

The role of astrocyte metabolic reprogramming in ischemic stroke (Review)

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Abstract. Ischemic stroke, a leading cause of disability and mortality worldwide, is characterized by the sudden loss of blood flow in specific area of the brain. Intravenous thrombolysis with recombinant tissue plasminogen activator is the only approved pharmacological treatment for acute ischemic stroke; however, the aforementioned treatment has significant clinical limitations, thus there is an urgent need for the development of novel mechanisms and therapeutic strategies for ischemic stroke. Astrocytes, abundant and versatile cells in the central nervous system, offer crucial support to neurons nutritionally, structurally and physically. They also contribute to blood-brain barrier formation and regulate neuronal extracellular ion concentrations. Accumulated evidence has revealed the involvement of astrocytes in the regulation of host neurotransmitter metabolism, immune response and tissue repair, and different metabolic characteristics of astrocytes can contribute to the process and development of ischemic stroke, suggesting that targeted regulation of astrocyte metabolic reprogramming may contribute to the treatment and prognosis of ischemic stroke. In the present review, the current understanding of the multifaceted mechanisms of astrocyte metabolic reprogramming in ischemic stroke, along with its regulatory factors and pathways, as well as the strategies

to promote its polarization balance, which hold promise for astrocyte immunometabolism-targeted therapies in the treatment of ischemic stroke, were summarized.

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1. Introduction

Stroke, a prevalent cerebrovascular disease, is characterized by high incidence, recurrence, morbidity and mortality rates, ranking as the second leading cause of disability and death globally (1). It primarily encompasses two major categories: Ischemic stroke and hemorrhagic stroke, with ischemic stroke being more prevalent, accounting for ~60-80% of all stroke cases (2). Ischemic stroke, also known as cerebral infarction, is a clinical syndrome that arises from cerebral ischemia and hypoxia due to stenosis or occlusion of cerebral vessels, leading to tissue damage or necrosis and subsequent rapid onset of corresponding neurological deficits. In the pursuit of therapeutic strategies, it has gradually become apparent that non-neuronal cells within the central nervous system (CNS), particularly astrocytes, play a pivotal role in the pathophysiological processes of ischemic stroke.

As one of the most abundant and versatile cell types in the CNS, astrocytes not only provide essential nutritional support, structural scaffolding, and physical protection to neurons, but also contribute to the formation of the blood-brain barrier (BBB), regulate potassium ion concentration in the neuronal extracellular environment, and maintain the stability of the

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neuronal milieu. Furthermore, astrocytes play critical roles in neurotransmitter metabolism, immune responses, pathological processes and tissue repair, underscoring their indispensable function in safeguarding the health and functionality of the nervous system (3). Metabolic reprogramming refers to the mechanism by which cells alter their metabolic patterns to facilitate growth, proliferation and adaptation to environmental changes in response to energy and biosynthetic demands. As a crucial strategy for cells to cope with external environmental alterations, metabolic reprogramming encompasses, but is not limited to, the regulation of multiple metabolic pathways such as glycolysis, oxidative phosphorylation, fatty acid metabolism and amino acid metabolism (4). During ischemic stroke, astrocytes swiftly respond by initiating a series of intricate metabolic reprogramming processes to adapt to the extreme ischemic and hypoxic conditions. However, the specific roles and underlying mechanisms of astrocytes in ischemic stroke remain to be further systematically investigated.

Therefore, the current understanding of the roles and mechanisms of astrocyte metabolic reprogramming in ischemic stroke have been summarized, delving into their molecular mechanisms, functional alterations and interactions with other cell types. By consolidating existing literature, it is aimed to uncover the central role of astrocyte metabolic reprogramming in the pathophysiological processes of ischemic stroke, thereby providing a theoretical basis for the development of novel therapeutic strategies.

2. The physiological function of astrocyte

The CNS is composed of a large number of non-neuronal cells called glia, with astrocytes being the primary type of glial cells that are ubiquitous throughout the entire CNS and interact with a variety of cells.

Formation and maintenance of the BBB. The BBB, situated between the blood and brain tissues, serves as a highly selective permeable interface that safeguards the brain from harmful substances. It is primarily composed of brain microvascular endothelial cells, astrocytes, pericytes and the basal lamina, playing a crucial role in maintaining normal CNS function and internal environmental homeostasis (5). Structurally, the BBB can be divided into three layers: The inner layer, consisting of brain microvascular endothelial cells held together by tight and adherens junctions, serves as the core component that restricts the passage of blood-borne substances into the brain. The middle layer is composed of the basal lamina formed by the extracellular matrix and pericytes embedded within it. The outer layer comprises astrocyte foot processes adhering to the microvascular basal lamina (6).

Astrocytes, with their unique morphology and functions, play a pivotal role in the formation and maintenance of BBB integrity, being essential cells that contribute to the physiological homeostasis of the CNS (7). Once the BBB is formed, mature astrocytes regulate and maintain the barrier. These cells extend numerous processes from their cell bodies, which tightly envelop cerebral capillaries, providing support and separation for neuronal cells. This intimate contact not only reinforces the structural stability of the cerebral capillary walls but also participates in the formation of the basal lamina through the

secretion of matrix proteins by the astrocytes, further enhancing the barrier function of the BBB (8). Additionally, astrocytes are crucial for water and potassium homeostasis in the CNS, as they control the exchange of water and certain solutes through abundant expression of aquaporin-4 (9).

Ion transport and neuromodulation. Astrocytes are the primary cell type responsible for regulating brain homeostasis, encompassing the maintenance of ionic homeostasis and neuronal regulation. Potassium and sodium ions are crucial for neuronal electrical activity, and the stability of their concentration is essential for maintaining the normal function of neurons. Potassium ions predominantly reside within cells, whereas a large inward electrochemical gradient of sodium ions serves to generate action potentials. Upon neuronal excitation, a significant concentration of potassium ions is released into the extracellular space, leading to a local increase in potassium ion concentration. Astrocytes, through the expression of inward rectifier potassium channels such as Kir4.1, can rapidly uptake these excess potassium ions and distribute them to adjacent astrocytes via gap junctions, thereby maintaining a stable potassium ion concentration around neurons. This spatial buffering of potassium ions helps prevent neuronal hyper-excitation and damage (10,11). Sodium ions play a pivotal role in regulating the intracellular pH of astrocytes. While the activation of the sodium-potassium ATPase in response to elevated extracellular potassium levels may decrease intracellular sodium ions, the co-transport of neurotransmitters such as glutamate with sodium ions leads to an increase in sodium ions within astrocytes, thereby modulating downstream metabolic pathways (12).

Astrocytes also play a vital role in neuromodulation within the CNS. They are capable of sensing and responding to neurotransmitters and other signaling molecules released by neurons, and influence neuronal excitability and synaptic plasticity through the release of their own neuroactive substances (13). Furthermore, astrocytes form intricate network structures through gap junctions among themselves and with neurons, enabling them to synchronize their activities and transmit information. This signal transduction and neuromodulation function contribute to maintaining the homeostasis and adaptability of the nervous system (14).

Nutrition and support. Neurotrophic factors are proteins that play a crucial role in the development, survival and apoptosis of neurons. Under normal physiological conditions, astrocytes can release various neurotrophic factors, such as brain-derived neurotrophic factor and nerve growth factor. These neurotrophic factors are essential for the growth, development, survival and functional maintenance of neurons. They facilitate the growth of neuronal axons and dendrites, enhance synaptic connections between neurons, and thereby increase the complexity and functionality of neural networks.

3. Relationship between astrocyte and ischemic stroke

In response to the damage of CNS, neurodegenerative diseases, or other infectious diseases, the genes, morphology, and functions of astrocytes undergo rapid changes, and these reactions are collectively referred to as astrocyte reactivity (15). In

recent years, with the intensifying exploration into the intricate functional diversity of astrocytes, researchers have uncovered their ability to differentiate into distinct functional phenotypes under various pathological conditions, notably the A1 and A2 subtypes. After the onset of stroke, astrocytes are activated and release pro-inflammatory or anti-inflammatory factors, leading to a complex neuroinflammatory cascade reaction, which has a dual effect on neuroinflammation after ischemic stroke (16). These subtypes exhibit profoundly different mechanisms of action during the pathological process of ischemic stroke, significantly impacting disease progression, outcome and neural repair.

Through genetic profiling of reactive astrocytes in mouse models of ischemic stroke and neuroinflammation, Zamanian *et al* (17) demonstrated that reactive astrocytes can be induced by different types of insults to adopt either an A1 or A2 phenotype. Specifically, ischemic injury triggers the emergence of so-called trophic A2 astrocytes, whereas inflammatory insults induce the more neurotoxic A1 astrocytes (17). Liddelow *et al* (18) further elucidated that ischemia and neuroinflammation can prompt M1 microglia to secrete cytokines, which in turn induce astrocytes to transform into the neurotoxic A1 phenotype. These A1 astrocytes typically display reduced normal functions and significantly upregulate numerous genes previously shown to be detrimental to synapses. Additionally, A1 astrocytes may secrete neurotoxins, contributing to the death of neurons and oligodendrocytes (18). By contrast, A2 astrocytes appear to upregulate neurotrophic factors or anti-inflammatory genes that promote neuronal survival and growth, and support repair functions, such as TGF- β , which can promote synaptogenesis and exhibit neuroprotective effects against cerebral ischemic injury (19). To ascertain the relative roles of A1/A2 astrocytes in CNS diseases, intervention with the critical intracellular and extracellular signaling pathways that drive the polarization of astrocytes into either beneficial or detrimental phenotypes is necessary. Research strongly indicates that the Stat3-mediated signaling pathway may be crucial for A2 astrocytes to proliferate and support neuronal regeneration in acute injury models, while the NF- κ B signaling pathway may underlie the induction of A1 astrocytes (20,21). While the simplistic A1/A2 dichotomy does not fully capture the broad spectrum of astrocyte phenotypes, it provides a valuable framework for understanding astrocyte reactivity in various CNS diseases.

Glial fibrillary acidic protein (GFAP) is a type of intermediate filament protein specifically expressed in astrocytes within the central and peripheral nervous systems. It plays a crucial role in maintaining the morphology, structure and function of astrocytes, while also participating in their reactive and proliferative processes. In the event of ischemic stroke, oxygen levels in the brain tissue decrease, leading to damage to surrounding cellular tissues. Consequently, astrocytes become activated and release GFAP, which subsequently enters the bloodstream through the compromised BBB. In patients with acute ischemic stroke, serum GFAP levels exhibit a moderate positive correlation with the degree of neurological deficit and brain injury as assessed by the National Institutes of Health Stroke Scale (NIHSS) score. Elevated serum GFAP levels are associated with higher NIHSS scores, indicating more severe neurological deficits (22). Furthermore, high serum

GFAP levels serve as a marker for poor neurological prognosis in patients with ischemic stroke, enabling the prediction of neurological outcomes one-year post-stroke (23). The overview of astrocyte related to ischemic stroke is demonstrated in Table I (16,17,24-33).

4. The role of astrocyte in ischemic stroke

A close connection between astrocytes and the pathogenesis of CNS diseases has been recently suggested (34). Alzheimer's disease (AD) is the most prevalent progressive neurodegenerative disorder, characterized clinically by comprehensive dementia manifestations such as memory impairment, aphasia, apraxia and agnosia. It constitutes the primary cause of dementia in the elderly. In AD, astrocytes undergo sustained activation and release significant levels of inflammatory cytokines and neurotoxic substances. This process triggers or exacerbates the hyperphosphorylation pathology of tau protein and amyloid- β protein, thereby facilitating the formation of amyloid plaques and neurofibrillary tangles, as well as contributing to neuronal death and the decline of cognitive function (35-37). Furthermore, the distinct pathological phenotypes they develop may exert crucial influences on the progression of AD (38). Parkinson's disease (PD), the second most common neurodegenerative disorder, is primarily characterized by heterogeneous classic motor features associated with Lewy bodies and the loss of dopaminergic neurons in the substantia nigra. Additionally, it exhibits clinically significant non-motor features. Research has demonstrated that patients with PD exhibit abnormal proliferation and increased senescence of astrocytes in the brain, which participate in inflammatory responses within the substantia nigra, thereby promoting disease progression (39-41). Multiple sclerosis (MS) is a neurological autoimmune disorder primarily characterized by inflammatory demyelination in the white matter of the CNS, ultimately leading to progressive physical disability in patients. Astrocytes play a pivotal role in MS by modulating immune responses and inflammatory reactions, thereby influencing the severity and progression rate of the disease (42-44). Furthermore, ischemic stroke, as another prevalent disorder of the CNS, is also intimately associated with abnormal functions of astrocytes.

Dual roles of glial scar formation. In the pathological process of ischemic stroke, astrocytes exhibit diverse roles in the CNS, with a notable response being the formation of glial scars. During the acute phase of the disease, this process aids in sealing the injury site, remodeling tissues, and controlling local immune responses. However, during the recovery phase, it may restrict the recovery of neurological function.

At the onset of the disease, damaged cells produce and release cytokines, triggering reactive proliferation of astrocytes that migrate towards the injury area to form glial scars (45). The formation of glial scars helps limit the spread of inflammatory reactions, reduces further tissue damage, and provides a physical barrier around the injured area to prevent the infiltration of harmful substances, thus maintaining CNS homeostasis and creating conditions for subsequent repair processes. However, during neural recovery, excessive formation and persistence of glial scars become physical barriers that hinder neuronal synaptic reconnection. Glial scars are

Table I. Overview of astrocyte related to ischemic stroke.

First author/s year	Object of study	Cohort description	Sample type	Outcome characteristics	Microbiota analysis approach	(Refs.)
Zamanian <i>et al.</i> , 2012	Mice from the transgenic mouse line	Transient ischemia was induced by occluding the MCAO	Brain tissues	Reactive astrocyte phenotype strongly depended on the type of inducing injury	Affymetrix GeneChip arrays	(17)
Song <i>et al.</i> , 2020	SD rats	Rats subjected to MCAO/R	Brain tissues	Increase the glutamate disposal by astrocytes and protect neurons from excitotoxicity in response to I/R insults	Decrease the oxidative stress mediated by SDH	(24)
Shi <i>et al.</i> , 2021	MEGF10-flox founder mice	The surgery of MCAO	Brain tissues	Reactive microgliosis and astrogliosis hinder brain repair by engulfing synapses	Immunostaining, fluorescence <i>in situ</i> hybridization, western blotting, quantitative PCR, Golgi-Cox staining	(25)
Williamson <i>et al.</i> , 2021	C57BL/6 mice	Photothrombotic infarcts were created in forelimb motor cortex	Vasculature	Reactive astrocytes are crucial for vascular repair and remodeling after ischemic stroke in mice	<i>In vivo</i> two-photon imaging	(26)
Ma <i>et al.</i> , 2022	C57BL/6 mice	tMCAO model	Brain tissues	Significant differences in the expression of genes and metabolic pathways in the astrocytes at 12 and 24 h after ischemic stroke	Single-cell sequencing	(27)
Denecke <i>et al.</i> , 2022	Cell	Rat astrocytes were cultured in rat astrocyte basal medium containing growth serum	Cells	When subjected to hypoxia, and nutrient starvation, astrocytes within the penumbral region generated in the microdevice exhibited long-lasting, significantly altered signaling capacity	polystyrene-based microfluidic device	(28)
Wang <i>et al.</i> , 2023	C57BL/6 mice	reversible right MCAO surgery	Brain tissues	Astrocyte-derived KLF4 has a critical role in regulating the activation of A1/A2 reactive astrocytes following AIS	Immunofluorescent staining, antibodies, RNA extraction, reverse-transcription, western blot analysis and quantitative PCR	(16)
Lochhead <i>et al.</i> , 2023	SD rats	MCAO surgery	Brain tissues	Astrocyte activation may contribute to or be in response to neurodegeneration following MCAO	Confocal microscopy strategy, TTC Staining, Laser Doppler	(29)
Zhou <i>et al.</i> , 2024	C57BL/6J mice	Transient focal cerebral ischemia was induced by right MCAO	Brain tissues	Astrocytic LRP1 regulated the transfer of healthy mitochondria from astrocytes into neurons and protected against brain ischemia-reperfusion injury	Blood Flow, immunofluorescence staining Extracellular mitochondria collection	(30)

Table I. Continued.

First author/s year	Object of study	Cohort description	Sample type	Outcome characteristics	Microbiota analysis approach	(Refs.)
Scott <i>et al.</i> , 2024	C57/Bl6J mice	Stroke-injured or uninjured controls	Cells	The acquisition of different astrocytic states after stroke that are influenced by time and proximity to the stroke lesion site	tDISCO alongside two high-throughput platforms for spatial (Visium) and single-cell transcriptomics (10X Chromium)	(31)
Wang <i>et al.</i> , 2024	C57BL/6J mice	The barrel cortex ischemic stroke	Brain tissues	A2 astrocytes and A1 astrocytes are enriched in the acute and chronic phases of ischemic stroke respectively	Flow cytometry, Total RNA extraction, RNA-Seq, quantitative PCR, Vibrissae-Evoked Forelimb-Placing Test, Immunofluorescence	(32)
Bormann <i>et al.</i> , 2024	Wistar rats and mice	Cerebral ischemia was induced by intraluminal occlusion of the MCAO	Brain tissues	Astrocytes belong to one of the most transcriptionally perturbed populations and exhibit infarct and subtype specific molecular features.	Single nucleus RNA sequencing, immunofluorescence	(33)

MCAO/R, middle cerebral artery occlusion/reperfusion.

primarily composed of proliferated astrocytes and the extracellular matrix proteins they secrete, forming a dense barrier that severely impedes neuronal regeneration and axonal extension. Additionally, glial scars may further inhibit the neural repair process by releasing inhibitory factors, leading to limited restoration of neurological function (46).

Mediation of inflammatory response and oxidative stress. Astrocytes actively participate in the regulation of inflammatory responses and oxidative stress in ischemic stroke. Inflammatory response, while being one of the primary causes of CNS injury, can exacerbate brain tissue damage when excessive. Following ischemic stroke, astrocytes are activated into reactive astrocytes, releasing a surge of inflammatory factors and inducing the production of neurotoxic mediators. This inflammatory response leads to the disruption of the BBB and the upregulation of cellular adhesion molecules, increasing the permeability of the BBB and allowing immune cells to infiltrate into brain tissues. This fact further triggers inflammatory reactions such as cerebral edema, ultimately resulting in neuronal cell death (47). Concurrently, astrocytes can also release anti-inflammatory neuroprotective factors, attracting immune cells, clearing necrotic tissues, and promoting tissue repair, thereby inhibiting inflammation (48).

During ischemic stroke, the severe inflammatory response caused by ischemia and hypoxia in brain tissue induces the production of reactive oxygen species (ROS) and other oxidative products in large concentrations, resulting in the accumulation of numerous free radicals in the body. This, in turn, damages cell structures and human tissues, triggering an oxidative stress response. As the primary glial cell type in the CNS, astrocytes rapidly respond to this stress state by upregulating the expression and activity of antioxidant enzymes to combat excessive ROS accumulation and mitigate damage to neurons and their own cells. Glutathione (GSH) is a crucial antioxidant and free radical scavenger that participates in redox reactions in the body. It binds to peroxides and free radicals, reducing ROS toxicity and serving as a key factor in preventing the aggravation of ischemic injury in brain tissue. Studies have shown that astrocytes are rich in GSH and enzymes related to GSH metabolism. By enhancing the synthesis and release of antioxidants such as GSH and storing nitric oxide in the cytoplasm, astrocytes can reduce oxidative stress toxicity, alleviate oxidative stress damage to neurons, and thereby promote neuronal survival (49-51).

Antagonizing neurotoxicity and promoting neurological recovery. Glutamate is the primary excitatory neurotransmitter in the CNS, responsible for virtually all excitatory synaptic activities in the brain. This crucial amino acid circulates extensively between neurons and astrocytes, known as the glutamate-glutamine cycle. Extracellular glutamate is taken up by nearby astrocytes, converted into glutamine, which then migrates to the extracellular environment, enters presynaptic neurons, and is reconverted into glutamate (52). In the early stage of ischemic stroke, the brain tissue suffers from ischemia and hypoxia, leading to reduced ATP production, gradual energy depletion, and impaired ion pump function, which results in presynaptic calcium overload. The subsequent accumulation of glutamate in the synapses activates post-synaptic

glutamate receptors, causing post-synaptic calcium overload, initiating profound neurotoxicity, and ultimately triggering neuronal death (53). Astrocytes can effectively remove glutamate from the synaptic cleft by expressing high-affinity glutamate transporters, maintaining its homeostatic levels and preventing excessive neuronal excitation and damage (54). Synaptic regeneration after neural injury is a crucial process that enhances neural plasticity, and astrocytes contribute to this process in multiple ways. The close morphological relationship between astrocytic membranes and pre- and post-synaptic neurons, along with the widespread expression of neurotransmitter receptors in astrocytes, forms the astrocytic tripartite synapse. This structure prevents the diffusion of neurotransmitters from the synapse and serves as an important structural unit in the nervous system (55). Besides, astrocytes facilitate the release of various growth factors and neurotrophins. These factors are vital during ischemia for neuronal survival and growth, angiogenesis, synaptic regeneration, and the restoration of other neurological functions (56).

Transformation into neurons. Astrocytes are the most widely distributed cells in the CNS, and they can rapidly activate and proliferate under pathological conditions, making them the ideal target cell type for induction into neuronal cells (57). Reactive astrocytes can transform into neurons under specific circumstances (58). Although neural stem cells (NSCs) are the primary source of endogenous neural repair, their migratory capacity is limited. When the site of injury is far from the region where NSCs reside, reactive astrocytes can be activated through neurogenic programs, acquiring certain stem cell properties, and then re-differentiating into neurons to promote local neuronal regeneration. In addition, astrocytes also aid in the migration of differentiated NSCs (59,60).

5. Astrocyte metabolic reprogramming in ischemic stroke

In recent years, with the deepening of research into neurological diseases, the metabolic flexibility and functional diversity of astrocytes have garnered increasing attention, and notable advancements have been made in the study of metabolic reprogramming of astrocytes. Research has revealed that mutations in the intellectual disability-associated gene *SNX27* can induce metabolic reprogramming of astrocytes, subsequently impairing cognitive functions. Specifically, *SNX27* mutations lead to a decreased ability of astrocytes to uptake glucose via GLUT1, resulting in reduced lactate production and a transition from homeostatic astrocytes to reactive astrocytes. This transformation impacts the energy supply to neighboring neurons (61). Additionally, astrocytes possess the capacity to modulate the pathogenicity of glioblastoma by reprogramming the immune characteristics of the tumor microenvironment and supporting the non-oncogenic metabolic dependence of glioblastoma on cholesterol (62).

Astrocytes form functional networks through gap junctions, enabling intercellular communication with other cells via various mechanisms, playing a crucial role in maintaining homeostasis within the CNS (63). The unique cellular structure and quantitative characteristics of astrocytes confer upon them a high degree of metabolic plasticity, allowing them to adjust their metabolic pathways in response to environmental

changes and physiological demands. They not only harness glucose for energy production through glycolysis and aerobic oxidative phosphorylation but also acquire energy and synthesize essential biomolecules through fatty acid and amino acid metabolism pathways (64). However, during ischemic stroke, local cerebral blood flow is reduced or interrupted due to cerebral vascular occlusion, leading to insufficient oxygen supply and a precipitous decline in energy supply. In this emergent situation, astrocytes promptly respond by initiating metabolic reprogramming to adapt to the energy crisis.

Astrocyte glucose metabolism in ischemic stroke. Glucose serves as the primary energy source for the brain, and its metabolism directly impacts brain function, particularly the interplay between astrocytes and neurons (65). Under normal physiological conditions, astrocytes efficiently uptake glucose via glucose transporter proteins. Once inside the cell, glucose is initially phosphorylated to glucose-6-phosphate (G6P), marking the crucial initiating step in glucose metabolism. G6P then bifurcates into two primary metabolic routes: glycolysis and the pentose phosphate pathway (PPP). Glycolysis, one of the major branches of glucose metabolism, involves the gradual degradation of G6P into pyruvate, generating small amounts of ATP and NADH along the way. In aerobic conditions, the majority of pyruvate enters mitochondria where it undergoes complete oxidation to carbon dioxide and water through the tricarboxylic acid (TCA) cycle, releasing substantial energy for ATP synthesis. This process is known as aerobic oxidative phosphorylation (66). Furthermore, astrocytes also retain the capacity to convert a portion of pyruvate into lactate, which can be released extracellularly to regulate pH balance and contribute to energy supply. The PPP, as a shunt from glycolysis, diverges at G6P and is catalyzed by G6P dehydrogenase, yielding NADPH and 5-phosphoribose, among other products. NADPH, an essential cytosolic reductive equivalent, effectively scavenges ROS, thereby safeguarding cells from oxidative stress damage. Consequently, PPP activity is often regarded as an important indicator of cellular antioxidant defense. Notably, under hypoxic conditions, astrocytes upregulate glucose flux towards the PPP to provide additional NADPH for GSH synthesis, thereby protecting neurons from oxidative insult (67). During ischemic stroke, localized hypoxia in brain tissue ensues due to reduced blood flow, concurrently diminishing glucose and oxygen supply. In response to this emergency, astrocytes reprogram their glucose metabolic pathways by enhancing glucose uptake, accelerating glycolysis, and increasing lactate release. These concerted changes collectively enhance the tolerance of astrocytes to ischemic and hypoxic environments (68) (Fig. 1).

Astrocytes enhance their glucose uptake capacity by upregulating the expression of glucose transporter proteins, with GLUT1, a 45 kDa subtype, being primarily responsible for basal glucose transport in astrocytes (69). GLUT1 is a transmembrane protein widely distributed in vascular endothelial cells of the BBB and various brain tissue cells. It exhibits high specificity and affinity, enabling rapid transfer of glucose from the bloodstream into cells, providing essential energy sources (70). During ischemia, astrocytes increase the quantity and activity of GLUT1 to ensure enhanced glucose influx into the cells, meeting the urgent metabolic demands (71). By enhancing glucose uptake efficiency, astrocytes sustain a certain level of

energy, enabling them to continue supporting neuronal function and regulating the intracranial environment. Under hypoxic conditions resulting from ischemic stroke, the aerobic oxidative phosphorylation pathway is severely inhibited, leading to a drastic reduction in ATP production. In response to this energetic crisis, most eukaryotic cells reprogram their primary metabolic route, shifting from mitochondrial respiration to glycolysis, in order to sustain ATP levels. This hypoxia-induced metabolic reprogramming is crucial for meeting cellular energy demands during acute hypoxic stress (72). Glycolysis, a glucose metabolic pathway that operates even under anaerobic or hypoxic conditions, albeit generating fewer ATP molecules compared with aerobic oxidative phosphorylation, operates at a faster rate and is independent of oxygen. By enhancing the proportion of aerobic glycolysis, astrocytes can rapidly generate sufficient ATP to maintain fundamental cellular functions, which is pivotal in preserving cellular stability and preventing further damage. However, this process also leads to a corresponding elevation in lactate levels, which promotes the formation of K_{la} protein, significantly exacerbating brain injury in ischemic stroke (73). Excessive accumulation of lactate also causes a significant decrease in cellular pH, exposing brain tissue to acidosis-induced damage (74). To alleviate this crisis, astrocytes not only adapt to their own metabolic changes but also release lactate into the extracellular space through the lactate shuttle mechanism. This lactate is then taken up by neurons, serving as an alternative energy source under hypoxic conditions. Through gluconeogenesis, it can be reconverted into glucose or enter the TCA cycle for oxidative phosphorylation to generate ATP, thereby effectively protecting neurons from further damage. This process is known as the astrocyte-neuron lactate shuttle (75). Not only does this process provide crucial energy support for neurons, but it also promotes the recycling of glucose and lactate within the brain, enhancing overall metabolic efficiency.

Astrocyte fatty acid metabolism in ischemic stroke. As the preferred energy substrate for the brain, when glucose supply decreases, fatty acid oxidation and the resulting ketone bodies (KBs) become the primary alternative energy sources, assisting in maintaining the stability of neuronal synaptic function and structure (76). Astrocytes serve as the primary site of fatty acid oxidation in the brain (77). Fatty acids first enter astrocytes through specific transporters and are then stored as lipid droplets (LDs) in the endoplasmic reticulum. When needed, these LDs are converted into fatty acyl-CoA and transported to mitochondria to participate in β -oxidation, ultimately generating acetyl-CoA, which enters the TCA cycle and other pathways to produce energy. Furthermore, fatty acids are transported to support myelin formation or regeneration. Additionally, astrocytes are the primary source of KBs production in the brain (78).

Under normal physiological conditions, fatty acid oxidation constitutes a pivotal pathway for astrocytes to derive energy. However, during ischemic stroke, the brain tissue rapidly becomes ischemic and hypoxic, necessitating a steep rise in neuronal energy demands. In response to this energy crisis, astrocytes swiftly engage their distinctive metabolic adaptation mechanisms. They upregulate the expression of fatty acid transporter proteins, such as fatty acid-binding proteins, to

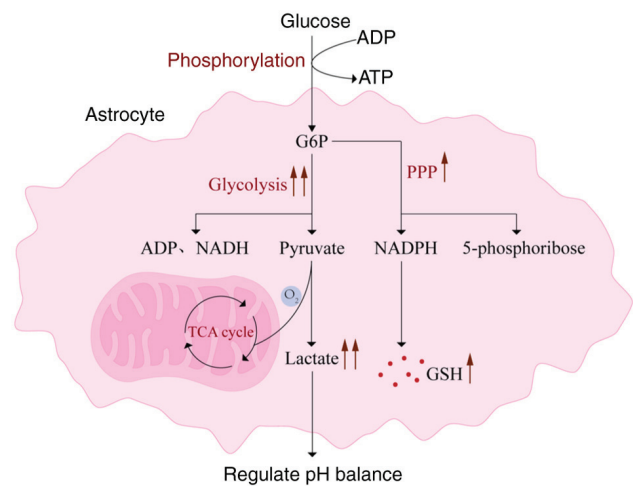


Figure 1. Astrocyte glucose metabolism in ischemic stroke. Under normal physiological conditions, astrocytes efficiently uptake glucose via glucose transporter proteins. Upon entering the cell, glucose is initially phosphorylated to G6P. Subsequently, G6P diverges into two primary metabolic pathways: glycolysis and the pentose phosphate pathway. In glycolysis, G6P is gradually degraded into pyruvate. Under aerobic conditions, the majority of pyruvate enters the mitochondria and undergoes complete oxidation to carbon dioxide and water through the TCA cycle, releasing substantial energy for ATP synthesis. Meanwhile, a portion of pyruvate is converted into lactate, which is released extracellularly. In the PPP, G6P is catalyzed by G6PDH to yield NADPH and 5-phosphoribose, among other products. During ischemic stroke, astrocytes reprogram their glucose metabolic pathways by enhancing glucose uptake, accelerating glycolysis, and increasing lactate release. G6P, glucose-6-phosphate; TCA, tricarboxylic acid; G6PDH, G6P dehydrogenase; PPP, pentose phosphate pathway.

augment their capacity for fatty acid uptake and concurrently activate lipid synthesis pathways to augment intracellular fatty acid storage. While this process may be somewhat hindered by the deficient energy supply, astrocytes persist in maintaining their metabolic functions (79). Nevertheless, excessive expression of fatty acid transporter proteins in ischemic stroke is not uniformly beneficial. In certain scenarios, it may lead to lipid droplet accumulation within astrocytes, further impeding normal cellular physiology. LDs, fundamental components of astrocytic lipid metabolism, modulate fatty acid storage and hydrolysis in eukaryotes (80). Their primary purpose is to provide fuel for fatty acid oxidation, offering an alternative energy-generating route for astrocytes and other tissues during energy source depletion, ensuring an adequate fatty acid reserve for cell survival and neuronal metabolism (81). At the onset of ischemia and hypoxia, astrocytes intensify fatty acid oxidation and breakdown to generate more ATP, crucial for maintaining cellular survival and fulfilling neuronal energy demands, thereby conferring neuroprotection. Consequently, metabolites associated with fatty acid catabolism may elevate initially (82). Yet, over time, mitochondrial dysfunction and impairment of oxidative phosphorylation may hinder effective fatty acid entry into mitochondria, suppressing fatty acid oxidation (83) (Fig. 2). Additionally, reduced activity of vital enzymes such as carnitine palmitoyl-transferase 1A (CPT1A), a crucial regulator for long-chain fatty acid entry into mitochondria for oxidation, further decelerates fatty acid oxidation rates. The decreased CPT1A activity directly contributes to reduced fatty acid oxidation, instigating fatty acid metabolic disturbances and exacerbating the energy supply crisis (84).

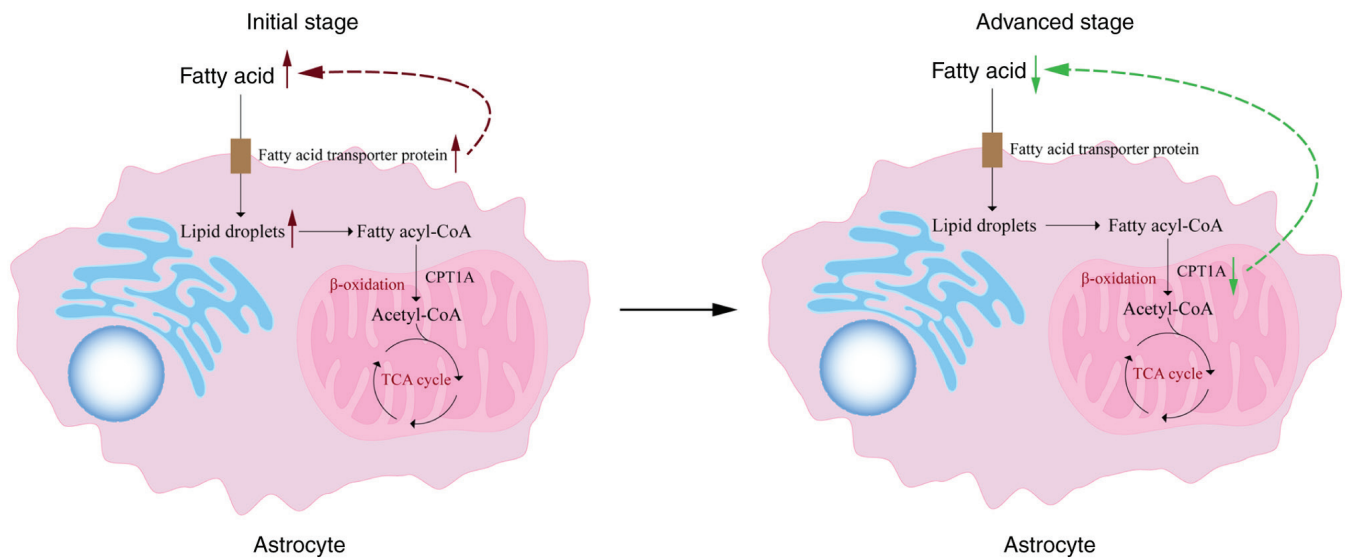


Figure 2. Astrocyte fatty acid metabolism in ischemic stroke. Fatty acids initially enter astrocytes through specific transporter proteins and are subsequently stored as LDs in the endoplasmic reticulum. These LDs are converted into fatty acyl-CoA when needed and transported to mitochondria to participate in β -oxidation, ultimately generating acetyl-CoA, which enters the TCA cycle and other pathways to produce energy. However, following ischemic stroke, astrocytes upregulate the expression of fatty acid transporter proteins, leading to the accumulation of LDs within astrocytes. Over time, mitochondrial dysfunction and impairment of the oxidative phosphorylation pathway may prevent fatty acids from effectively entering mitochondria, thereby inhibiting the progression of fatty acid oxidation. LDs, lipid droplets; TCA, tricarboxylic acid; CPT1A, carnitine palmitoyl-transferase 1A.

Astrocyte amino acid metabolism in ischemic stroke. In parallel with energy metabolic pathways, amino acid metabolism within astrocytes plays a pivotal role in regulating brain function. As fundamental constituents of proteins, amino acids not only participate in protein synthesis and degradation but also modulate neuronal excitability, synaptic plasticity, and the synthesis and release of neurotransmitters through their transport and metabolic processes.

Glutamate serves as the primary excitatory neurotransmitter in the CNS, with neurons and astrocytes being the primary players in its metabolism. The exchange of glutamate, γ -aminobutyric acid (GABA), and glutamine between these two cell types, known as the glutamate/GABA-glutamine cycle, is crucial for maintaining CNS homeostasis (85). During cerebral ischemia and hypoxia, neuronal damage leads to the release of excess glutamate into the synaptic cleft, where it acts as an excitatory neurotransmitter binding to post-synaptic receptors. Under these conditions, the expression of excitatory glutamate transporters such as GLT-1 and GLAST-1 is significantly downregulated, resulting in reduced clearance of glutamate from the synaptic cleft (86). The subsequent accumulation of glutamate excessively stimulates post-synaptic neurons, leading to excitotoxicity. A portion of the unbound glutamate is sequestered by astrocytes through high-affinity glutamate transporters and converted to glutamine within the cells, thereby reducing extracellular glutamate concentrations and protecting neurons from excitotoxic damage to a certain extent. In some instances, this unbound glutamate may also be retrogradely transported back to neurons via glutamate transporters, participating in new rounds of neurotransmission (87). Additionally, astrocytes have been shown to release small amounts of glutamate to surrounding neurons, contributing to the synchronization of action potential firing and regulating neural excitability transmission (88). Concurrently, GABA, synthesized by neurons, is released

as an inhibitory neurotransmitter to dampen post-synaptic neuronal excitability. Imbalances between excitatory and inhibitory neurotransmitter signaling contribute to the onset of excitotoxicity. After release, GABA can also be taken up by astrocytes, where it is converted to succinic semialdehyde by GABA transaminase and enters the TCA cycle for energy metabolism (89). Moreover, astrocytes can synthesize and release GABA into the extracellular space, fine-tuning local neural networks (90). However, extensive uptake of glutamate and GABA by astrocytes depletes the corresponding neurotransmitter pools in neurons. To counteract this, astrocytes convert ingested glutamate into glutamine and shuttle it back to neurons via the glutamine-glutamate cycle for reuse, which is essential for replenishing glutamate and GABA at neuronal terminals (91) (Fig. 3).

In the pathological process of ischemic stroke, metabolic reprogramming of astrocytes plays a pivotal role. From the basal metabolism, glucose metabolism, fatty acid metabolism, to amino acid metabolism of astrocytes, all aspects exhibit adaptive changes to ischemic and hypoxic environments. Such metabolic reprogramming not only enhances the survival capacity of astrocytes but also provides robust support for neuronal and brain tissue repair by modulating various aspects including antioxidation, energy supply, inflammatory response and neuroprotection. Consequently, a profound understanding of the mechanisms underlying metabolic reprogramming of astrocytes in ischemic stroke holds significant importance for the development of novel therapeutic strategies.

6. Regulatory factors of astrocyte metabolic reprogramming in ischemic stroke

Hypoxia-inducible factors (HIFs) constitute pivotal transcription factors that are responsive to intracellular oxygen concentration fluctuations. Under hypoxic conditions, HIFs

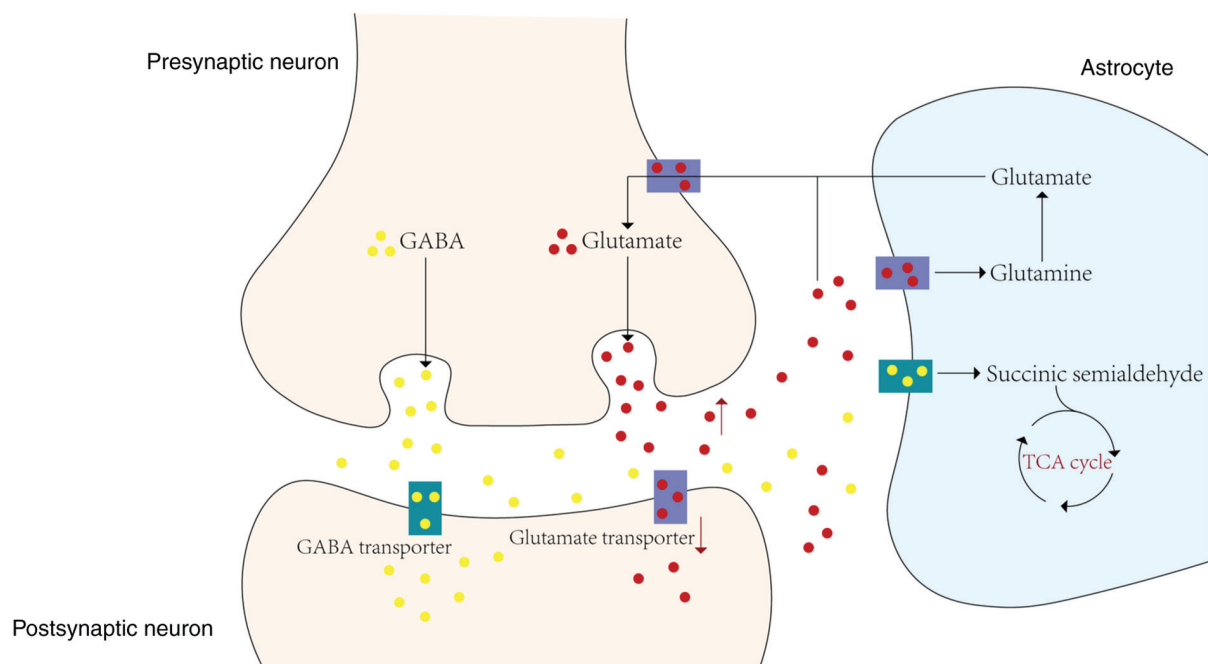


Figure 3. Astrocyte amino acid metabolism in ischemic stroke. When the brain is in a state of ischemia and hypoxia, a substantial level of glutamate is released into the synaptic cleft, resulting in a significant downregulation of excitatory glutamate transporters expression. This leads to a reduction in the efficiency of glutamate clearance from the synaptic cleft. Among the glutamate released, some that is not bound by post-synaptic neurons is received by astrocytes via high-affinity glutamate transporters and converted into glutamine within the cells. In certain circumstances, this unbound glutamate may also be directly retrogradely transported back to neurons via glutamate transporters, participating in a new round of neurotransmission. Simultaneously, GABA, synthesized by neurons, is released as an inhibitory neurotransmitter to inhibit the excitability of post-synaptic neurons. The imbalance between the release of excitatory and inhibitory neurotransmitter signals leads to the occurrence of excitotoxicity. Released GABA can also be taken up by astrocytes and converted into succinate semialdehyde via GABA transaminase within the astrocytes, entering the TCA cycle for energy metabolism. However, the extensive uptake of glutamate and GABA by astrocytes depletes the corresponding neurotransmitter pools in neurons. To counteract this, astrocytes convert the received glutamate into glutamine and transport it back to neurons through the glutamine-glutamate cycle for reuse, which is crucial for replenishing glutamate and GABA at neuronal terminals. GABA, γ -aminobutyric acid; TCA, tricarboxylic acid.

exert transcriptional regulatory activity, governing the expression of an array of metabolism-related genes, thereby facilitating cellular and systemic adaptation to hypoxic environments. They also emerge as crucial regulators in metabolic reprogramming of astrocytes. By modulating the expression of an extensive network of target genes, HIFs orchestrate reprogramming of astrocyte pathways associated with glucose metabolism, fatty acid metabolism and amino acid metabolism, markedly enhancing astrocytic resilience against ischemic and hypoxic insults. In ischemic stroke, the ensuing inflammatory response and cellular damage induced by ischemia and hypoxia activate various signaling cascades. Numerous of these pathways are intricately linked to the reactivity of astrocytes, with the Jak-STAT3 signaling pathway playing a pivotal role in coordinating the proliferation of reactive astrocytes by modulating the production of cytokines and chemokines. This pathway serves as a central regulatory hub for numerous molecular and functional alterations in reactive astrocytes (92). A previous study revealed a marked upregulation of the transcription factor STAT3 in reactive astrocytes following ischemic stroke (93). STAT3 has been demonstrated to control phenotypic changes and metabolic reprogramming of astrocytes during the inflammatory phase of ischemic stroke, upregulating lactate-directed glycolysis while impeding mitochondrial function, thus serving as a key modulator of astrocyte phenotype, metabolic shift and associated neurotoxicity. Moreover, in reactive astrocytes,

elevated expression of activated pSTAT3 correlates with larger infarct sizes and reduced synaptic densities in the peri-infarct zone (94). Beyond cell proliferation, STAT3 also regulates GFAP expression in reactive astrocytes, as the GFAP promoter harbors STAT3 consensus binding sites essential for GFAP induction. Consequently, the STAT3 signaling pathway emerges as a promising pharmacological target for modifying reactive astrocytes in the context of ischemic stroke (95).

Glycophagy, as a selective autophagy process for glycogen, is emerging as a pivotal metabolic pathway for the delivery of glycolytic fuel substrates, playing a crucial role in maintaining cellular metabolic homeostasis in peripheral tissues (96). It regulates cellular redox homeostasis, glutamine utilization, fatty acid oxidation in skeletal muscle, and lipid droplet formation in adipocytes (97,98). Guo *et al* (99) discovered during reperfusion in ischemic stroke patients and mice that dysfunction in glycophagy in astrocytes is induced by the downregulation of GABA A receptor-associated protein-like 1, with the activation of the PI3K-Akt pathway also involved. Following ischemic stroke, as key enzymes in glycolysis in astrocytes are inhibited, glucose sourced from glycophagy enters the PPP more significantly than it does glycolysis and the TCA cycle. Restoring glycophagy in astrocytes can not only enhance their resistance to ischemic and hypoxic environments but also aid in the survival of nearby neurons when the entire brain is under energy stress (99).

Table II. Therapeutic approaches targeting astrocyte metabolic reprogramming in ischemic stroke.

First author/s, year	Strategy	Regulation on astrocytes polarization and metabolism	(Refs.)
Liu <i>et al.</i> , 2020	Cottonseed oil	Reduce A1 phenotype neurotoxic astrocyte activation by inhibiting TLR4/NF- κ B pathway, which may affect glucose metabolism	(109)
Zhang <i>et al.</i> , 2024	AD16	Reduce A1 polarization of astrocytes by downregulating NF- κ B and JAK2/STAT3 pathways, which may affect glucose metabolism	(110)
Zou <i>et al.</i> , 2024	Scutellarin	Inhibit the activation of astrocytes to A1 type by inhibiting the activation of NF- κ B pathway, which may affect glucose metabolism	(111)
Zhou <i>et al.</i> , 2022	Tetrahedral framework nucleic acid	Facilitate the astrocytic polarization from the proinflammatory A1 phenotype to the neuroprotective A2 phenotype by downregulating the TLRs/NF- κ B pathway, which may affect glucose metabolism	(112)
Liu <i>et al.</i> , 2024	Genistein-3'-sodium sulfonate	Enhance astrocyte polarization to A2 phenotype by inactivating TLR4/NF- κ B pathway, which may affect glucose metabolism	(113)
Chen <i>et al.</i> , 2024	Edaravone Dexborneol	Suppress activation of neurotoxic A1 astrocytes by inhibiting NF- κ B pathway, which may affect glucose metabolism	(114)
Wang <i>et al.</i> , 2023	Kruppel-like transcription factor-4	Inhibit the activation of A1 astrocyte and promote A2 astrocyte polarization by modulating expressions of NF- κ B pathway, which may affect glucose metabolism	(16)
Li <i>et al.</i> , 2024	Buyang Huanwu Decoction	Suppress astrocytes A1 polarization and promote astrocyte A2 polarization by increasing expression of phosphorylated AMPK and inhibiting NF- κ B pathway, which may affect glucose metabolism	(115)
Xia <i>et al.</i> , 2024	Gypenosides	Inhibit astrocytes' polarization into the A1 type, by inhibiting STAT-3/HIF1- α and TLR-4/NF- κ B/HIF1- α pathways, which may affect glucose metabolism	(116)
Xiong <i>et al.</i> , 2024	Oxamate	Inhibit the activation of A1 astrocyte by inhibiting the production of lactate, blocking the shuttle of lactate to neurons, and inhibiting the formation of K _{la} protein, which may affect glucose metabolism	(73)
Cao <i>et al.</i> , 2021	N-3 polyunsaturated fatty acids	Reduce the A1 astrocyte polarization both <i>in vivo</i> and <i>in vitro</i> by attenuating mitochondrial oxidative stress and increasing the mitophagy of astrocytes, which may affect fatty acid metabolism	(104)

HIF, hypoxia-inducible factor.

7. Therapeutic approaches targeting astrocyte metabolic reprogramming in ischemic stroke.

Currently, the frontline treatments for ischemic stroke encompass intravenous administration of recombinant tissue plasminogen activator (rt-PA) and mechanical thrombectomy (100). Nevertheless, due to their narrow therapeutic windows, the options for treating ischemic stroke remain limited. As such, the pursuit of novel candidate drugs for ischemic stroke management poses an urgent challenge. In the context of ischemic stroke, astrocytes undergo significant metabolic reprogramming, transitioning from a quiescent state to a reactive state. Thus, the therapeutic strategies targeting metabolic reprogramming of astrocytes in ischemic stroke focus on modulating their metabolic pathways and functional states, with the aim of inhibiting excessive astrocyte activation or regulating the ratio of A1/A2 phenotypes, thereby maximizing neuroprotective effects while minimizing neurotoxicity, ultimately facilitating repair and regeneration following brain injury.

In the early stages of ischemic stroke, due to blood flow interruption, brain tissue experiences hypoxia, prompting astrocytes to shift towards anaerobic glycolysis for rapid ATP production. However, this metabolic pathway is prone to lactate accumulation, leading to acidosis. Following ischemic reperfusion, astrocyte glycogen mobilization augments the production of NADPH and GSH via the PPP, resulting in a reduction in ROS levels. This, in turn, triggers the inhibition of the NF- κ B signaling pathway and the activation of the STAT3 signaling pathway, ultimately leading to the suppression of A1 astrocytes and the enhancement of A2 astrocytes (101). HIF-1 enhances the intrinsic tolerance of brain tissue to ischemia by augmenting glucose uptake in astrocytes, facilitating glycogen synthesis, and initiating a metabolic shift towards glycolytic energy production (68). Similarly, AMPK exerts a specific influence on glycolysis during ischemic preconditioning in brain tissue (102). These pathways present promising therapeutic targets for addressing reperfusion injury in ischemic stroke. Under ischemic and hypoxic stimuli, astrocytes release free fatty acids from LDs into mitochondria, causing

mitochondrial damage, reducing metabolic support from astrocytes, and thereby exacerbating neuronal injury (103). Cao *et al* (104) revealed that n-3 polyunsaturated fatty acids can decrease the cerebral infarction volume and improve neurological function in mice with transient middle cerebral artery occlusion. Additionally, it reduced the polarization of A1 astrocytes induced by ischemic stroke both *in vivo* and *in vitro* (104). In addition, the interaction between glutamate and astrocytes jointly influences the pathological process of ischemic stroke. In ischemic stroke, glutamate, acting as a neurotransmitter, experiences an abnormal elevation in its levels, exerting neurotoxic effects on neurons. Conversely, astrocytes are responsible for modulating the uptake and metabolism of glutamate, thereby mitigating its deleterious impact on neurons. However, to date, no literature has confirmed the existence of drugs that target this mechanism to affect astrocyte phenotype changes during ischemic stroke.

As a crucial therapeutic target in ischemic stroke, promoting the differentiation of astrocytes towards the A2 phenotype may offer novel neuroprotective strategies with profound therapeutic implications. Research has demonstrated that the overexpression of the chemokine-like signaling protein prokineticin-2 and its small molecule agonist IS20 in primary astrocytes or in the brains of mice *in vivo* can induce the A2 astrocyte phenotype. This leads to the upregulation of key protective genes and A2 reactive markers, while simultaneously reducing inflammatory cytokines (105). The TGF- β secreted by M2 macrophages potentially elicits the differentiation of astrocytes towards the A2 phenotype through the activation of the PI3K/Akt signaling cascade (106). Furthermore, cytokines such as IL-4, IL-10 and IL-1 β can induce the differentiation of astrocytes towards the A2 phenotype *in vitro*, further elucidating their protective and repair functions under inflammatory responses (107,108). In summary, therapeutic approaches aimed at restoring tissue damage and metabolic balance in the brain through the modulation of astrocyte metabolic reprogramming have emerged as promising targets for the treatment of ischemic stroke. However, this area remains relatively under-explored, and there is a pressing need for future research endeavors to delve deeper into this domain. The relevant therapeutic approaches targeting astrocyte metabolic reprogramming in ischemic stroke are demonstrated in Table II (16,73,104,109-116).

8. Conclusions and perspectives

In conclusion, ischemic stroke, a prevalent and devastating condition, poses significant challenges in terms of disability and mortality globally. The current pharmacological treatment, intravenous thrombolysis with rt-PA, while effective, has notable limitations, necessitating the exploration of novel therapeutic approaches. Astrocytes, as crucial and versatile cells in the CNS, play multifaceted roles in supporting neuronal function, maintaining the BBB, and regulating ion concentrations. Importantly, recent research has highlighted the involvement of astrocytes in neurotransmitter metabolism, immune response and tissue repair, with their metabolic characteristics influencing the progression and outcome of ischemic stroke. This understanding underscores the potential of targeting astrocyte metabolic reprogramming as a therapeutic strategy for ischemic

stroke. By summarizing the current knowledge on astrocyte metabolic reprogramming mechanisms, regulatory factors and pathways, as well as strategies to promote polarization balance, the present review provides insights into the promising potential of astrocyte immunometabolism-targeted therapies.

However, there is still a long way to go in the study of metabolic reprogramming of astrocytes in ischemic stroke. Given the intricate involvement of multiple molecular and signaling pathways, the specific molecular mechanisms and regulatory networks underlying astrocyte metabolic reprogramming in ischemic stroke have yet to be fully elucidated. Therefore, future studies should delve deeper into the precise molecular mechanisms of astrocyte metabolic reprogramming, particularly its dynamic evolution across different stages of ischemic stroke, the interplay and regulatory relationships among various metabolic pathways, and the intricate molecular mechanisms of its complex interactions with neurons. A profound understanding of the molecular mechanisms and regulatory networks of astrocyte metabolic reprogramming holds significant clinical implications for developing novel therapeutic strategies for ischemic stroke and identifying potential drug targets. Currently, research on astrocytes in ischemic stroke primarily focuses on cellular levels and animal models, and the applicability and translatability of these findings in humans remain to be validated. Future endeavors should concentrate on drug targets capable of modulating astrocyte metabolic pathways and functional states, emphasizing human-level exploration and validation. This includes investigating astrocyte function and metabolic changes using clinical samples, conducting relevant clinical trials, and leveraging structural biology, medicinal chemistry and pharmacology to design and optimize targeted therapies against these identified targets. Ultimately, these efforts aim to assess the efficacy and safety of astrocyte-targeted therapies.

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Authors' contributions

LW and TYM conceived and designed the study. WXC wrote the first draft of the manuscript. RH, RM and YXX participated in editing of specific paragraphs and figures. TYM supervised the study and critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

- Saini V, Guada L and Yavagal DR: Global epidemiology of stroke and access to acute ischemic stroke interventions. *Neurology* 97 (20 Suppl 2): S6-S16, 2021.
- GBD 2019 Stroke Collaborators: Global, regional, and national burden of stroke and its risk factors, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol* 20: 795-820, 2021.
- Han RT, Kim RD, Molofsky AV and Liddelow SA: Astrocyte-immune cell interactions in physiology and pathology. *Immunity* 54: 211-224, 2021.
- Chiellini G: Metabolic reprogramming in health and disease. *Int J Mol Sci* 21: 2768, 2020.
- Candelario-Jalil E, Dijkhuizen RM and Magnus T: Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. *Stroke* 53: 1473-1486, 2022.
- Wu D, Chen Q, Chen X, Han F, Chen Z and Wang Y: The blood-brain barrier: Structure, regulation, and drug delivery. *Signal Transduct Target Ther* 8: 217, 2023.
- Verkhratsky A and Nedergaard M: Physiology of astroglia. *Physiol Rev* 98: 239-389, 2018.
- Lacoste B, Prat A, Freitas-Andrade M and Gu C: The blood-brain barrier: Composition, properties, and roles in brain health. *Cold Spring Harb Perspect Biol*: a041422, 2024 (Epub ahead of print).
- Vandebroek A and Yasui M: Regulation of AQP4 in the central nervous system. *Int J Mol Sci* 21: 1603, 2020.
- Hertz L and Chen Y: Importance of astrocytes for potassium ion (K⁺) homeostasis in brain and glial effects of K⁺ and its transporters on learning. *Neurosci Biobehav Rev* 71: 484-505, 2016.
- Seifert G, Henneberger C and Steinhäuser C: Diversity of astrocyte potassium channels: An update. *Brain Res Bull* 136: 26-36, 2018.
- Felix L, Delekate A, Petzold GC and Rose CR: Sodium fluctuations in astroglia and their potential impact on astrocyte function. *Front Physiol* 11: 871, 2020.
- Allen NJ and Eroglu C: Cell biology of astrocyte-synapse interactions. *Neuron* 96: 697-708, 2017.
- Oliveira JF and Araque A: Astrocyte regulation of neural circuit activity and network states. *Glia* 70: 1455-1466, 2022.
- Hara M, Kobayakawa K, Ohkawa Y, Kumamaru H, Yokota K, Saito T, Kijima K, Yoshizaki S, Harimaya K, Nakashima Y and Okada S: Interaction of reactive astrocytes with type I collagen induces astrocytic scar formation through the integrin-N-cadherin pathway after spinal cord injury. *Nat Med* 23: 818-828, 2017.
- Wang C and Li L: The critical role of KLF4 in regulating the activation of A1/A2 reactive astrocytes following ischemic stroke. *J Neuroinflammation* 20: 44, 2023.
- Zamanian JL, Xu L, Foo LC, Nouri N, Zhou L, Giffard RG and Barres BA: Genomic analysis of reactive astrogliosis. *J Neurosci* 32: 6391-6410, 2012.
- Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, *et al*: Neurotoxic reactive astrocytes are induced by activated microglia. *Nature* 541: 481-487, 2017.
- Patel MR and Weaver AM: Astrocyte-derived small extracellular vesicles promote synapse formation via fibulin-2-mediated TGF- β signaling. *Cell Rep* 34: 108829, 2021.
- Anderson MA, Burda JE, Ren Y, Ao Y, O'Shea TM, Kawaguchi R, Coppola G, Khakh BS, Deming TJ and Sofroniew MV: Astrocyte scar formation aids central nervous system axon regeneration. *Nature* 532: 195-200, 2016.
- Lian H, Yang L, Cole A, Sun L, Chiang AC, Fowler SW, Shim DJ, Rodriguez-Rivera J, Taghialatela G, Jankowsky JL, *et al*: NF- κ B-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's disease. *Neuron* 85: 101-115, 2015.
- Amalia L: Glial fibrillary acidic protein (GFAP): Neuroinflammation biomarker in acute ischemic stroke. *J Inflamm Res* 14: 7501-7506, 2021.
- Liu G and Geng J: Glial fibrillary acidic protein as a prognostic marker of acute ischemic stroke. *Hum Exp Toxicol* 37: 1048-1053, 2018.
- Song X, Gong Z, Liu K, Kou J, Liu B and Liu K: Baicalin combats glutamate excitotoxicity via protecting glutamine synthetase from ROS-induced 20S proteasomal degradation. *Redox Biol* 34: 101559, 2020.
- Shi X, Luo L, Wang J, Shen H, Li Y, Mamtilahun M, Liu C, Shi R, Lee JH, Tian H, *et al*: Stroke subtype-dependent synapse elimination by reactive gliosis in mice. *Nat Commun* 12: 6943, 2021.
- Williamson MR, Fuertes CJA, Dunn AK, Drew MR and Jones TA: Reactive astrocytes facilitate vascular repair and remodeling after stroke. *Cell Rep* 35: 109048, 2021.
- Ma H, Zhou Y, Li Z, Zhu L, Li H, Zhang G, Wang J, Gong H, Xu D, Hua W, *et al*: Single-cell RNA-sequencing analyses revealed heterogeneity and dynamic changes of metabolic pathways in astrocytes at the acute phase of ischemic stroke. *Oxid Med Cell Longev* 2022: 1817721, 2022.
- Denecke KM, McBain CA, Hermes BG, Teertam SK, Farooqui M, Virumbrales-Muñoz M, Panackal J, Beebe DJ, Famakin B and Ayuso JM: Microfluidic model to evaluate astrocyte activation in penumbral region following ischemic stroke. *Cells* 11: 2356, 2022.
- Lochhead JJ, Williams EI, Reddell ES, Dorn E, Ronaldson PT and Davis TP: High resolution multiplex confocal imaging of the neurovascular unit in health and experimental ischemic stroke. *Cells* 12: 645, 2023.
- Zhou J, Zhang L, Peng J, Zhang X, Zhang F, Wu Y, Huang A, Du F, Liao Y, He Y, *et al*: Astrocytic LRP1 enables mitochondrial transfer to neurons and mitigates brain ischemic stroke by suppressing ARF1 lactylation. *Cell Metab* 36: 2054-2068.e14, 2024.
- Scott EY, Safarian N, Casasbuenas DL, Dryden M, Tockovska T, Ali S, Peng J, Daniele E, Nie Xin Lim I, Bang KWA, *et al*: Integrating single-cell and spatially resolved transcriptomic strategies to survey the astrocyte response to stroke in male mice. *Nat Commun* 15: 1584, 2024.
- Wang S, Pan Y, Zhang C, Zhao Y, Wang H, Ma H, Sun J, Zhang S, Yao J, Xie D and Zhang Y: Transcriptome analysis reveals dynamic microglial-induced A1 astrocyte reactivity via C3/C3aR/NF- κ B signaling after ischemic stroke. *Mol Neurobiol* 61: 10246-10270, 2024.
- Bormann D, Knoeflach M, Poreba E, Riedl CJ, Testa G, Orset C, Levilly A, Cottureau A, Jauk P, Hametner S, *et al*: Single-nucleus RNA sequencing reveals glial cell type-specific responses to ischemic stroke in male rodents. *Nat Commun* 15: 6232, 2024.
- Endo F, Kasai A, Soto JS, Yu X, Qu Z, Hashimoto H, Gradinaru V, Kawaguchi R and Khakh BS: Molecular basis of astrocyte diversity and morphology across the CNS in health and disease. *Science* 378: eadc9020, 2022.
- Preman P, Alfonso-Triguero M, Alberdi E, Verkhratsky A and Arranz AM: Astrocytes in Alzheimer's disease: Pathological significance and molecular pathways. *Cells* 10: 540, 2021.
- Price BR, Johnson LA and Norris CM: Reactive astrocytes: The nexus of pathological and clinical hallmarks of Alzheimer's disease. *Ageing Res Rev* 68: 101335, 2021.
- Cai Z, Wan CQ and Liu Z: Astrocyte and Alzheimer's disease. *J Neurol* 264: 2068-2074, 2017.
- Kim J, Yoo ID, Lim J and Moon JS: Pathological phenotypes of astrocytes in Alzheimer's disease. *Exp Mol Med* 56: 95-99, 2024.
- Booth HDE, Hirst WD and Wade-Martins R: The role of astrocyte dysfunction in Parkinson's disease pathogenesis. *Trends Neurosci* 40: 358-370, 2017.
- Wang T, Sun Y and Dettmer U: Astrocytes in Parkinson's disease: From role to possible intervention. *Cells* 12: 2336, 2023.
- Cohen J and Torres C: Astrocyte senescence: Evidence and significance. *Ageing Cell* 18: e12937, 2019.
- Ponath G, Park C and Pitt D: The role of astrocytes in multiple sclerosis. *Front Immunol* 9: 217, 2018.
- Yi W, Schlüter D and Wang X: Astrocytes in multiple sclerosis and experimental autoimmune encephalomyelitis: Star-shaped cells illuminating the darkness of CNS autoimmunity. *Brain Behav Immun* 80: 10-24, 2019.
- Aharoni R, Eilam R and Arnon R: Astrocytes in multiple sclerosis-essential constituents with diverse multifaceted functions. *Int J Mol Sci* 22: 5904, 2021.

45. Xu S, Lu J, Shao A, Zhang JH and Zhang J: Glial cells: Role of the immune response in ischemic stroke. *Front Immunol* 11: 294, 2020.
46. Liu Z and Chopp M: Astrocytes, therapeutic targets for neuroprotection and neurorestoration in ischemic stroke. *Prog Neurobiol* 144: 103-120, 2016.
47. Alsbrook DL, Di Napoli M, Bhatia K, Biller J, Andalib S, Hinduja A, Rodrigues R, Rodriguez M, Sabbagh SY, Selim M, *et al*: Neuroinflammation in acute ischemic and hemorrhagic stroke. *Curr Neurol Neurosci Rep* 23: 407-431, 2023.
48. Lu W, Chen Z and Wen J: Flavonoids and ischemic stroke-induced neuroinflammation: Focus on the glial cells. *Biomed Pharmacother* 170: 115847, 2024.
49. Shen XY, Gao ZK, Han Y, Yuan M, Guo YS and Bi X: Activation and role of astrocytes in ischemic stroke. *Front Cell Neurosci* 15: 755955, 2021.
50. Zhu G, Wang X, Chen L, Lenahan C, Fu Z, Fang Y and Yu W: Crosstalk between the oxidative stress and glia cells after stroke: From mechanism to therapies. *Front Immunol* 13: 852416, 2022.
51. Chen Y, Qin C, Huang J, Tang X, Liu C, Huang K, Xu J, Guo G, Tong A and Zhou L: The role of astrocytes in oxidative stress of central nervous system: A mixed blessing. *Cell Prolif* 53: e12781, 2020.
52. Hertz L and Rothman DL: Glucose, lactate, β -hydroxybutyrate, acetate, GABA, and succinate as substrates for synthesis of glutamate and GABA in the glutamine-glutamate/GABA cycle. *Adv Neurobiol* 13: 9-42, 2016.
53. Wang F, Xie X, Xing X and Sun X: Excitatory synaptic transmission in ischemic stroke: A new outlet for classical neuroprotective strategies. *Int J Mol Sci* 23: 9381, 2022.
54. Andersen JV, Markussen KH, Jakobsen E, Schousboe A, Waagepetersen HS, Rosenberg PA and Aldana BI: Glutamate metabolism and recycling at the excitatory synapse in health and neurodegeneration. *Neuropharmacology* 196: 108719, 2021.
55. Perea G, Navarrete M and Araque A: Tripartite synapses: Astrocytes process and control synaptic information. *Trends Neurosci* 32: 421-431, 2009.
56. Patabendige A, Singh A, Jenkins S, Sen J and Chen R: Astrocyte activation in neurovascular damage and repair following ischaemic stroke. *Int J Mol Sci* 22: 4280, 2021.
57. Yu X, Nagai J and Khakh BS: Improved tools to study astrocytes. *Nat Rev Neurosci* 21: 121-138, 2020.
58. Mollinari C, Zhao J, Lupacchini L, Garaci E, Merlo D and Pei G: Transdifferentiation: A new promise for neurodegenerative diseases. *Cell Death Dis* 9: 830, 2018.
59. Popa-Wagner A, Hermann D and Gresita A: Genetic conversion of proliferative astroglia into neurons after cerebral ischemia: A new therapeutic tool for the aged brain? *Geroscience* 41: 363-368, 2019.
60. Jiang MQ, Yu SP, Wei ZZ, Zhong W, Cao W, Gu X, Wu A, McCrory MR, Berglund K and Wei L: Conversion of reactive astrocytes to induced neurons enhances neuronal repair and functional recovery after ischemic stroke. *Front Aging Neurosci* 13: 612856, 2021.
61. Zhang H, Zheng Q, Guo T, Zhang S, Zheng S, Wang R, Deng Q, Yang G, Zhang S, Tang L, *et al*: Metabolic reprogramming in astrocytes results in neuronal dysfunction in intellectual disability. *Mol Psychiatry* 29: 1569-1582, 2024.
62. Perelroizen R, Philoso B, Budick-Harmelin N, Chernobylsky T, Ron A, Katzir R, Shimon D, Tessler A, Adir O, Gaoni-Yogev A, *et al*: Astrocyte immunometabolic regulation of the tumour microenvironment drives glioblastoma pathogenicity. *Brain* 145: 3288-3307, 2022.
63. Giaume C, Naus CC, Sáez JC and Leybaert L: Glial connexins and pannexins in the healthy and diseased brain. *Physiol Rev* 101: 93-145, 2021.
64. Zhang YM, Qi YB, Gao YN, Chen WG, Zhou T, Zang Y and Li J: Astrocyte metabolism and signaling pathways in the CNS. *Front Neurosci* 17: 1217451, 2023.
65. Falkowska A, Gutowska I, Goschorska M, Nowacki P, Chlubek D and Baranowska-Bosiacka I: Energy Metabolism of the brain, including the cooperation between astrocytes and neurons, especially in the context of glycogen metabolism. *Int J Mol Sci* 16: 25959-25981, 2015.
66. Chandel NS: Glycolysis. *Cold Spring Harb Perspect Biol* 13: a040535, 2021.
67. Takahashi S: Neuroprotective function of high glycolytic activity in astrocytes: Common roles in stroke and neurodegenerative diseases. *Int J Mol Sci* 22: 6568, 2021.
68. Madai S, Kilic P, Schmidt RM, Bas-Orth C, Korff T, Büttner M, Klinke G, Poschet G, Marti HH and Kunze R: Activation of the hypoxia-inducible factor pathway protects against acute ischemic stroke by reprogramming central carbon metabolism. *Theranostics* 14: 2856-2880, 2024.
69. Koepsell H: Glucose transporters in brain in health and disease. *Pflügers Arch* 472: 1299-1343, 2020.
70. Veys K, Fan Z, Ghobrial M, Bouché A, García-Caballero M, Vriens K, Concinha NV, Seuwen A, Schlegel F, Gorski T, *et al*: Role of the GLUT1 glucose transporter in postnatal CNS angiogenesis and blood-brain barrier integrity. *Circ Res* 127: 466-482, 2020.
71. Alquisiras-Burgos I and Aguilera P: Involvement of glucose transporter overexpression in the protection or damage after ischemic stroke. *Neural Regen Res* 17: 783-784, 2022.
72. Kierans SJ and Taylor CT: Regulation of glycolysis by the hypoxia-inducible factor (HIF): Implications for cellular physiology. *J Physiol* 599: 23-37, 2021.
73. Xiong XY, Pan XR, Luo XX, Wang YF, Zhang XX, Yang SH, Zhong ZQ, Liu C, Chen Q, Wang PF, *et al*: Astrocyte-derived lactate aggravates brain injury of ischemic stroke in mice by promoting the formation of protein lactylation. *Theranostics* 14: 4297-4317, 2024.
74. M Tóth O, Menyhart Á, Frank R, Hantosi D, Farkas E and Bari F: Tissue acidosis associated with ischemic stroke to guide neuroprotective drug delivery. *Biology (Basel)* 9: 460, 2020.
75. Bonvento G and Bolaños JP: Astrocyte-neuron metabolic cooperation shapes brain activity. *Cell Metab* 33: 1546-1564, 2021.
76. Romano A, Koczwara JB, Gallelli CA, Vergara D, Micioni Di Bonaventura MV, Gaetani S and Giudetti AM: Fats for thoughts: An update on brain fatty acid metabolism. *Int J Biochem Cell Biol* 84: 40-45, 2017.
77. Ebert D, Haller RG and Walton ME: Energy contribution of octanoate to intact rat brain metabolism measured by ^{13}C nuclear magnetic resonance spectroscopy. *J Neurosci* 23: 5928-5935, 2003.
78. Le Foll C and Levin BE: Fatty acid-induced astrocyte ketone production and the control of food intake. *Am J Physiol Regul Integr Comp Physiol* 310: R1186-R1192, 2016.
79. Guo Q, Kawahata I, Cheng A, Jia W, Wang H and Fukunaga K: Fatty acid-binding proteins: Their roles in ischemic stroke and potential as drug targets. *Int J Mol Sci* 23: 9648, 2022.
80. Mallick K, Paul S, Banerjee S and Banerjee S: Lipid droplets and neurodegeneration. *Neuroscience* 549: 13-23, 2024.
81. Lee JA, Hall B, Allsop J, Alqarni R and Allen SP: Lipid metabolism in astrocytic structure and function. *Semin Cell Dev Biol* 112: 123-136, 2021.
82. Wang X, Zhang L, Sun W, Pei LL, Tian M, Liang J, Liu X, Zhang R, Fang H, Wu J, *et al*: Changes of metabolites in acute ischemic stroke and its subtypes. *Front Neurosci* 14: 580929, 2021.
83. Sayre NL, Sifuentes M, Holstein D, Cheng SY, Zhu X and Lechleiter JD: Stimulation of astrocyte fatty acid oxidation by thyroid hormone is protective against ischemic stroke-induced damage. *J Cereb Blood Flow Metab* 37: 514-527, 2017.
84. Du W, Zhang L, Brett-Morris A, Aguila B, Kerner J, Hoppel CL, Puchowicz M, Serra D, Herrero L, Rini BI, *et al*: HIF drives lipid deposition and cancer in ccRCC via repression of fatty acid metabolism. *Nat Commun* 8: 1769, 2017.
85. Andersen JV, Schousboe A and Verkhratsky A: Astrocyte energy and neurotransmitter metabolism in Alzheimer's disease: Integration of the glutamate/GABA-glutamine cycle. *Prog Neurobiol* 217: 102331, 2022.
86. Hsu PC, Lan YJ, Chen CC, Lee LY, Chen WP, Wang YC and Lee YH: Erinacine A attenuates glutamate transporter 1 downregulation and protects against ischemic brain injury. *Life Sci* 306: 120833, 2022.
87. Shen Z, Xiang M, Chen C, Ding F, Wang Y, Shang C, Xin L, Zhang Y and Cui X: Glutamate excitotoxicity: Potential therapeutic target for ischemic stroke. *Biomed Pharmacother* 151: 113125, 2022.
88. Mahmoud S, Gharagozloo M, Simard C and Gris D: Astrocytes maintain glutamate homeostasis in the CNS by controlling the balance between glutamate uptake and release. *Cells* 8: 184, 2019.
89. Andersen JV, Jakobsen E, Westi EW, Lie MEK, Voss CM, Aldana BI, Schousboe A, Wellendorph P, Bak LK, Pinborg LH and Waagepetersen HS: Extensive astrocyte metabolism of γ -aminobutyric acid (GABA) sustains glutamine synthesis in the mammalian cerebral cortex. *Glia* 68: 2601-2612, 2020.

90. Kwak H, Koh W, Kim S, Song K, Shin JI, Lee JM, Lee EH, Bae JY, Ha GE, Oh JE, *et al*: Astrocytes control sensory acuity via tonic inhibition in the thalamus. *Neuron* 108: 691-706.e10, 2020.
91. Qureshi T, Bjørkmo M, Nordengen K, Gundersen V, Utheim TP, Watne LO, Storm-Mathisen J, Hassel B and Chaudhry FA: Slc38a1 conveys astroglia-derived glutamine into GABAergic interneurons for neurotransmitter GABA synthesis. *Cells* 9: 1686, 2020.
92. Ceyzériat K, Abjean L, Carrillo-de Sauvage MA, Ben Haim L and Escartin C: The complex STATES of astrocyte reactivity: How are they controlled by the JAK-STAT3 pathway? *Neuroscience* 330: 205-218, 2016.
93. Rakers C, Schleif M, Blank N, Matušková H, Ulas T, Händler K, Torres SV, Schumacher T, Tai K, Schultze JL, *et al*: Stroke target identification guided by astrocyte transcriptome analysis. *Glia* 67: 619-633, 2019.
94. Borbör M, Yin D, Brockmeier U, Wang C, Doeckel M, Pillath-Eilers M, Kaltwasser B, Hermann DM and Dzyubenko E: Neurotoxicity of ischemic astrocytes involves STAT3-mediated metabolic switching and depends on glycogen usage. *Glia* 71: 1553-1569, 2023.
95. Wu M, Wang L, Li F, Hu R, Ma J, Zhang K and Cheng X: Resveratrol downregulates STAT3 expression and astrocyte activation in primary astrocyte cultures of rat. *Neurochem Res* 45: 455-464, 2020.
96. Koutsifeli P, Varma U, Daniels LJ, Annandale M, Li X, Neale JPH, Hayes S, Weeks KL, James S, Delbridge LMD and Mellor KM: Glycogen-autophagy: Molecular machinery and cellular mechanisms of glycophagy. *J Biol Chem* 298: 102093, 2022.
97. Heden TD, Chow LS, Hughey CC and Mashek DG: Regulation and role of glycophagy in skeletal muscle energy metabolism. *Autophagy* 18: 1078-1089, 2022.
98. Mayeuf-Louchart A, Lancel S, Sebti Y, Pourcet B, Loyens A, Delhay S, Duhem C, Beauchamp J, Ferri L, Thorel Q, *et al*: Glycogen dynamics drives lipid droplet biogenesis during brown adipocyte differentiation. *Cell Rep* 29: 1410-1418.e6, 2019.
99. Guo H, Li Y, Wang S, Yang Y, Xu T, Zhao J, Wang J, Zuo W, Wang P, Zhao G, *et al*: Dysfunction of astrocytic glycophagy exacerbates reperfusion injury in ischemic stroke. *Redox Biol* 74: 103234, 2024.
100. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, *et al*: Guidelines for the early management of patients with acute ischemic stroke: 2019 Update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 50: e344-e418, 2019.
101. Guo H, Fan Z, Wang S, Ma L, Wang J, Yu D, Zhang Z, Wu L, Peng Z, Liu W, *et al*: Astrocytic A1/A2 paradigm participates in glycogen mobilization mediated neuroprotection on reperfusion injury after ischemic stroke. *J Neuroinflammation* 18: 230, 2021.
102. Geng J, Zhang Y, Li S, Li S, Wang J, Wang H, Aa J and Wang G: Metabolomic profiling reveals that reprogramming of cerebral glucose metabolism is involved in ischemic preconditioning-induced neuroprotection in a rodent model of ischemic stroke. *J Proteome Res* 18: 57-68, 2019.
103. Huang XX, Li L, Jiang RH, Yu JB, Sun YQ, Shan J, Yang J, Ji J, Cheng SQ, Dong YF, *et al*: Lipidomic analysis identifies long-chain acylcarnitine as a target for ischemic stroke. *J Adv Res* 61: 133-149, 2024.
104. Cao J, Dong L, Luo J, Zeng F, Hong Z, Liu Y, Zhao Y, Xia Z, Zuo D, Xu L and Tao T: Supplemental N-3 polyunsaturated fatty acids limit A1-specific astrocyte polarization via attenuating mitochondrial dysfunction in ischemic stroke in mice. *Oxid Med Cell Longev* 2021: 5524705, 2021.
105. Neal M, Luo J, Harischandra DS, Gordon R, Sarkar S, Jin H, Anantharam V, Désaubry L, Kanthasamy A and Kanthasamy A: Prokineticin-2 promotes chemotaxis and alternative A2 reactivity of astrocytes. *Glia* 66: 2137-2157, 2018.
106. Pang QM, Zhang Q, Wu XC, Yang RL, Fu SP, Fan ZH, Liu J, Yu LM, Peng JC and Zhang T: Mechanism of M2 macrophages modulating astrocyte polarization through the TGF- β /PI3K/Akt pathway. *Immunol Lett* 259: 1-8, 2023.
107. Chistyakov DV, Gavrish GE, Goriainov SV, Chistyakov VV, Astakhova AA, Azbukina NV and Sergeeva MG: Oxylipin profiles as functional characteristics of acute inflammatory responses in astrocytes pre-treated with IL-4, IL-10, or LPS. *Int J Mol Sci* 21: 1780, 2020.
108. Shiow LR, Favrais G, Schirmer L, Schang AL, Cipriani S, Andres C, Wright JN, Nobuta H, Fleiss B, Gressens P and Rowitch DH: Reactive astrocyte COX2-PGE2 production inhibits oligodendrocyte maturation in neonatal white matter injury. *Glia* 65: 2024-2037, 2017.
109. Liu M, Xu Z, Wang L, Zhang L, Liu Y, Cao J, Fu Q, Liu Y, Li H, Lou J, *et al*: Cottonseed oil alleviates ischemic stroke injury by inhibiting the inflammatory activation of microglia and astrocyte. *J Neuroinflammation* 17: 270, 2020.
110. Zhang L, Zhao G, Luo Z, Yu Z, Liu G, Su G, Tang X, Yuan Z, Huang C, Sun HS, *et al*: AD16 attenuates neuroinflammation induced by cerebral ischemia through down-regulating astrocytes A1 polarization. *Biomed Pharmacother* 178: 117209, 2024.
111. Zou Y, Pei J, Wan C, Liu S, Hu B, Li Z and Tang Z: Mechanism of scutellarin inhibition of astrocyte activation to type A1 after ischemic stroke. *J Stroke Cerebrovasc Dis* 33: 107534, 2024.
112. Zhou M, Zhang T, Zhang X, Zhang M, Gao S, Zhang T, Li S, Cai X, Li J and Lin Y: Effect of tetrahedral framework nucleic acids on neurological recovery via ameliorating apoptosis and regulating the activation and polarization of astrocytes in ischemic stroke. *ACS Appl Mater Interfaces* 14: 37478-37492, 2022.
113. Liu R, Yu Y, Ge Q, Feng R, Zhong G, Luo L, Han Z, Wang T, Huang C, Xue J and Huang Z: Genistein-3'-sodium sulfonate promotes brain functional rehabilitation in ischemic stroke rats by regulating astrocytes polarization through NF- κ B signaling pathway. *Chem Biol Interact* 400: 111159, 2024.
114. Chen Z, Li T, Tang HB, Lu ZW, Chen ZY, Zhao ZH, Yang XL, Zhao LL, Dang MJ, Li Y, *et al*: Edaravone Dexborneol provides neuroprotective effect by inhibiting neurotoxic activation of astrocytes through inhibiting NF- κ B signaling in cortical ischemia. *Brain Res Bull* 218: 111097, 2024.
115. Li MC, Li MZ, Lin ZY, Zhuang YM, Wang HY, Jia JT, Lu Y, Wang ZJ, Zou HY and Zhao H: Buyang Huanwu Decoction promotes neurovascular remodeling by modulating astrocyte and microglia polarization in ischemic stroke rats. *J Ethnopharmacol* 323: 117620, 2024.
116. Xia X, Chen J, Ren H, Zhou C, Zhang Q, Cheng H and Wang X: Gypenoside pretreatment alleviates the cerebral ischemia injury via inhibiting the microglia-mediated neuroinflammation. *Mol Neurobiol* 61: 1140-1156, 2024.



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