays a pivotal role in astrocyte activation and scarring [27]. Down-regulating ASK1 levels in astrocytes diminishes the activity of the p38 pathway, reducing glial scar formation in the chronic phase and favoring neuronal recovery. Kezuka et al. observed that the deletion of the transcription factor Atf6α leads to impaired astrocyte activation and a decrease in glial scarring [28]. The role of RIP1 kinase is also noteworthy in the formation of glial scars post-cerebral infarction, and inhibiting RIP1 kinase activity proves effective in reducing glial scarring, thereby facilitating neurological function recovery [29]. EphA4 emerges as a primary regulator of gliosis following cerebral infarction. The activation of Eph/ephrin signaling in astrocytes post-cerebral infarction is age-related, with juvenile animals exhibiting relatively less scarring and more accessible nerve regeneration compared to adult animals [29]. Notably, ephrin-A1 intervention has the potential to delay glial scarring, inducing an "infantile-like" glial scar formation in adult animals. This alteration promotes nerve regeneration and contributes to functional recovery after cerebral infarction [30]. The nuanced understanding of these molecular mechanisms opens avenues for targeted interventions aimed at optimizing the balance between glial scar formation and nerve regeneration in the treatment of cerebral infarction.

Reactive astrocytes promote nerve regeneration

Following cerebral infarction, astrocytes exhibit a remarkable capacity to facilitate nerve regeneration through various pathways. Research conducted by Zhang et al. has unveiled that post-cerebral infarction, astrocytes express transcription factors such as Sox, Neurog-2, NeuroD1, Ascl1, Lmx1B, Nurr1, Oct4, Sox2, or Nanog [31]. These transcription factors play a pivotal role in promoting the transformation of astrocytes into neuroblasts and neurons, subsequently differentiating to form new neurons under specific conditions [32]. This transformative ability holds promising implications for replacing damaged neurons and enhancing neural regeneration. Furthermore, insights from studies by Mo et al. [33] highlight the significance of the Notch signaling pathway in astrocytes after cerebral infarction. Attenuating this pathway is deemed essential for promoting the regeneration of astrocytes into neurons in the striatum. Notably, even in the absence of cerebral infarction, blocking the Notch signaling pathway induces astrocytes in the striatum and medial cortex to enter the neurogenic program. This indicates the pivotal role of the Notch signaling pathway in regulating astrocytic transformation into neurons. PAX6, as identified in studies, plays a critical role in the conversion of astrocytes into neurons [33]. Elevated levels of miR-365 post-cerebral infarction is found to inhibit the transformation of astrocytes into neurons by targeting PAX6. This inhibition aggravates nerve damage, emphasizing the potential therapeutic approach of antagonizing miR-365 to promote PAX6-mediated nerve regeneration and alleviate neuronal damage. The intricate interplay between transcription factors, signaling pathways, and regulatory molecules within astrocytes presents a multifaceted landscape for potential interventions in promoting nerve regeneration after cerebral infarction.

Reactive astrocytes maintain brain barrier integrity and promote angiogenesis

After a cerebral infarction, reactive astrocytes play a crucial role in preserving the integrity of the blood–brain barrier through diverse mechanisms. In the initial phase of ischemia, there is an upregulation in the expression of angiopoietin-3 in reactive astrocytes. This upregulation helps in maintaining the blood–brain barrier by modulating vascular endothelial growth factor (VEGF) to reduce permeability in endothelial cells [34]. Additionally, astrocytes have the capability to release sonic hedgehog (Shh), which interacts with receptors on vascular endothelial cells. This interaction activates the Hedgehog signaling pathway, contributing to the formation of the blood–brain barrier. Furthermore, Shh upregulates the expression of tight junction proteins in vascular endothelial cells, thereby reinforcing the integrity of the blood–brain barrier [35–36]. Moreover, findings by Chu et al. reveal that Apelin-13 can enhance the expression of aquaporin 4 on astrocyte membranes [37]. This enhancement, in turn, contributes to the maintenance of the blood–brain barrier's integrity. The multifaceted nature of these astrocyte-mediated mechanisms underscores their significance in preserving the structural integrity of the blood–brain barrier after cerebral infarction. The orchestration of these pathways showcases the potential for targeted therapeutic interventions to support the vascular and endothelial integrity critical for optimal brain function post-infarction.

During the late ischemic stage, there is an upregulation of vascular endothelial growth factor (VEGF) expression in reactive astrocytes, contributing to cerebral angiogenesis and facilitating improved neurological recovery. Simultaneously, the release of sonic hedgehog (Shh) by reactive astrocytes serves to activate the RhoA/ROCK signaling pathway in brain microvascular endothelial cells, actively participating in the process of angiogenesis [38]. Angiogenesis not only enhances blood perfusion in ischemic cerebral tissues but also supports the release of neurotrophic factors from brain parenchymal cells, including astrocytes. This, in turn, promotes nerve regeneration, facilitating brain remodeling and ultimately contributing to long-term neurological recovery after cerebral infarction. Thus, promoting angiogenesis emerges as a pivotal strategy in the comprehensive treatment of cerebral infarction. Studies indicate that administering ecdysone following regional cerebral ischemia in rats has the potential to promote astrocyte activation and angiogenesis, ultimately leading to an improvement in neurological function [39]. Additionally, omega-3 polyunsaturated fatty acids have been identified as agents that can stimulate endothelial cell proliferation. Through the induction of astrocytes to synthesize angiopoietin 2, these fatty acids contribute to the enhancement of endogenous angiogenesis. This process, in turn, promotes vascular regeneration and aids in the recovery of the blood–brain barrier after cerebral infarction [40]. These innovative approaches underscore the importance of promoting angiogenesis as a key therapeutic strategy in the multifaceted treatment of cerebral infarction, offering potential avenues for enhancing long-term neurological outcomes (Fig. 2).

Immunomodulatory effects of reactive astrocytes

Reactive astrocytes play a crucial role in limiting the inflammatory response post-cerebral infarction through various mechanisms, including the production of glial scarring, and signaling via pathways such as transforming growth factor-beta (TGF-β) [41]. Following cerebral infarction, there is an increase in TGF-β expression in reactive astrocytes. TGF-β can be activated by thrombospondin-1 (TSP-1), which acts on corresponding receptors to restrict the infiltration and activation of immune cells. This action ultimately leads to a reduction in neuroinflammation and neuronal damage in the periinfarct cortex. Importantly, this process forms a positive feedback loop, with TGF-β signaling stimulating the upregulation of both TGF-β itself and the activator TSP-1 [41].

Despite the potential therapeutic benefits of modulating the immune response in cerebral infarction being relatively underexplored, studies by Lee et al. shed light on the significance of interleukin-15 (IL-15) expression in astrocytes post-cerebral infarction [42]. Upregulation of IL-15 in astrocytes is associated with exacerbation of brain tissue damage mediated by CD8 T cells and natural killer (NK) cells' immune responses. This finding underscores the potential of IL-15 as a promising therapeutic target in the management of cerebral infarction [42]. Expanding research in this area could lead to novel therapeutic strategies aimed at modulating immune responses to mitigate neuronal damage and enhance recovery following cerebral infarction.

Reactive astrocytes after intracerebral hemorrhage

Activated microglia, the primary immune cells of the CNS, play a significant role in inducing astrocyte activation, thereby influencing their functional phenotype [43]. The fate of activated astrocytes, whether neuroprotective or detrimental to neuronal function, is determined by signals received from microglia. Conversely, astrocytes are also actively involved in neuroinflammatory processes, secreting both proinflammatory (e.g., IL-1β, IL-6) and anti-inflammatory cytokines that can modulate microglial activation and function [44]. Under conditions of neuroinflammation, the proinflammatory state induced by M1 microglia triggers the transformation of astrocytes into a deleterious A1 phenotype. A1 astrocytes upregulate the expression of proinflammatory cytokines, chemokines, and growth factors, leading to aberrant neurotransmitter synthesis and release, synaptic damage, and disruption of homeostatic functions. These impairments include failure to stimulate neuronal growth and survival, as well as the release of neurotoxic substances, ultimately leading to neuronal apoptosis and damage to surrounding oligodendrocytes [45]. Conversely, there is a hypothetical A2 astrocyte condition that occurs under ischemic conditions. A2 astrocytes exhibit activation of neurotrophic factors and secretion of proteins that promote synaptogenesis, suggesting a neuroprotective role in ischemic injury [46]. This dichotomy in astrocyte function highlights their dynamic and context-dependent nature of neuroinflammatory responses.

Astrocytes are increasingly recognized for their pivotal role in the aftermath of intracerebral hemorrhage (ICH), where their aggregation in the perihematomal region occurs within a narrow time frame of 1 to 3 days post-ictus [47]. Within this critical window, reactive A1 astrocytes emerge as central players in the neuroinflammatory cascade, wielding profound influence over the ensuing pathophysiological events. One notable mechanism driving astrocytic activation stems from the presence of hemoglobin within the brain parenchyma, catalyzing a cascade of oxidative stress responses that culminate in the upregulation of matrix metalloproteinase-9 (MMP-9) within astrocytes [48]. This MMP-9 induction is particularly significant, as it contributes to the breakdown of the blood–brain barrier (BBB), exacerbating cerebral edema formation and intensifying neuronal injury in the aftermath of ICH [49]. Furthermore, the extravasation of blood into the brain parenchyma brings forth another potent mediator of astrocytic activation: thrombin. As thrombin infiltrates the extracellular matrix, it triggers the activation of protease-activated receptor-1 (PAR-1), predominantly localized at perisynaptic endfeet of astrocytes [50]. The ensuing activation of PAR-1 instigates a cascade of events, precipitating rapid synaptic remodeling and prompting

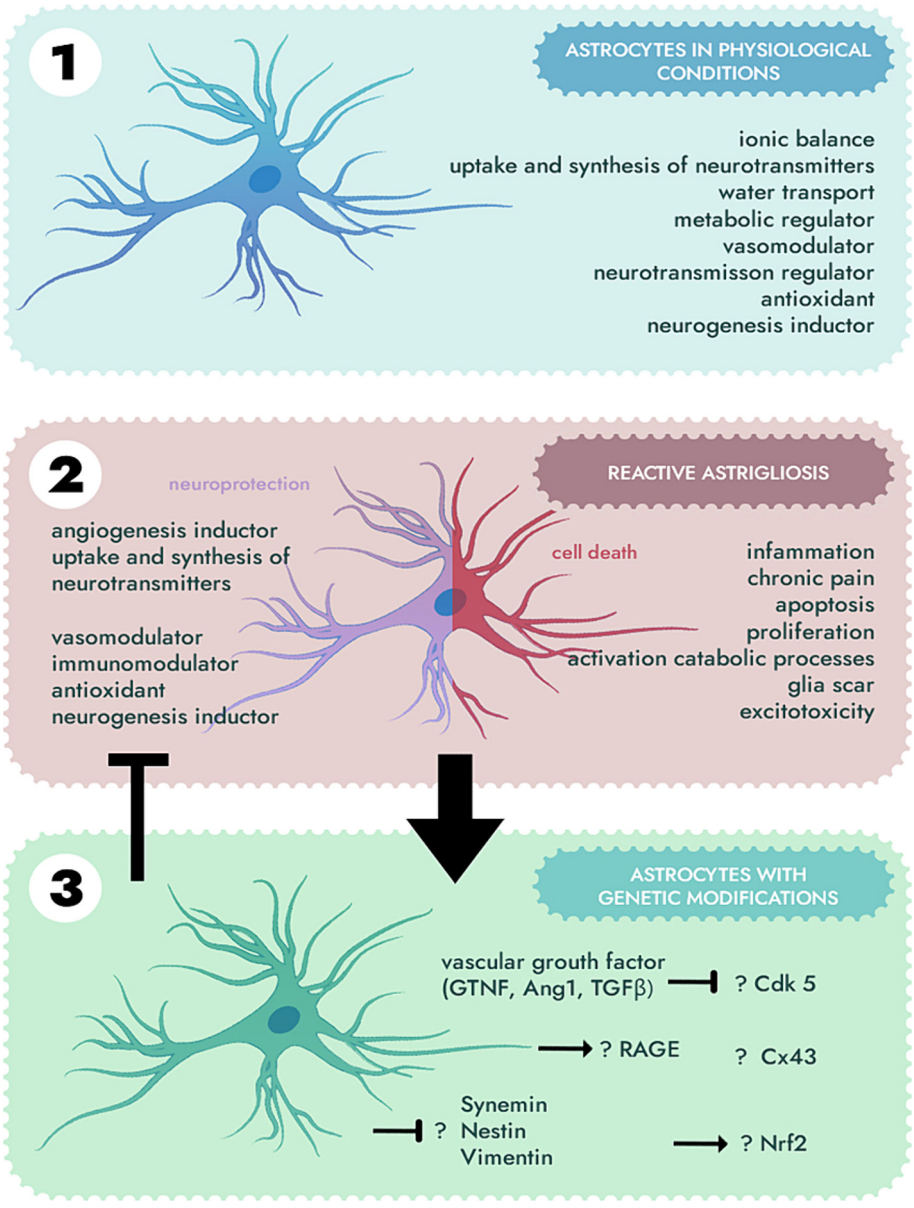

Fig. 2. The role of astrocytes varies depending on the microenvironment. In (A), astrocytes function to maintain the nervous tissue's homeostasis under normal physiological conditions. In (B), reactive astrocytosis is observed, where the role of astrocytes is debated; they may contribute to cell death or exhibit pro-neuroprotective properties, potentially in a context-dependent manner. In (C), astrocytes with genetically reduced expression of certain upregulated genes could be preserved as a source of neuroprotection to support neuronal survival. However, the mechanism by which they sustain this neuroprotective state for an extended period remains unknown.

the migration of astrocytic processes away from excitatory glutamatergic synapses [51]. This synaptic rearrangement disrupts the delicate balance of neurotransmission, resulting in a reduction of glutamatergic receptors and impeding long-term synaptic plasticity—a phenomenon that may underpin the cognitive deficits often observed post-ICH [51]. Emerging evidence underscores the potential therapeutic relevance of targeting astrocytic activity in the management of ICH-related pathology. Experimental evidence suggests that suppression of astrocytic reactivity holds promise in mitigating hematoma expansion, preserving BBB integrity, and ultimately ameliorating neurological outcomes in preclinical models of ICH [52]. Nonetheless, despite these compelling findings, therapeutic avenues centered on astrocyte modulation remain largely uncharted territory, necessitating further exploration and validation in translational studies. Unraveling the intricate molecular mechanisms governing astrocyte-mediated neuroinflammation in the context of ICH represents a pressing imperative in the quest for effective therapeutic interventions. By elucidating the multifaceted roles of astrocytes in ICH pathophysiology and delineating specific molecular targets amenable to therapeutic manipulation, we stand poised to usher in a new era of precision medicine aimed at alleviating the burden of ICH and improving outcomes for afflicted individuals.

Conclusion

Following a cerebral infarction, the pivotal role of astrocytes in neuronal protection and recovery unfolds across a multifaceted landscape. These dynamic cells extend critical support through metabolic assistance, antioxidant functions, secretion of neuroprotective substances, scarring formation, maintenance of the blood–brain barrier, and modulation of immune responses. Furthermore, astrocytes serve as potent facilitators of neuronal function recovery

by orchestrating nerve regeneration and angiogenesis. However, it's imperative to acknowledge that astrocytes may also impede neuronal regeneration and exacerbate brain damage through immune responses or scarring. Therefore, there is a pressing imperative to explore strategies that preserve and amplify the beneficial effects of reactive astrocytes while concurrently mitigating and eliminating adverse outcomes. While substantial strides have been made in elucidating the morphology and proliferation dynamics of astrocytes post-ischemia, further inquiry into the nuanced changes in gene expression among astrocytes across different stages of cerebral infarction remains paramount. Additionally, investigating the unique responses of reactive astrocytes in specific populations such as diabetic and elderly patients hold significant clinical relevance and may unveil tailored treatment modalities. In summation, delving into the intricate dynamics of post-ischemic reactive astrocytes and their associated signaling pathways offers a promising avenue for identifying novel therapeutic targets in the clinical management of cerebral infarction. This pursuit merits sustained and comprehensive investigation to drive advancements in therapeutic interventions and ultimately enhance outcomes for individuals affected by cerebral infarction [42,53].

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CRediT authorship contribution statement

Ozal Beylerli: Funding acquisition, Conceptualization. **Ilgiz Gareev:** Writing – review & editing. **Aferin Beilerli:** Data curation, Writing – original draft. **Tatiana Ilyasova:** Formal analysis, Writing – original draft. **Huaizhang Shi:** Supervision, Data curation. **Albert Sufianov:** Supervision.

Declaration of competing interest

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

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