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Unlocking the therapeutic potential of tumor-derived EVs in ischemia-reperfusion: a breakthrough perspective from glioma and stroke

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Abstract

Clinical studies have revealed a bidirectional relationship between glioma and ischemic stroke, with evidence of spatial overlap between the two conditions. This connection arises from significant similarities in their pathological processes, including the regulation of cellular metabolism, inflammation, coagulation, hypoxia, angiogenesis, and neural repair, all of which involve common biological factors. A significant shared feature of both diseases is the crucial role of extracellular vesicles (EVs) in mediating intercellular communication. Extracellular vesicles, with their characteristic bilayer structure, encapsulate proteins, lipids, and nucleic acids, shielding them from enzymatic degradation by ribonucleases, deoxyribonucleases, and proteases. This structural protection facilitates long-distance intercellular communication in multicellular organisms. In gliomas, EVs are pivotal in intracranial signaling and shaping the tumor microenvironment. Importantly, the cargos carried by glioma-derived EVs closely align with the biological factors involved in ischemic stroke, underscoring the substantial impact of glioma on stroke pathology, particularly through the crucial roles of EVs as key mediators in this interaction. This review explores the pathological interplay between glioma and ischemic stroke, addressing clinical manifestations and pathophysiological processes across the stages of hypoxia, stroke onset, progression, and recovery, with a particular focus on the crucial role of EVs and their cargos in these interactions.

Keywords Glioma, Ischemic stroke, Extracellular vesicles, Immunomodulation, Angiogenesis

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Introduction

Gliomas are primary brain tumors thought to originate from neuroglial stem or progenitor cells. They constitute nearly 30% of all primary brain tumors and 80–85% of malignant cases, accounting for the majority of deaths caused by primary brain tumors [1, 2]. Stroke is the second leading cause of disability and death worldwide, with the highest burden observed in low- and middle-income countries, where ischemic stroke accounts for approximately 85% of all cases [3, 4]. In this context, clinical studies have demonstrated a bidirectional relationship between glioma and ischemic stroke. The induction of ischemic stroke in glioma patients has been widely reported in clinical studies [5, 6]. On one hand, this is due to the direct infiltration or compression of blood vessels by the tumor [7]; on the other hand, the effects of paraneoplastic syndrome and anticancer treatments have also been mentioned [8–10]. Conversely, ischemic stroke survivors exhibit a higher age-adjusted annual cancer incidence rate compared to the general population, with evidence of spatial consistency observed [11, 12]. This bidirectional interaction between glioma and ischemic stroke, as reported in clinical studies, can be attributed to the significant overlap in their underlying pathologies, which will be illustrated in detail below.

The pathogenesis of intracranial tumors is complex, involving angiogenesis, immune suppression, metabolic alterations, genetic and epigenetic mutations, as well as changes in the tumor microenvironment and blood-brain barrier disruption [2, 13]. Ischemic stroke occurs when blood flow to a part of the brain is blocked, typically due to a blood clot or occlusion of the brain artery, which leads to a lack of oxygen and nutrients, resulting in brain cell damage [14, 15]. As the disease progresses, it involves vascular pathology, tertiary collateral circulation, tissue ischemia and necrosis, inflammatory cascades at onset, oxidative stress, disruption of the blood-brain barrier (BBB), inflammation modulation with scar formation and resolution, angiogenesis, and neural function compensation [14, 16]. It is obvious that gliomas share numerous pathological similarities with stroke, including immune modulation, oxidative stress, blood-brain barrier disruption, and angiogenesis. These mechanisms are also involved in stroke risk factors, stroke onset, and recovery.

The construction of the tumor microenvironment (TME) plays a critical role in glioma development, as the tumor modulates intracranial cell function through the TME, creating a supportive environment for its growth [17]. During this process, various bio factors, such as chemokines, are secreted via autocrine or paracrine mechanisms through extracellular vesicles (EVs), diffusing within the central nervous system [18–20]. EVs play a key role in complex, long-distance intercellular signaling in multicellular organisms by protecting their cargos from enzymatic degradation through a lipid bilayer structure that prevents enzyme penetration [21, 22]. Given the pivotal role of EVs in TME construction and intercellular communication, understanding the molecular interplay between glioma and ischemic stroke, particularly through the involvement of EVs, provides valuable insights into their shared pathophysiology and offers potential therapeutic targets for managing both conditions simultaneously [23–25].

In this review, we will elucidate the interplay between glioma and ischemic stroke, with a particular focus on EVs, which facilitate complex intercellular signaling in multicellular organisms and share numerous common cargos between glioma and ischemic stroke [26, 27].

Extracellular vesicles

EVs are small, membrane-bound vesicles secreted by cells into the extracellular environment. Since 2004, the term "exosome" has been widely used in the scientific literature to refer to various types of EVs. However, in September 2011, the International Society for Extracellular Vesicles (ISEV) formally adopted "extracellular vesicles" as a general term, leading to its widespread use [28]. This shift in terminology reflects a growing recognition that EVs are not merely a cellular waste disposal mechanism but also play a critical role in cell-to-cell communication [29].

The therapeutic and diagnostic potential of EVs arises from their ability to shield cargos during circulation and function as natural carriers of complex biological materials—including proteins, lipids, and nucleic acids (mRNA, miRNA, circRNA, lncRNA, and rRNA)—between cells [30–32]. Because ribonucleases, deoxyribonucleases, and proteases cannot penetrate the EV lipid bilayer, encapsulating sensitive cargos within vesicles protects it from enzymatic degradation in the extracellular environment [21, 22]. Thus, EV biogenesis represents a significant evolutionary advancement, facilitating complex intercellular signaling in multicellular organisms [26, 27]. EVs are secreted by all cell types and can be found in nearly all body fluids, including blood [33], saliva [34], cerebrospinal fluid (CSF) [35], breast milk [36], urine [37], and semen [38], underscoring their promising value of EVs in clinical biomarker studies. Their ability to travel through these fluids enables them to deliver functional information to distant sites within the body [39]. These findings confirm the unique role of EVs in cell-to-cell material transport, particularly over long distances, and provide insights into cellular processes in both pathological and physiological contexts [40].

Despite extensive research, the clear classification of EVs remains challenging. Traditionally, EVs are broadly divided into three main categories: (a) microvesicles, which are generated by outward budding and fission of the plasma membrane; (b) exosomes, formed within the

endosomal system and released when multivesicular bodies fuse with the plasma membrane; and (c) apoptotic bodies, which are shed as blebs from cells undergoing apoptosis [41]. However, because assigning an EV to a specific biogenesis pathway is complex, ISEV recommends using operational terms for EV subtypes based on their physical characteristics. For example, "small EVs" (sEVs) refer to particles smaller than 100–200 nm, while "medium/large EVs" (m/l EVs) refer to those larger than 200 nm. Additionally, EVs can be categorized by density into low, middle, and high ranges, each with specific definitions [42].

EVs play a significant role in the pathogenesis of various diseases, including cancer and stroke [31, 43]. They contribute not only through intercellular communication but also by altering the extracellular environment at lesion sites and influencing both physiological and pathological metabolic processes [22, 43, 44].

Interplay revealed in clinical reports between glioma and ischemic stroke

Although ischemic stroke and glioma are separate and distinct conditions, each with its unique characteristics, numerous clinical investigations have demonstrated a distinct bidirectional relationship between glioma and stroke, as shown in Fig. 1. On the one hand, glioma can increase the risk of ischemic stroke. Certain intracranial gliomas, particularly those located in regions such as the insula, operculum, and temporal lobe, may infiltrate or compress blood vessels, potentially leading to the occurrence of ischemic stroke [7]. In a case report, two adult patients with supratentorial glioblastomas (GBM)

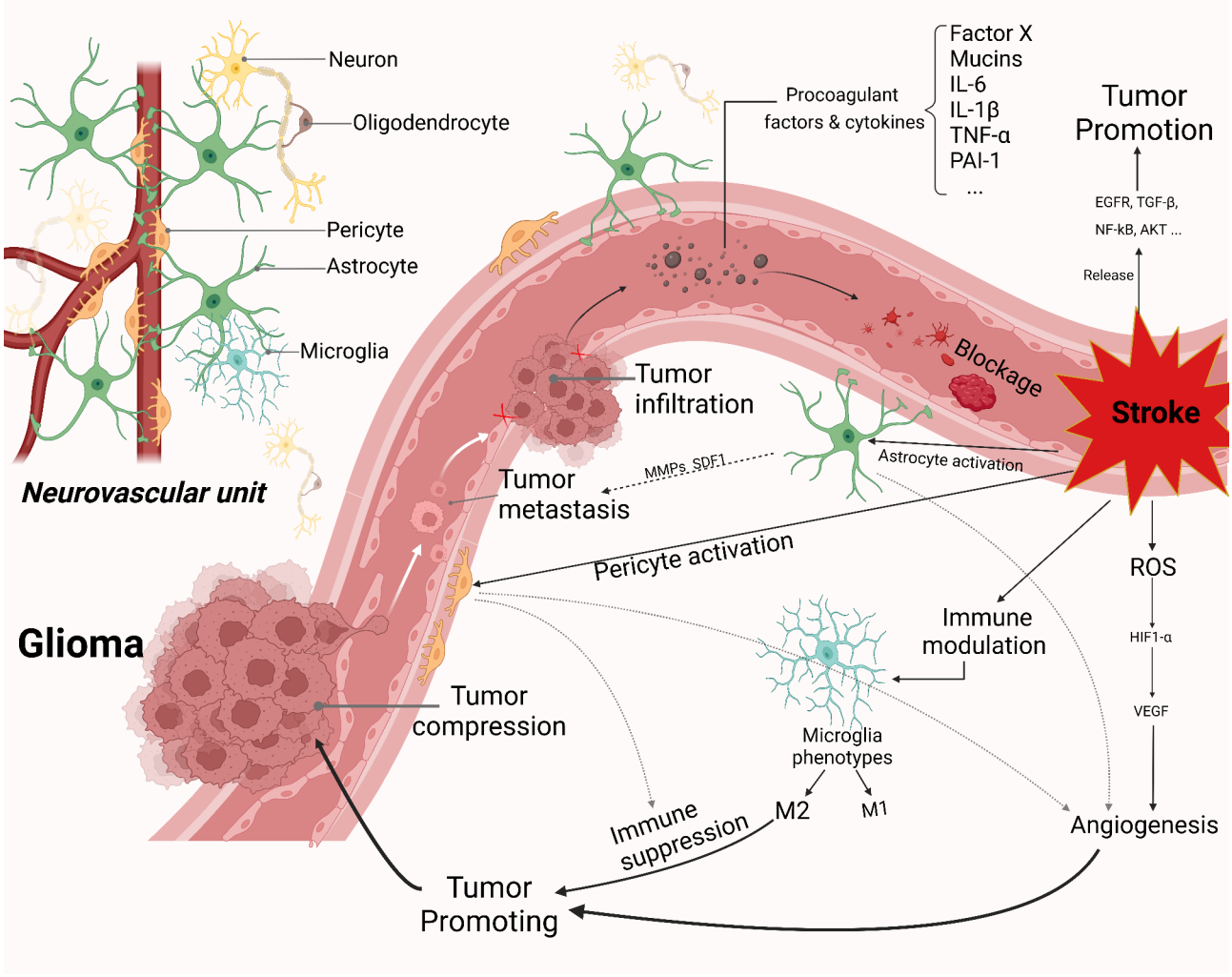

Fig. 1 Neurovascular unit and the interplay between stroke and glioma. Numerous clinical investigations have demonstrated a distinct bidirectional enhancement between glioma and stroke, suggesting their reciprocal interaction in mechanisms. Abbreviations: ROS = reactive oxygen species, Factor X = coagulation factor X, IL-6 = interleukin-6, IL-1β = interleukin-1 beta, TNF-α = tumor necrosis factor alpha, PAI-1 = plasminogen activator inhibitor-1, EGFR = epidermal growth factor receptor, NF-kB = nuclear factor kappa-light-chain-enhancer of activated B cells, AKT = protein kinase B, MMPs = matrix metalloproteinases, SDF1 = stromal cell-derived factor 1, HIF1-α = hypoxia-inducible factor 1 alpha, VEGF = vascular endothelial growth factor

experienced ischemic stroke precisely at the tumor site [5, 6]. A clinical study further demonstrated that patients afflicted with gliomas face an increased risk of ischemic stroke, with incidence rates up to 9%, compared to 2.7% in the general population [45, 46]. Stroke has also been identified as a common postoperative and late complication of radiotherapy, and it is linked to tumor-induced hypercoagulability or nonbacterial thrombotic endocarditis [9, 10]. In their research, Schlehofer and colleagues found a combined odds ratio of 1.9, indicating a potential association between self-reported stroke within two years before meningioma or glioma diagnosis, indicating stroke as a possible risk factor for glioma [47]. Additionally, the migration of metastatic glioma cells increases the likelihood of emboli formation, potentially leading to the onset of stroke, as revealed previously [8]. On the other hand, evidence also suggests that patients with prior stroke may have a higher risk of glioma. Wojtasiewicz et al. [12] reported a case in which a patient developed glioblastoma in a previously infarcted area, two years after experiencing an ischemic stroke. Qureshi et al. [11] recorded 3680 noncancerous adults and found that ischemic stroke survivors had a higher age-adjusted annual cancer incidence rate than the general population. A correlation has been observed between stroke and malignant glioma development. Chen et al. [48] uncovered that female patients aged 40–60 years who experienced stroke demonstrated a heightened vulnerability to glioma development, with adjusted hazard ratios of 7.41 and 16.3, respectively.

Alterations in the pathophysiological dimensions of glioma and ischemic stroke

The rapid proliferation of glioma cells, metastatic activity, blood-brain barrier disruption, and the release of micro- and macroparticles into circulation collectively contribute to thrombosis and capillary obstruction in glioma [49, 50]. This complex glioma-induced complex homeostatic changes often result in localized ischemia. Glioma cells release various procoagulant factors and cytokines, such as factor X and mucins, which activate monocytes, endothelial cells, and platelets [51, 52]. Additionally, they stimulate neutrophils to form neutrophil extracellular traps (NETs) and inhibit protein C activation [53]. These processes induce localized inflammation and ischemic hypoxia within the glioma microenvironment. Numerous studies have indicated that various forms of glioma therapy, namely platinum-based drugs, angiogenesis inhibitors, and radiotherapy, are associated with an elevated susceptibility to thromboembolism [7]. As shown in Fig. 2, we demonstrate the significant interplay between the pathophysiological dimensions of glioma and ischemic stroke, which will be described in detail in the following sections. This indicates that investigating the shared pathological mechanisms from glioma to stroke holds substantial importance in enhancing our comprehension of stroke occurrences related to cancer.

Hypoxia-related reactive oxygen species (ROS)

Glioma and ischemic stroke share numerous pathological pathways, including hypoxia [43]. In tumors, hypoxia can arise from either disrupted vascular supply or when

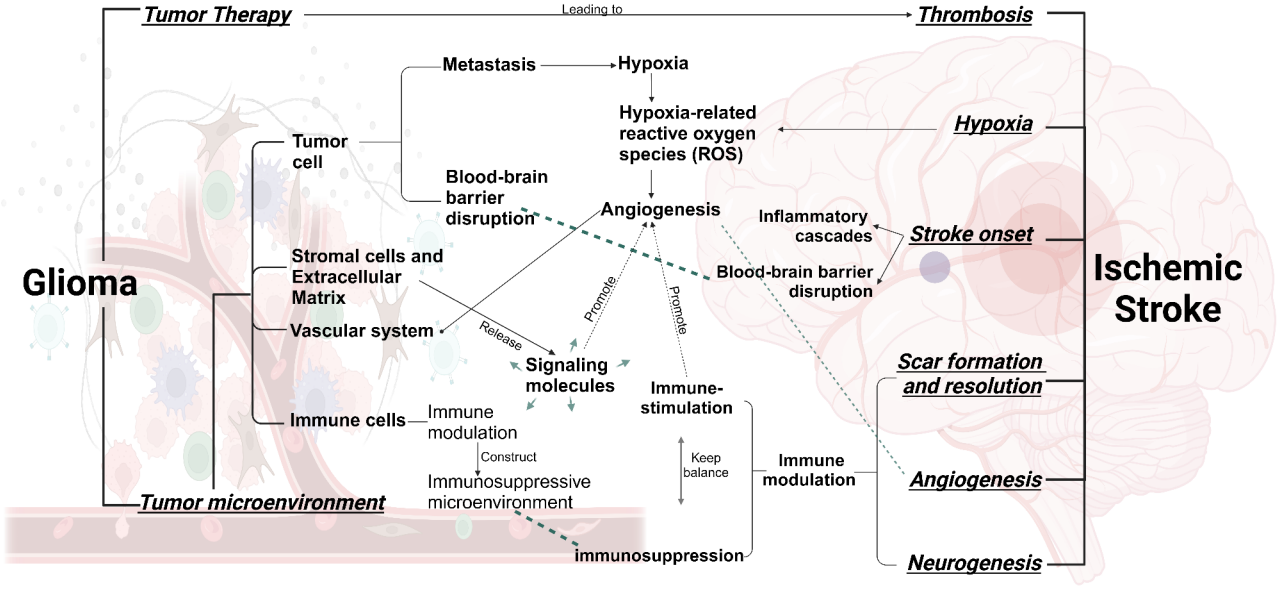

Fig. 2 The pathological overlap between stroke and glioma is significant. Pathological interactions between glioma and stroke are highly overlapping, forming a complex network. This suggests that the impact of glioma on stroke encompasses various stages, including risk factors, pre-stroke hypoxic conditions, stroke onset, and post-stroke recovery

tumor growth outpaces existing vascular blood support. During ischemic stroke, sudden blockage of cerebral blood flow results in rapid oxygen depletion, leading to immediate and irreversible neuronal death, accompanied by extensive brain damage at the infarct core. Numerous origins of ROS generation have been documented in both ischemia and glioma. Notably, these two conditions exhibit a shared interconnected signaling network involved in ROS production and subsequent downstream effects [7]. ROS are reactive molecules formed due to unpaired electrons in the outer orbits of specific molecules resulting from oxygen's partial reduction [54]. This unstable state of oxygen leads to the generation of free radicals through a process of partial reduction [55].

During the progression of glioma, elevated intrinsic ROS levels are implicated in a wide array of activities, including the stimulation of oncogenes, augmentation of metabolic processes, and disruption of mitochondrial functionality [55]. In ischemic stroke, ROS levels transition from baseline to peak concentrations during the reperfusion phase [56]. This surge in ROS level potentially plays a role in processes such as apoptosis and cellular necrosis. ROS at a toxic level due to an imbalance in production and antioxidant neutralization by antioxidant enzymes, leads to cellular injury via lipid peroxidation, protein oxidation, and DNA damage [56]. Intracellular reactive ROS are generated predominantly by electron transfers from nicotinamide adenine dinucleotide phosphate (NADPH) oxidase to molecular oxygen [57].

Blood-brain barrier (BBB)

The BBB consists of the contiguous endothelial lining of capillaries, closely interlinked cellular junctions, an undamaged basement membrane, pericytes enwrapping vessels, microglial cells, and glial membrane enveloped by astrocytes [58]. Glioma advancement is closely intertwined with the development of new blood vessels, with a key clinical complication being vasogenic brain edema, which significantly elevates intracranial pressure due to compromised BBB integrity and increased permeability [59]. Glioma cells exert influences on the BBB both directly, through interactions with nearby BBB regions, and indirectly, by releasing various biochemical substances [60]. These cells secrete factors such as vascular endothelial growth factor (VEGF), which compromise BBB integrity, increase permeability, and enable tumors to access nutrients and oxygen from the bloodstream [61]. The BBB also allows immune cells, including tumor-associated macrophages, to infiltrate the brain, potentially accelerating tumor progression [62]. In the context of an ischemic stroke, disrupted BBB leads to the leakage of blood-borne cells, chemicals, and fluid into the brain parenchyma [63, 64]. This occurs due to heightened paracellular and transcellular permeability, along with significant damage to the endothelial cells that form the barrier [63, 64]. This disruption destabilizes water and ion balance in the brain, resulting in cerebral edema [64, 65]. The infiltration of leukocytes further exacerbates inflammation, intensifying damage to brain tissue [64, 66]. In stroke or glioma, although BBB dysfunction generally leads to adverse outcomes, it may offer a potential advantage by allowing therapeutic agents to reach intended brain targets more effectively.

Neurovascular unit

Pericytes

Pericytes envelop a significant portion of the surface of brain capillary endothelial cells, especially in regions with a pericyte-to-endothelial cell ratio of 1:3 [67]. As essential components of the neurovascular unit and BBB, pericytes act as gatekeepers, regulating the passage of brain cells as well as the transport of nutrients and other substances between the bloodstream and the brain's interstitial fluid [68]. Numerous studies suggest an association between pericytes and pathological changes in the BBB, which have been linked to stroke. Ischemic injury to pericytes within the cerebral microvasculature has a detrimental effect on the damage caused by stroke and the development of brain edema [69, 70]. This injury disrupts microvascular blood flow and compromises the integrity of the blood-brain barrier, exacerbating the overall impact of the stroke on brain tissue [69, 70]. Conversely, signaling pathways activated in pericytes within the vasculature of the peri-infarct area in response to ischemia positively impact stroke outcomes. These signaling events promote post-stroke angiogenesis and neurogenesis, contributing to recovery and healing after a stroke [70, 71]. While in the glioma context, glioblastoma cells leverage interactions with pericytes to promote GBM cell proliferation and enhance tumor growth [72]. An in vivo investigation of glioblastoma cell proliferation was conducted by grafting co-cultured human RFP-labeled glioblastoma cells and GFP-labeled mouse pericytes onto the brain cortex of an immunocompetent mouse model. Mice with these xenografts exhibited an enhanced level of perivascular infiltration of glioblastoma cells in their brain tissues [73]. Pericytes play crucial roles in tumor angiogenesis. Huizer et al. indicated that pericytes serve as the primary source of periostin in human gliomas, where periostin plays a vital role in facilitating blood vessel growth and branching [74]. Furthermore, pericytes can modulate their own immune properties, enabling immune evasion. In vitro, analysis of membrane molecules involved in suppressing antitumor immune responses, such as interleukin-1 receptor antagonists, revealed that pericytes display an immunosuppressive pattern of surface molecules after interacting with glioblastoma cells [72].

Astrocytes

Astrocytes, especially their extended endfeet encompassing the extracellular matrix and pericytes, serve as the final barrier against the entry of undesirable proteins and molecules. These astrocyte-loaded endfeet al.so play a crucial role in strengthening the BBB by releasing specific bioactive substances including growth factors such as VEGF and glial cell-derived neurotrophic factor [75–77]. Astrocytic dysfunction, marked by the detachment of endfeet from the basement membrane, occurs shortly after a stroke [77, 78]. In response to minor ischemic injury, astrocytes begin proliferating, causing enlargement of both their cell bodies and processes along with elevated expression of glial fibrillary acidic protein (GFAP). As the extent of injury escalates, astrocytes undergo substantial proliferation, resulting in a more pronounced increase in GFAP expression. Glioma cells establish attachments to blood vessels utilizing bradykinin, a chemotactic signaling peptide produced by vascular endothelial cells [79]. Glioma cells then proceed to envelop the external surface of the existing blood vessels through invasive and parasitic mechanisms, infiltrating the adjacent space [80]. This invasive conduct disrupts the connection between astrocyte end feet and endothelial cells, which ultimately results in the breakdown of the BBB [81]. Notably, ischemia-induced astrocyte activation, followed by mutations in genes like neurofibromatosis type 1 and glycoprotein podoplanin during reactive gliosis, has been implicated in gliomagenesis [7]. This is due to the proposition that both glial progenitor cells and reactive astrocytes are suggested sources of identical lineages. Reactive astrocytes also enhance glioma cell proliferation and migration by producing matrix metalloproteinases (MMPs) and releasing stromal cell-derived factor 1 (SDF1) [82, 83]. Furthermore, tunneling nanotubes and the secretion of various molecules such as Interleukin-6 (IL-6), IL-19, Insulin-like Growth Factor 1 (IGF-1), transforming Growth Factor-β (TGF-β), monocyte Chemoattractant Protein 4 (MCP4), and VEGF also contribute to the role of reactive astrocytes in promoting glioma infiltration [84, 85].

Microglia

In a normal physiological state, microglia, the resident immune cells of the central nervous system (CNS), exhibit a ramified morphology and contribute significantly to brain homeostasis, thus forming an integral component of the neurovascular unit [86]. Upon exposure to environmental stress or injury, microglia transform morphologically, adopting an amoeboid shape with shorter projections and larger cell bodies. The diverse biological characteristics exhibited by microglia in response to injury correspond to distinct phenotypes, as indicated by the pro-inflammatory M1 phenotype and the anti-inflammatory M2 phenotype [87]. These phenotypes are marked by unique secretion patterns. M1 microglia release pro-inflammatory cytokines, including IL-6, IL-1β, ROS, tumor necrosis factor-α (TNF-α), inducible nitric oxide synthase (iNOS), and reactive nitrogen species (RNS). In contrast, M2 microglia predominantly secrete anti-inflammatory cytokines such as IL-4, IL-10, TGF-β1, IGF-1, and nerve growth factor (NGF) [88, 89]. Manipulating the transition of resident microglia from the M1 to the M2 state presents an intriguing target for potential therapeutic interventions in stroke treatment [90].

In glioma, microglia and macrophages constitute the most abundant population of infiltrating cells, collectively accounting for at least one-third of the total tumor mass [91]. Evidence supports that microglia significantly contribute to creating a tumor-promoting microenvironment that promotes the growth of gliomas [92]. Specifically, the presence of transformed microglia, transitioning from the M1 (tumor-suppressive) to the M2 (tumor-promoting) state, is a key facilitator in inducing immune suppression within the tumor region [7]. This transformation and immune suppression contribute to the augmentation of tumor expansion, metastasis, angiogenesis, and the maintenance of glioma stem cells. These processes are mediated through the secretion of various factors, such as MMPs, VEGF, IL-10, TGF, TNF, chemokine ligand 18 (CCL18), and CCL22, CXCL12, and Fas ligand [7].

Angiogenesis

Recent studies have highlighted the importance of neurovascular networks, underscoring the critical communication between neurons and blood vessels for proper brain function [93]. Sprouting angiogenesis, which involves the emergence of new blood vessels from existing ones, plays a crucial role in both physiological processes such as tissue regeneration, wound healing, and morphogenesis, as well as in pathological conditions like tumor growth and ischemic stroke [94]. Although both stroke and tumor angiogenesis involve the formation of new blood vessels, their underlying mechanisms, purposes, and outcomes are distinct. Poststroke angiogenesis is generally regarded as a favorable defense response against hypoxia by improving the blood supply to the brain tissue. In contrast, increased angiogenesis within cancer tissue supplies oxygen and nutrients to cancer cells, thereby promoting tumor growth, invasion, and metastasis [95].

Angiogenesis typically begins 4 to 7 days after cerebral ischemia, primarily at the boundary between the ischemic core and the surrounding tissue. This post-ischemic angiogenesis potentially supports the remodeling of neurons by promoting neurogenesis and participating in the guidance of sprouting axons, facilitated by signaling

pathways involving vascular endothelial growth factor and laminin/β1-integrin [96]. In tumors, the expanding cell mass leads to both an increased oxygen demand and an increased diffusion distance between nearby capillaries and the central region, which together contribute to decreased oxygen availability [97]. This phenomenon further contributes to the establishment of a hypoxic microenvironment. Cancer angiogenesis is then activated to meet the nutritional and oxygen demands of cancer cells, enabling their proliferation. This process includes multiple stages: basement membrane degradation, endothelial cell proliferation, migration, sprouting, branching, and tubular structure formation [43, 98].

Cancer cells produce a variety of proangiogenic factors while concurrently suppressing the action of antiangiogenic factors within their surrounding environment, thereby facilitating the growth of blood vessels [43]. It's important to mention that certain tumor cell secretions, such as extracellular vesicle-associated miR-181b-5p and miR-210, have been reported to promote post-stroke angiogenesis [43]. These findings suggest the therapeutic potential of glioma-derived EVs through post-stroke angiogenesis. However, comprehensive information regarding these phenomena is currently limited, and further substantiated evidence is required to fully understand and validate these aspects.

Immune response

The immune response is divided into two main branches: the innate and adaptive immune systems. The innate immune response, also known as the inflammatory response, acts as the body's first line of defense against pathogens and is the primary reaction to tissue injury [99]. In contrast, the adaptive immune system, involving lymphocytes (B cells and T cells), is more specialized and targets specific pathogens. While the adaptive response takes longer to activate initially, it develops immunological memory, allowing for a faster and more efficient reaction upon re-exposure to the same pathogen [99]. Inflammation can exacerbate tissue damage in acute stroke, but subsequent adaptive immune responses and anti-inflammatory processes are essential for tissue repair [14, 100]. After a stroke, damaged cells release alarm signals or molecules referred to as damage-associated molecular patterns (DAMPs), which encompass a variety of components, such as nuclear proteins, nucleic acids, heat-shock proteins, and other molecules [101]. DAMPs act as initiators, activating immune responses by binding to specialized pattern recognition receptors. Glioma cells, on the other hand, have the ability to attract various cells, including immune cells, to their microenvironment by releasing cytokines such as TGF-β and GM-CSF which serve as signals that guide these immune cells to the specific niche [102, 103]. Subsequently, the glioma cells influence these recruited cells, inducing them to adopt tumor-promoting phenotypes that facilitate the tumor's growth and progression [104]. Once recruited, these immune cells can form a physical barrier, impeding the access of additional immune cells and hindering their ability to target tumor cells effectively. Glioma-associated microglia and macrophages can drive immune cells into pro-inflammatory or anti-inflammatory phenotypes, modulate the immune response, and reduce the immune system's attack on tumor cells, thereby enhancing glioma survival [105]. Additionally, glioma-associated microglia and macrophages reorganize the extracellular matrix, making tumor cells more susceptible to invasion [106, 107]. In conclusion, in ischemic stroke, the immune response plays a dual role: it aims to repair damaged tissue and restore homeostasis, while also potentially exacerbating injury through inflammatory processes [100]. In contrast, the immune response in tumors focuses primarily on recognizing and eliminating abnormal cells within the complex tumor microenvironment [104, 105].

The impacts of diverse cargos within glioma-derived EVs on glioma progression

The tumor microenvironment comprises tumor cells and surrounding components, including innate and adaptive immune cells, mesenchymal fibroblasts, and vascular and lymphatic networks [17]. Various chemokines, secreted through autocrine or paracrine mechanisms, make up the TME [18, 19]. Tumor growth is driven by the interactions between tumor-residing cells and the TME, and alterations in the microenvironment can significantly affect tumorigenesis and progression [17, 25]. Glioma-derived EVs transport bioactive cargos into the TME and recipient cells, playing critical roles in intercellular communication [24, 108]. These EVs can alter cellular functions or reprogram recipient cells, influencing tumor immune tolerance, promoting malignant transformation, and mediating interactions within the TME. Additionally, glioma-derived EVs regulate glioma cell stemness, contribute to angiogenesis, drive treatment resistance, and are implicated in neurodegenerative disease pathology [24, 108].

The vesicles carry a range of molecular modifiers that facilitate communication between cancer cells and surrounding stromal cells, with numerous EV cargos identified in clinical reports [109–111]. This EV-mediated intercellular communication provides critical insights into the molecular characteristics of tumors, promoting tumor growth, metabolism, invasion, and resistance [23, 112]. Beyond their direct impact on glioma properties, EV cargos also have indirect effects, including immune suppression and angiogenesis. In this review, we compile recent reports on glioma-derived EV cargos, as shown in Table 1. We categorized them by function and ranked

Table 1 Cargos within glioma-derived EVs

Cargo	Patients / Models	Sample type of EVs	Proposed action of cargos	Ref.
Tumor growth, metabolism, invasion, and resistance				
L1CAM (L1, CD171)	GBM cell line	Culture media	Glioblastoma cell motility, proliferation, and invasiveness	[112]
MYO1C	Glioma-derived endothelial cells / glioma cell line	Culture media	Glioma cell migration	[252]
AHIF	GBM patients / cell lines	Culture media	Promotion of glioblastoma progression and radio resistance	[143]
TrkB	GBM patients / cell line	Plasma / Culture medium	Promotion of glioblastoma aggressiveness	[141]
AQP4	Glioma cell line	Conditioned medium	Influence on tumor cell fate toward invasiveness or apoptosis	[142]
miR-375	Glioma cell lines	Glioma tissue / Culture media	Suppression of glioma proliferation, migration, and invasion	[147]
miR-221	Glioma cell lines	Culture media	Tumor progression and temozolomide resistance	[156]
miR-301a	GBM patients	Serum	Tumor proliferation and invasion	[253]
miR-151a	TMZ-resistant cell lines / glioblastoma patients	Culture media / Serum and CSF	Inhibition of XRCC4-mediated DNA repair	[157]
miR-148a	GBM patients / cell line	Serum	Promotion of glioblastoma proliferation and metastasis	[151]
miR-1	GBM cell lines	Culture media	Inhibition of invasion, and neutrosphere formation	[131]
miR-9	Glioma cell lines	Culture medium	Induction of malignant phenotypes in glioma cells	[254]
miR-454-3p	Glioma patients / cell line	Serum	Inhibition of cell proliferation, autophagy, wound healing, and invasion	[255]
miR-30b-3p	Glioma stem-like cells	Culture media	Decrease in apoptosis, increase in proliferation, and TMZ resistance	[158]
lncRNAATB	Glioma cell line	Culture media	Promotion of tumor invasion	[256]
lncRNA ROR1-AS1	Glioma patients / Glioma cell line	Glioma tissue / Culture media	Promotion of tumor progression	[257]
lncRNA SBF2-AS1	GBM cell lines	Culture medium	Enhancement of chemoresistance to TMZ	[258]
Mitochondrial DNA	U87MG cell line	Culture media	Diffusion of altered mtDNA in cells	[109]
Angiogenesis				
CXCR4, VEGF, MMPs, plasminogen activators, PAI-PA, TGF-β	GBM cell line	Culture media	Angiogenesis	[174]
CAV1, IL-8, MMP9, PTX3, IL8, PDGFs, CD26, PAI1, etc.	GBM l lines / tumor-bearing mice / GBM patients	Plasma / Culture media	Vascular cell activation	[129]
miR-1	GBM cell lines	Culture media	Inhibition of angiogenesis	[131]
miR-26a	Glioma stem cells	Culture media	Angiogenesis	[126]
lncRNA HOTAIR	GBM cell line	Culture media	Pro-angiogenic activity	[198]
linc-CCAT2	Glioma cell lines	Culture supernatant	Enhancement of angiogenesis and inhibition of endothelial cell apoptosis	[125]
linc-POU3F3	Glioma cell lines	Culture media	Angiogenesis	[130]
Immunity				

Table 1 (continued)

Cargo	Patients / Models	Sample type of EVs	Proposed action of cargos	Ref.
EGFR, EGFR vIII, HSP/HSC70, TGF-β1	Glioma cell line	Culture media	Immune modulation	[115, 259]
miR-451/miR-21	Primary human GBM cell / glioma lines	Culture media	Immune suppression	[114]
	Phagocyte polarization			
Arginase-1	GBM cell line	Culture supernatant	M2 macrophage polarization	[213]
IL-6, and miR-155-3p	GBM cell lines	Culture supernatant	M2 macrophage polarization	[193]
HMGB3	Glioma patients / glioma cell lines	Culture medium	M2 macrophage polarization, NLRP3 inflammasome activation, and pyroptosis	[260]
microRNA-1246	GBM cell line	Culture supernatant	M2 macrophage polarization	[123]
circNEIL3	Glioma patients / glioma cell lines	Culture media / Tissues	Promotion of glioma progression and macrophage immunosuppressive polarization	[261]
	Myeloid-derived suppressor cells (MDSCs)			
SDF-1α	Glioma cell lines	Culture media	Immunosuppressive function mediated by MDSCs	[216]
miR-10a/miR-21	Glioma cell lines / mice	Culture media	Immunosuppressive function mediated by MDSCs	[119]
miR-29a and miR-92a	GBM and glioma cell lines / mice	Culture media	Immunosuppressive function mediated by MDSCs	[262]
miR-1246	Glioma patients / glioma cell line	CSF and plasma / Culture medium	Differentiation / immunosuppressive function of MDSCs	[219]
miR-1298-5p	Glioma patients / glioma cell line	CSF	Immunosuppressive function mediated by MDSCs	[220]
	T cell modulation			
CD73	GBM patient	CSF / Blood	Inhibition of T-cell clonal expansion	[242]
IFN-γ and Granzyme B	GBM cell line / mice	Culture medium	inhibition of CD8 + T cells	[121]
PD-L1 and PD-L1 DNA	Primary human GSCs Cell	Conditioned medium / serum and plasma	inhibition of T cell function	[238]
	NK cells Related			
miR-1983	Glioma cell line / mice	Culture medium	Stimulation of anti-glioma NK activity	[120]
	Biomarker study			
PTRF/Cavin1	Glioma cell line/glioma patients	Cell supernatant / Glioma sample / Blood	Biomarker analysis	[263]
EGFR, EGFRvIII, PDGFR, PDPN, EphA2, IDH1 R132H, CD41, MHCII, HSP-90, Alix, Tsg101, CD9, CD63, CD81, flotillins-1	GBM cell line / patients	Culture media / Blood samples	Biomarker profiling	[110]
ACTR3, ANXA1, CALR, CTSD, ECM1, ITGB1, IGF2R, IPO5, MVP, PDCD6IP, PSMD2, PSAP	GBM cell line	Culture media	Proteome profiling analysis	[264]
EGFRvIII	GBM patients	CSF	Biomarker analysis	[134]
CD9, CD63, and CD81	GBM stem-like cells	Culture media / Plasma	Characterization analysis of extracellular vesicles	[265]
SDC1	Glioma patients / glioma cells	Culture media / Plasma	Plasma extracellular vesicle immune profiling	[266]
GFAP and Tau	GBM cell lines / patients	Culture media / Plasma	Biomarker analysis with DEP platform	[267]
IFN-γ, IL-10, IL-13, B7-1, B7-2, ICOSL, CD63, and Flotillin-1	Glioma patients	Plasma	Biomarker analysis	[111]
vWF, APCS, C4B, AMBP, APOD, AZGP1, C4BPB, Serpin3, FTL, C3, and APOE	Patients with GBM	Plasma	Proteomic analysis	[268]
vWF	GBM patient	Plasma	Biomarker analysis	[269]

Table 1 (continued)

Cargo	Patients / Models	Sample type of EVs	Proposed action of cargos	Ref.
FASN	Glioma patients, GSC cell lines, GBM cell lines	Plasma / Conditioned medium	Biomarker analysis	[270]
ALDOA, 14-3-3E, ECH1, and TM11B	GBM patients	Saliva	Proteome profiling	[271]
LGALS3BP	Glioma patients	Plasma	Biomarker analysis	[272]
IDH1 mRNA	Patient with glioma	CSF / Serum	Biomarker analysis	[273]
MGMT and APNG mRNA	Patient with glioma / GBM cell lines / mouse model	Culture media / Serum	Biomarker analysis	[274]
miR-21	GBM patient / cell lines	CSF / Culture media	Biomarker analysis	[133]
miRNA-21	Glioma patients	CSF and Serum	Biomarker analysis	[228]
miR-320 and miR-574-3p	Patients with GBM	Serum	Biomarker analysis	[275]
miR-29a and miR-30e	Glioma cell line	Culture media	Biomarker analysis	[128]
CV575560, RKHD1, ZNF784, SERPINB1 RNA	Primary GBM patients	Blood sample	Microarray study	[276]
miR-21, miR-103, miR-24, and miR-125	GBM patients	CSF	Enrichment of miRNA in EVs	[226]
miR-21, miR-222, and miR-124-3p	Glioma patients	Serum	Biomarker analysis	[227]
mRNA of IL-8, TIMP-1, TGF-β, PD-1 and ZAP70	Glioma patients	Plasma	Biomarker analysis	[277]
miR-210, miR-185, miR-5194, and miR-449	GBM patients	Plasma	MicroRNA profiling	[278]
circATP8B4	Radioresistant U251 cells	Culture media	circRNA expression profile	[154]
sncRNA RNU6	Patients with GBM	Serum	Biomarker analysis	[275]
IDH1G395A gDNA	Primary GBM cells / Mice	Blood sample / Culture media	Biomarker analysis	[279]

them based on chemical properties, such as proteins and nucleic acids.

Glioma-derived EVs participate in constructing an immunosuppressive TME

In the immunosuppressive tumor microenvironment, immune cells and glioma cells compete for nutrients, and the metabolites produced during this competition can influence immune cell differentiation and function [17, 113]. This competition contributes to the immunosuppressive environment, where tumor-released cargos in EVs transmit signals that are taken up by immune cells in the brain, shifting their cytokine profiles toward immune suppression [114, 115]. In this process, the recipient cells of these cargos include monocytes, myeloid-derived suppressor cells (MDSCs), NK cells, CD8 + T cells, CD4 + T cells, microglia, and macrophages, often resulting in the suppression of immune cell activity, induction of M2 macrophage polarization, regulation of microglia, activation of MDSCs, and modulation of T cell expansion or function. Ultimately, these interactions facilitate metastasis and immune evasion [116–123]. Though immunosuppressive cargos are predominant, immune-activating cargos have also been identified. For instance, Shah et al. found that miR-1983, a glioma-derived cargo, enables NK cells to kill glioma cells through the miR-1983-TLR7-IFNβ circuit [120].

Glioma-derived EVs enhance glioma-related angiogenesis

Tumor-derived EVs have been reported to facilitate angiogenesis by delivering functional and regulatory factors that induce proangiogenic or anti-apoptosis changes in brain microvascular endothelial cells [124, 125]. GBM-derived EVs can not only transfer mRNAs into endothelial cells, leading to transcriptional changes and the subsequent synthesis of functional proteins in these recipient cells [126]. These vesicles are also enriched in angiogenic protein factors and promote tubule formation [127, 128]. Interestingly, the proteome and mRNA profiles of EVs closely reflect the oxygenation status of donor glioma cells [124]. EVs are also enriched with angiogenesis-related regulatory factors and are released with increased autocrine and promigratory activation of GBM cells [129]. Recent research has identified long noncoding RNAs, such as CCAT2 and POU3F3, as enhancers of angiogenesis [125, 130]. Conversely, EV-derived miR-1 and Annexin A2 (ANXA2) have been reported as orchestrators of neovascularization, targeting multiple pro-oncogenic signals [131].

Glioma-derived EVs represent a promising field in clinical biomarker studies

Due to their intracranial location, glioma tissues are less accessible than other solid tumors, making the identification of prominent biomarkers in biological fluids essential. Given the unique characteristics of the blood-brain barrier, studies of cerebrospinal fluid hold particular significance for gliomas compared to other tumors [126]. Following this perspective, numerous studies on CSF and serum have been conducted, highlighting glioma-derived EVs due to their enrichment of specific factors [35]. Particularly following the extensive application of proteome profiling, genomics, and microarray analysis, various biomarkers, such as epidermal growth factor receptor variant III (EGFRvIII) and miR-21, have been widely studied within glioma-derived EVs and found in CSF and plasma [132–134].

Potential effects of cargos in glioma-derived EVs on ischemic stroke

The pathogenesis of ischemic stroke is complex and multifactorial, with common etiologies including large artery atherosclerosis, cardioembolism, and small artery occlusion [135, 136]. Progression of ischemic stroke involves vascular pathology, formation of tertiary collateral circulation, tissue ischemia and necrosis, inflammatory cascades, oxidative stress, blood-brain barrier disruption, scar formation and resolution, and neural function compensation [14, 16]. Hemorrhagic stroke, on the other hand, primarily involves mass effect and hematoma absorption, both significantly influenced by inflammation [137]. As shown in Fig. 3, glioma-derived extracellular vesicles carry cargos originating from the tumor microenvironment and spread intracranially. Notably, these cargos have been widely implicated in stroke, where they exhibit coherent roles in both conditions, as detailed in the following sections. Given the efficiency and ubiquity of EVs in intercellular communication and their role in pathological processes like inflammation and angiogenesis, we hypothesize that glioma-derived EVs may provide a critical link between prevalent neurovascular diseases and intracranial tumors.

Glioma-derived EV cargos associated with tumor growth, metabolism, invasion, and metastasis, and their effects on ischemic stroke

An important aspect of glioma growth and invasion is the communication and manipulation of other cells within the brain microenvironment, which supports tumor progression and resistance to therapy. In this process, extracellular vesicles play a crucial role [25, 138]. In addition to their indirect effects on immune suppression and angiogenesis, glioma-derived EVs directly impact glioma characteristics by promoting motility, proliferation, and invasiveness [138]. Notably, as shown in Table 2, some EV cargos commonly observed in ischemic stroke pathology also play similar roles in glioma. For example, Pace et al. demonstrated through in vitro experiments that L1

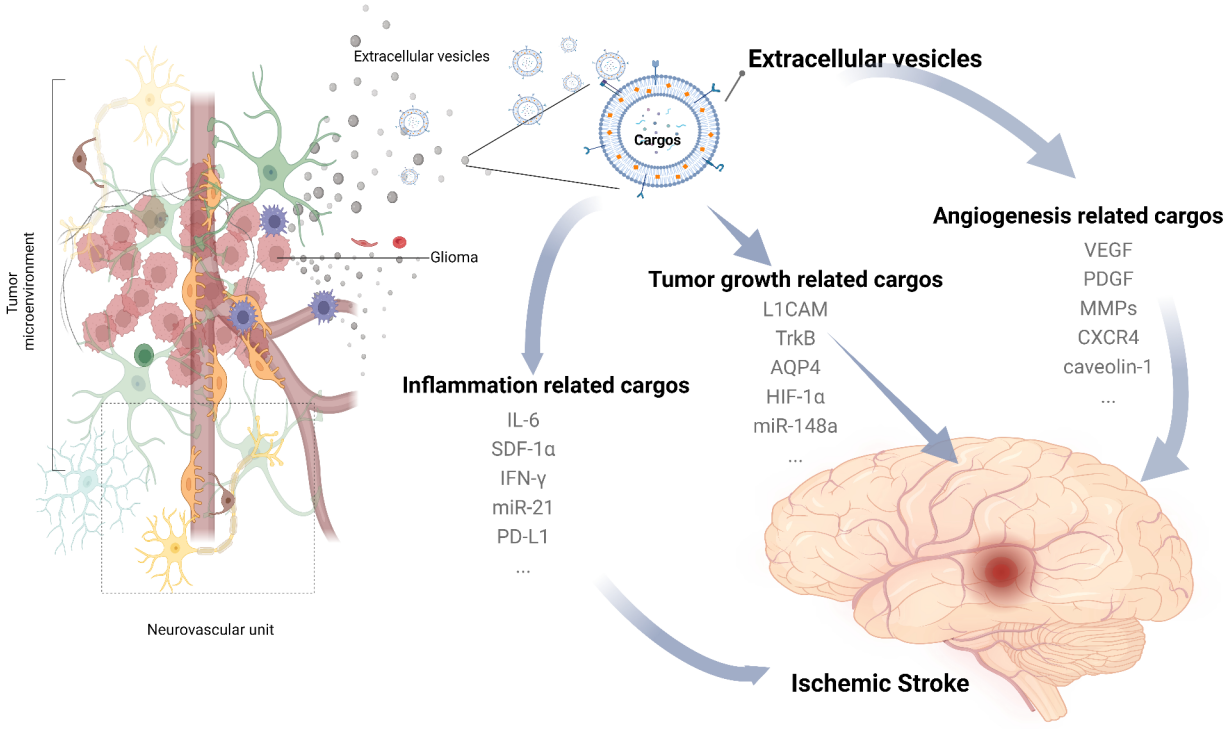

Fig. 3 Glioma-derived EVs and their role in stroke. Glioma-derived extracellular vesicles carry cargos that have been widely reported in stroke and play coherent roles in both conditions. Abbreviations: IL-6 = interleukin-6, SDF-1α = stromal cell-derived factor 1 alpha, IFN-γ = interferon gamma, PD-L1 = programmed cell death ligand-1, L1CAM = neural cell adhesion molecule L1, TrkB = tropomyosin receptor kinase B, AQP4 = aquaporin 4, HIF-1α = hypoxia-inducible factor 1 alpha, VEGF = vascular endothelial growth factor, PDGF = platelet-derived growth factor, MMPs = matrix metalloproteinases, CXCR4 = C-X-C chemokine receptor type 4

cell adhesion molecule-decorated exosomes increase the motility, proliferation, and invasiveness of cell lines [112]. Interestingly, L1CAM has also been identified as a biomarker in stroke patients [139]. Similarly, Colombo et al., using wild-type and tropomyosin receptor kinase B-deficient astrocytes, found that astrocyte-derived tropomyosin receptor kinase B (TrkB) expression is upregulated in stroke, promoting Aquaporin 4 (AQP4) upregulation via hypoxia-inducible factor 1 alpha (HIF1-α) activation under hypoxic conditions. This contributes to brain injury and edema formation [140]. Notably, these same factors—TrkB, AQP4, and HIF1-α—are also identified as EV cargos in glioma, where they significantly contribute to tumor cell proliferation, migration, and resistance [141–143]. This section will provide a detailed discussion of these individual cargos.

The enhancing or suppressing roles in cellular activity and behavior are generally consistent in both stroke and glioma contexts. For example, TrkB exhibits an enhancing role in both contexts. Studies using YKL-40-silenced glioblastoma cells have highlighted that TrkB-containing exosomes contribute to glioblastoma by promoting tumor cell proliferation and activating endothelial cells [141]. In stroke, TrkB's role in neurological recovery is well-documented, where it enhances corticospinal synaptic connections and neuroplasticity, thus improving patient outcomes [144–146]. In contrast, MiR-375 functions as a suppressor in cellular activities within both glioma and stroke. In glioma, MiR-375, a cargo of glioma-derived EVs, is found to play a protective role by suppressing glioma proliferation, migration, and invasion [147]. In stroke, downregulation was found in patients with ischemic stroke and in rat models, and protection of MiR-375 was approved in stroke which may achieved by reducing apoptosis and oxidative stress [148]. AQP4, another cargo found in both glioma and stroke, is released through EVs in glioma and influences the glioblastoma microenvironment by promoting a migratory phenotype in adjacent tumor cells [142]. While AQP4 plays a complex, dual role in stroke, where it exacerbates cerebral edema formation in the early stages but mitigates it in later stages [149, 150]. Lastly, miR-148a, a glioblastoma proliferation-promoting cargo, has also been identified as a biomarker for ischemic stroke in blood samples [151–153].

In gliomas, the influence of EV cargos on proliferation and invasiveness frequently coincides with the development of treatment resistance. For example, in the

Table 2 Cargos associated with tumor growth, metabolism, invasion, and metastasis, along with their roles in stroke

Biomarker	Function in glioma	Patients / Models	Samples / treatment	Proposed Action in Stroke	Ref.
L1CAM	Glioblastoma cell motility, proliferation, and invasiveness	Stroke Patients	Plasma	Biomarker Analysis	[139]
TrkB	Promotion of glioblastoma aggressiveness	MCAO Mice / Stroke Patients	Primary astrocytes / Brain tissue	Promotion of Brain Injury and edema formation	[140]
		BDNF TrkB receptor inhibitor-treated stroke mice model	Brain Tissue	Enhancement of neuroplasticity and acceleration of motor recovery	[144]
		Post-stroke depression mice model	Brain tissue	Reduction of post-stroke depression	[146]
		MCAO Rats		Enhancement of corticospinal synaptic connections	[145]
AQP4	Influence on tumor cell fate toward invasiveness or apoptosis	$AQP4^{-/-}$ mice	Brain tissue	Promotion of brain edema	[280]
miR-148a	Promotion of glioblastoma proliferation and metastasis	Patients with acute ischemic stroke	Peripheral Blood Cells	Biomarker analysis	[152]
		Patients with ischemic stroke	Blood sample	Biomarker analysis	[153]
HIF-1α	Promotion of glioblastoma progression and radioresistance	MCAO Mice	Brain tissue	Time-based biomarker analysis	[162]
		H_2O_2 or hypoxia treated cell	Cell lysates	Protection against oxidative stress	[165]
		Infected Mice / OGD cells	brain tissue / Cells	Modulation of ferroptosis-induced brain injury and neuroinflammation	[164]
miR-221	Tumor progression and temozolomide resistance	Acute ischemic stroke patients / MCAO Mice	Plasma / Brain tissue	Modulation of proinflammatory response	[159]
miR-151a	Inhibition of XRCC4-mediated DNA repair	Acute cerebral infarction Patients	Serum	Biomarker analysis	[160]
miR-301a	Tumor proliferation and invasion	MCAO Mice	Brain Tissue	Promotion of cell apoptosis and inflammatory response	[281]
MiR-375	suppress glioma proliferation, migration, and invasion	Acute ischemic stroke patients	Serum	Expression profile analysis	[148]
		Ischemia/reperfusion rats / hypoxia/reoxygenation PC12 cell	Brain tissue / MiR-375 mimic	Suppression of apoptosis and oxidative stress	[282]

radioresistant U251 glioma cell line, circATP8B4 has been identified as a radioresistance-related cargo and is associated with enhanced glioma cell proliferation, motility, and invasion [154, 155]. Temozolomide resistance in gliomas is also usually accompanied by tumor proliferation, growth, and invasion, which has been extensively studied due to its clinical significance. Numerous temozolomide resistance-related cargos have been identified, including miR-221, miR-151a, miR-30b-3p, and lncRNA SBF2-AS1 [156–158]. While miR-221 and miR-151a are also recognized in the pathology of stroke [159, 160]. Using the U87-MG glioblastoma cell line, glioblastoma-derived EVs carrying HIF-1α were shown to promote tumor progression and radioresistance [143]. The expression of HIF-1α induced by stroke is time-dependent, and plays an extensive role in the pathophysiology of stroke, including neuronal survival, neuroinflammation, angiogenesis, glucose metabolism, and blood-brain barrier regulation [161–163]. Through experiments involving lentivirus-infected mice and primary brain cells, Cui et al. demonstrated HIF-1α's modulatory effects on brain injury and neuroinflammation [164]. The protective function may arise from both non-transcriptional mechanisms and its function as a nuclear transcription factor [165].

Glioma-derived EV cargos associated with angiogenesis and their effects on ischemic stroke

Angiogenesis plays a crucial role after stroke and indicates a better outcome [16, 166, 167]. This is because neurogenesis and angiogenesis are highly coupled, working together to create restorative microenvironments within ischemic tissue, which leads to improved neurological function [168, 169]. Interestingly, angiogenesis can develop before stroke onset as a structural and functional adaptation to hypoxia, which often occurs due to chronic conditions like atherosclerosis or Moyamoya disease [170–172]. Key biomarkers, such as VEGF, MMPs, HIF-1α, TGF-β1, IL-6, and IL-8, serve as indicators of new blood vessel formation in stroke [127, 128, 173]. In the meantime, they are also angiogenesis-promoting cargos widely reported in glioma-derived EVs [174]. Similarly, as shown in Table 3, a large number of angiogenesis-related cargos from glioma-derived EVs overlap with angiogenesis-promoting factors in ischemic stroke. Due to the significant overlap in the underlying mechanisms and involved biological factors, it is reasonable to hypothesize that cargos from glioma may influence angiogenesis in the context of stroke.

Using wound closure assay and tube formation assay, Giusti et al. demonstrated a dose-dependent effect of glioblastoma-derived EVs on endothelial growth [174]. In the current study, many angiogenesis-related cargos were identified in these EVs, including plasminogen activators (tPA and uPA), PAI-PA, CXCR4, VEGF, MMPs (MMP-2 and − 9), and TGF-β, most of which are also crucial angiogenic factors in stroke [174]. In the ischemic stroke context, the fibrinolytic system plays an important role in angiogenesis, in which tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA) function as plasminogen activators, promoting fibrinolysis by converting plasminogen to plasmin. While plasminogen activator inhibitor-1 (PAI-1) serves as an inhibitor by forming inhibitory complexes (PAI-PA) with tPA and uPA, thereby maintaining the balance between coagulation and fibrinolysis [175, 176]. CXCR4 typically serves as the receptor in the SDF-1/CXCR4 pathway and plays an important role in neuroprotection and angiogenesis after stroke [177–179]. Additionally, CXCR4 is involved in the migration of stem cells to infarcted brain areas, promoting recovery after stroke [180]. The VEGF family is well known for regulating vascularization. In the brain, VEGFs are crucial for angiogenesis, neuroprotection, and neurogenesis [181, 182]. Matrix metalloproteinases, key extracellular endopeptidases, digest extracellular proteins and serve as biomarkers for stroke. Among them, gelatinases (MMP-2 and MMP-9) are the most studied and can promote neurological recovery via angiogenesis in stroke [183, 184]. Lastly, using an oxygen-glucose deprivation model, Zhang et al. found that EVs from hypoxia-preconditioned microglia promote angiogenesis through the TGF-β/Smad2/3 pathway [185].

Using both in vivo and in vitro models, Kucharzewska et al. demonstrated alterations in the proteome and mRNA profiles under hypoxic conditions. Compared to normoxic exosomes, hypoxic exosomes were found to correlate with tumor vascularization, pericyte vessel coverage, glioblastoma cell proliferation, and decreased tumor hypoxia in a mouse xenograft model [129]. Their study identified caveolin-1, PTX3, IL-8, MMP9, platelet-derived growth factors (PDGFs), CD26, PAI1, and lysyl oxidase as cargos of glioma-derived EVs [129]. In the context of stroke, these cargos are similarly involved. Blochet et al. observed increased caveolin-1 expression in new blood vessels within the lesion and in reactive astrocytes in peri-lesion areas, promoting neovascularization, astrogliosis, and scar formation [186]. Rajkovic et al. reported significantly decreased vessel diameter, vessel proliferation, vascular density, and reactive astrocytes in PTX3 knockout (KO) mice, revealing the angiogenic role of PTX3 in stroke [187]. The PDGF family, well-studied in vascular physiology and pathology, including angiogenesis, is also relevant in stroke [188]. Elevated levels of VEGF in stroke are associated with better outcomes, potentially due to the angiogenic role of PDGF [189–191]. Moreover, human bone marrow mesenchymal stem cells derived VEGF were found to be stimulated by IL-8 after stroke. IL-8 is an inflammatory chemokine with

Table 3 Cargos associated with angiogenesis and their roles in ischemic stroke

Biomarker	Patients / Models	Samples	Proposed Action in Stroke	Reference
CXCR4	MCAO Mice	Brain tissue	Angiogenesis via SDF-1/CXCR4 pathway	[177]
	MCAO Mice	Brain tissue	Angiogenesis	[179]
	stroke patients	Serum	Stroke-induced mesenchymal stem cell migration	[180]
VEGF	MCAO rats	Brain tissue	Promotion of angiogenesis and neurogenesis	[283]
	CD-1 mice	VEGF protein	Promotion of angiogenesis	[284]
	MCAO Rats	Brain tissue	Amplification of angiogenesis and vascular stabilization	[285, 286]
MMP-9	MCAO Mice	Brain tissue	Promotion of angiogenesis and glial scar degradation	[184]
PDGF	human umbilical vein endothelial cells / Fertilized chicken embryos	endothelial cells	Augmentation of angiogenesis	[190]
PDGF-D	MCAO Mice	Brain tissue	Contribution to neovascularization by rescuing pericyte functions	[189]
PDGF-BB	Stroke Patients	plasma	Plasma biomarker analysis	[191]
PTX3	acute cerebral infarction Patients	plasma	Biomarker analysis	[287]
	MCAO Mice	Brain tissue	Promotion of angiogenesis and neuronal survival	[187]
IL-6	Cerebrovascular injury Model	Brain tissue	Repair of damaged brain vasculature	[194]
	MCAO mice	Brain tissue	Angiogenesis and functional recovery	[288]
IL-8	MCAO rats	Brain tissue	Increase in VEGF production and angiogenesis	[192]
TGF-β	MCAO Mice	oxygen – glucose deprivation model	Promotion of angiogenesis and repression of apoptosis	[185]
caveolin-1	MCAO Mice	Brain tissue	Neovascularization and astrogliosis	[186]
	patients with Moyamoya disease	plasma	Biomarker analysis	[289]
MiRNA-26a	MCAO Rats	Brain tissue	Promotion of angiogenesis	[200, 201]
miR-210	MCAO Mice	Brain tissue	Promotion of angiogenesis	[202]
lncRNA HOTAIR	OGD hBMVECs cell/neonatal patients with HIE	Plasma / cell	Promotion of angiogenesis	[203]

potent proangiogenic properties in stroke and also serves as angiogenesis-related cargo from glioma EVs [129, 192]. Additionally, IL-6, another inflammatory chemokine found in EVs from glioma, is involved in microglia-mediated vascular repair and functional recovery after cerebrovascular injury [193, 194].

Non-coding RNAs (ncRNAs), when acting as cargos of glioma-derived EVs, exhibit significant overlap in angiogenesis-related functions between gliomas and indicators of vascular development in stroke. ncRNAs, including microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), are functional RNA molecules that regulate the expression and function of various genes through different mechanisms [195–197]. Glioma-derived EVs contain microRNAs such as miR-29a, miR-30e, miR-26a, and miR-1, which have been identified as pro-angiogenic microRNAs [126, 128, 131]. In addition to microRNAs, long non-coding RNA HOTAIR has been identified as a cargo of glioma-derived EVs by Ma et al. It was found to enhance angiogenesis by induction of VEGFA expression in glioma cells and facilitating its transmission to endothelial cells via glioma cell derived-extracellular vesicles [198]. Regarding the role of ncRNA cargos in stroke, various non-coding RNAs (ncRNAs) have been identified as key players with studies demonstrating that changes in their expression levels during and after stroke can significantly influence angiogenesis [195, 199]. The microRNA cargos from glioma-derived EVs, previously mentioned, including miR-26a and miR-210, also play similar roles in promoting angiogenesis in stroke [200–202]. Lastly, using an oxygen-glucose deprivation/reperfusion model of human brain microvascular endothelial cells, lncRNA HOTAIR was identified as a common factor in both glioma-derived EV cargos and as a mediator of angiogenesis in hypoxic-ischemic conditions [203].

Glioma-derived EV cargos associated with inflammation and their effects on ischemic stroke

In the brain, the interaction between immune system activation and inflammation exerts both harmful and protective effects on central nervous system function [204, 205]. In stroke, although inflammatory cascades can exacerbate tissue damage in the acute phase, adaptive immune responses and inflammatory processes are essential for subsequent tissue repair [14]. Phagocyte activity exemplifies this dynamic: microglial cells, macrophages, and phagocyte-mediated inflammatory responses play pivotal roles in the onset, progression, and outcomes of brain injury following ischemic stroke [206]. In this process, the polarization of microglia or macrophages into the M1 phenotype typically results in the release of destructive pro-inflammatory mediators, whereas M2 polarization clears cellular debris through phagocytosis and releases numerous protective/trophic factors [100]. Due to this dualistic nature, subtle modulation is critical for maintaining the balance between these phenotypes in stroke [100]. The situation is different for glioma, as the formation of an immunosuppressive tumor microenvironment is essential. The cargos released by glioma cells generally contribute to the immunosuppression of immune cells, which is critical for tumor proliferation [17]. Thus, M2 macrophage polarization, rather than M1, becomes significant, promoting tumor growth, invasion, and even angiogenesis; consequently, glioma-derived EV cargos frequently drive macrophages toward an M2 phenotype [193]. Using in vivo and in vitro models, van der Vos et al. directly visualized the release of EVs from glioma cells and their uptake by brain microglia and monocytes/macrophages, which led to increased microglial proliferation and a cytokine profile shift toward immune suppression [114]. In the current study, miR-451 and miR-21 have been identified as EV cargos, where they are also recognized as protective agents in ischemic stroke, potentially by regulating apoptosis [207–210].

As shown in Table 4, the overlap of biofactors is evident in the polarization of phagocytes (microglia and macrophages), both of which participate in immune modulation in glioma and ischemic stroke. For example, in glioma, Qian et al. discovered an enrichment of miR-1246 in the cerebrospinal fluid of GBM patients, which decreased after tumor resection. Their study found that hypoxic glioma-derived exosomes (H-GDEs) significantly promote M2 macrophage polarization, with miR-1246 identified as the most enriched microRNA in H-GDEs through microRNA sequencing analysis [123]. Notably, miR-1246 has also been identified as a potential diagnostic biomarker for ischemic stroke in serum [211]. Additional polarization-related cargos in glioma-derived EVs include IL-6 and miR-155-3p, which promote M2 macrophage polarization via the IL-6-pSTAT3-miR-155-3p-autophagy-pSTAT3 positive feedback loop, further enhancing glioma progression [193]. Meanwhile, IL-6 is critical in stroke for modulating immune responses and the acute phase reaction [212]. Interestingly, in turn, these tumor-associated macrophages can also produce EVs decorated by immunosuppressive and tumor-growth-promoting proteins, which can promote tumor cell migration and proliferation [213].

The overlap extends to myeloid-derived suppressor cell-related EV cargos in glioma and inflammation modulators in ischemic stroke, as shown in Table 4. Myeloid-derived suppressor cells (MDSCs) belong to a key cell population responsible for regulating immune responses and are highly effective at suppressing T cell function, and play a crucial role in both tumor progression and stroke [214, 215]. Using glioma cell lines, Zhang et al. found that basic leucine zipper ATF-like transcription factor 2

Table 4 Cargos associated with inflammation and their roles in ischemic stroke

Biomarker	Function in glioma	Patients / Models	Sample / treatment	Proposed Action in Stroke	Ref.
miR-451	Immune suppression	MCAO Mice	MiR-451 mimic / inhibitor	Regulation of apoptosis	[207]
		Ischemia stroke patients / MCAO Mice	Peripheral blood /Brain tissue	Neuroprotective effect	[210]
		M2 macrophage polarization-related cargos			
miR-1246	M2 macrophage polarization	Patients with ischemic stroke	Serum	MiRNA microarray analysis	[211]
IL-6	M2 macrophage polarization	Cerebrovascular injured mice	Brain tissue	Angiogenesis and cerebrovascular repair	[194]
		MDSC related cargos			
SDF-1α	Immunosuppressive function mediated by MDSCs	MCAO Mice	Brain tissue	Recruiting of monocytes to the infarcted tissue	[217]
miR-21	Immunosuppressive function mediated by MDSCs	Post-stroke cognitive impairment Patients	Serum	Clinical biomarker analysis	[232]
		MCAO Rats	Brain tissue	Protection against ischemic neuronal death	[229]
		MCAO Mice	MiR-21 mimic	Decrease in post-stroke brain damage	[208, 209]
		Acute ischemic stroke patients / OGD cells	Plasma / Culture media	Pro-apoptotic effect	[231]
miR-29a	Immunosuppressive function mediated by MDSCs	MiR-29a-5p knockout MCAO Rats	Plasma / Brain tissues	Alleviation of neurological damage by controlling Pre-polarizing M1 Microglia	[221]
		Two-vessel occlusion rats / Primary astrocyte	Tissue / Culture media	Protective effect on cell injury and mitochondrial function	[223]
miR-92a	Immunosuppressive function mediated by MDSCs	Acute ischemic stroke patients	serum	Expression profiles analysis	[148]
miR-10a	Immunosuppressive function mediated by MDSCs	Ischemic stroke patient	Blood sample	Genetic polymorphism analysis	[290]
miR-10a		ApoE knocked out mice	Tissue / Plasma	Inhibition of atherosclerotic lesion formation	[224]
		T cell related cargos			
IFN-γ	Inhibition of CD8 + T cells	Stroke Patients	Serum	Biomarker analysis	[234]
		Stroke-associated infection patients	Plasma	Biomarker analysis	[235, 236]
		Post stroke depression patients	Plasma	Biomarker analysis	[291]
PD-L1	Inhibition of T cell function	MCAO mice	Soluble PD-L1	Upregulation of macrophage precursors	[239]
		PD-L1 knockout mice	Platelet cell	Regulation of platelet activation and thrombosis	[240]
		PD-L1 knockout mice	Brain inflammatory cells	Presence T cells	[241]
CD73	Inhibiting T-cell clonal expansion	MCAO mice	Brain tissue	Regulation of leukocyte trafficking	[243]

(BATF2) inhibits intracellular SDF-1α production, reducing SDF-1α levels in EVs and subsequently inhibiting the recruitment of MDSCs [216]. While in stroke, SDF-1α also modulates inflammation. As a chemokine, SDF-1α is crucial for monocyte homing and migration across the blood-brain barrier, playing a significant role in the late infiltration of the penumbra by recruiting monocytes to infarcted tissue in the later stages of stroke [217, 218]. Not only chemokine, miRNAs, including miR-1246, miR-1298-5p, miR-29a, miR-92a, miR-10a, and miR-21, were found to be enriched in the body fluids of glioma patients and shown to drive the activation of MDSCs through different pathways, some of which are also matters in stroke [119, 219, 220]. In stroke, elevation of miR-29a has been shown to have a protective function by controlling M1 microglia pre-polarization or by promoting axonal outgrowth and neurological recovery [221–223]. Protection function was also found in miR-10a by inhibiting atherosclerotic lesion formation, and in miR-92 by alleviating cerebral vascular injury [148, 224, 225]. Notably, miR-21, a glioma EV biomarker, has been detected in CSF and serum of glioma patients and correlates with poor prognosis and tumor recurrence [133, 226–228]. It plays an important role in maintaining the immunosuppressive environment in glioma, possibly mediated by MDSCs, and has an anti-apoptotic effect [114, 119]. MiR-21 also acts as an inflammation modulator in stroke and has been consistently shown to be a potent anti-apoptotic factor, playing a neuroprotective role in cerebral ischemic and reperfusion injury [209, 229, 230]. Additionally, miR-21 shows potential for promising clinical outcomes [208, 231, 232].

T cell-related glioma cargos similarly overlap with stroke-related inflammatory factors, as shown in Table 4. Liu et al. found, using the GL26 cell line, that glioblastoma-derived exosomes reduce CD8 + T cell numbers and functionality, fostering tumor growth in an immunosuppressive tumor microenvironment. IFN-γ and granzyme B were identified as key cargos in these EVs during this period [121]. IFN-γ serves as an indicator of inflammation in stroke, especially of T-cell function and stroke-associated infections, it can also serve as a protective biomarker in the clinic, which was reported to elevate in stroke patients [233–237]. Ricklefs et al. demonstrated that glioblastoma-derived EVs can suppress T cell activation and proliferation through T cell receptor interaction with anti-CD3, or alternatively, by antigen presentation via dendritic cells (DCs). In their study, PD-L1 was found on the surface of some glioblastoma-derived EVs, both PD-L1 and PD-L1 DNA were identified as cargos of glioma-derived EVs in the process of T cell inhibition [238]. In stroke, the T-cell regulatory role of PD-L1 has also been observed. Kim et al. demonstrated that soluble PD-L1 binds to PD-1, redirecting monocyte fates from pro-inflammatory, classical phenotypes to non-classical, anti-inflammatory ones, thereby protecting against damage after middle cerebral artery occlusion [239]. Beyond its immunosuppressive role, PD-L1 was also found to regulate platelet activation and thrombosis through the Caspase-3/GSDME pathway in stroke [240]. Conversely, a study by Bodhankar et al. challenges these findings, suggesting that PD-L1 may worsen stroke outcomes, possibly through effects on suppressor T cells [241]. Studies involving patient clinical samples have identified CD73 as a crucial cargo in glioblastoma EVs, capable of being taken up by T cells and inhibiting their clonal expansion in vivo [242]. CD73 has a similar function in stroke, where it regulates leukocyte (including T cell) trafficking in the ischemic brain and serves as an outcome indicator in MCAO mice [243, 244].

Retrospect and prospect

We have discussed the pathological overlap between glioma and ischemic stroke. The interplay between these two conditions is complex, particularly with the involvement of extracellular vesicles, which efficiently facilitate intracranial interactions. However, the precise influence of glioma and glioma-derived EVs on the entire ischemic stroke process remains unclear. We aim to speculate on the impact of glioma as a risk factor for stroke, as well as its effects during the pre-stroke phase, stroke onset, and post-stroke recovery.

Glioma can be a risk factor for stroke. As an intracranial tumor, its direct infiltration or compression of blood vessels is evident and commonly observed in clinical practice [7]. Additionally, the disruption of blood vessels may lead to hemorrhagic stroke in glioma patients [245]. Chronic activation of the coagulation system, particularly as part of paraneoplastic syndrome, represents another mechanism by which glioma acts as a risk factor for ischemic stroke [246]. Coagulation abnormalities are also a frequent postoperative and late complication of radiotherapy, contributing to stroke risk through tumor-induced hypercoagulability or nonbacterial thrombotic endocarditis [9, 10].

Before the onset of stroke, chronic hypoxia and angiogenesis may have already occurred. It is well established that tumor hypermetabolism increases the demand for nutrients and oxygen [97, 170–172]. Collateral circulation and angiogenesis are likely enhanced in the tumor's hypoxic microenvironment, facilitated by angiogenesis-related cargos from EVs. In the case of ischemic stroke onset, as discussed previously, the inflammatory cascade contributes to tissue damage by enlarging the infarct area, increasing blood-brain barrier permeability, and worsening cerebral edema. However, the immunosuppressive microenvironment created by glioma is speculated to provide a protective function during ischemic

stroke [247]. This protective effect may extend into the recovery phase, as M2 polarization—an essential feature of the glioma-associated immunosuppressive microenvironment—helps clear cellular debris via phagocytosis and releases protective/trophic factors that promote angiogenesis and neurogenesis [100, 248]. Additionally, glioma-derived EVs carry cargos that overlap with angiogenesis promoters are presumed to involve in stroke recovery.

In the context of clinic therapy, the simultaneous occurrence of glioma and ischemic stroke presents significant challenges in stroke management. On one hand, glioma's direct invasion exacerbates brain tissue damage, compresses and invades blood vessels, competes for oxygen and nutrients, and worsens cerebral edema. On the other hand, glioma-induced coagulation abnormalities and vascular disruption complicate clinical anticoagulation or antiplatelet therapies, increasing the risk of intracranial hemorrhage.

Understanding the molecular interplay between glioma and stroke, particularly through the involvement of EVs, offers new insights into their shared pathophysiology and provides potential therapeutic targets for managing both conditions simultaneously. However, further research is needed. The impact of glioma-derived EVs on ischemic stroke progression has not been fully confirmed, and the use of dual rodent models of glioma and stroke could be instrumental in investigating this interaction. Lipidomic analysis or specific labeling could help determine whether glioma-derived EVs play a role in the stroke-affected region. As discussed, stroke presents distinct characteristics in different phases, and the impact of glioma on stroke is complex; therefore, each phase should be studied separately. In the context of glioma, ischemic stroke treatment also faces challenges, particularly in the titration of anticoagulant or antiplatelet medications.

Though the therapeutic potential of glioma-derived EVs appears promising, the therapeutic application of glioma-derived EVs remains challenging and requires further investigation. Firstly, as EVs serve as therapeutic carriers, delivery efficiency and potential off-target effects must be carefully evaluated, particularly in the context of the blood-brain barrier [249]. Secondly, given that EVs are biologically isolated vesicles, their heterogeneity poses a major challenge in ensuring reproducibility and therapeutic consistency [250, 251]. Thirdly, considering the distinct pathophysiological stages of ischemic stroke, optimal administration timing is a crucial factor that must be optimized to maximize therapeutic efficacy. Further research is warranted in the areas of drug delivery strategies, precise administration timing, advanced purification techniques, and scalable biomanufacturing processes to enhance the clinical translation of glioma-derived EVs as a viable therapeutic approach.

Conclusion

The pathology of glioma and ischemic stroke significantly overlaps in their pathological processes, including the regulation of cellular metabolism, inflammation, coagulation, hypoxia, angiogenesis, and neural repair, all of which involve shared biological factors. This overlap is reflected in numerous clinical studies. Glioma-derived EVs play a crucial role in mediating intracranial interactions and shaping the tumor microenvironment, with their cargos closely aligning with stroke-related biological factors, which act as risk factors and participating in the phases of hypoxia, stroke onset, progression, and recovery. Therefore, though further studies are needed to confirm their precise role, EVs have the potential to mediate interactions between glioma and stroke and suggest therapeutic potential.

Author contributions

Zhongnan Hao wrote the main manuscript text and prepared Table 1, and 2; Wenxin Guan was responsible for revising the manuscript during the major revision; Wei Wei prepared Table 3, and 4; Meihua Li, Zhipeng Xiao, and Qinjian Sun prepared Figs. 1, 2 and 3; Zhongnan Hao, Yongli Pan and Wenqiang Xin concepted the manusctrip. All authors reviewed the manuscript.

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No datasets were generated or analysed during the current study.

Declarations

Ethical approval

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Competing interests

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