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Review

Novel insights into astrocyte-mediated signaling of proliferation, invasion and tumor immune microenvironment in glioblastoma

Hao Zhang[a,1], Yulai Zhou[b,c,1], Biqi Cui[d], Zhixiong Liu[a,**], Hong Shen[b,c,*]

[a] Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China
[b] Department of Oncology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China
[c] National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China
[d] Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan 410008, China

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ABSTRACT

Glioblastoma (GBM) continues to be the most aggressive cancer of the brain. The dismal prognosis is largely attributed to the microenvironment surrounding tumor cells. Astrocytes, the main component of the GBM microenvironment, play several fundamental physiological roles in the central nervous system. During the development of GBM, tumor-associated astrocytes (TAAs) directly contact GBM cells, which activate astrocytes to form reactive astrocytes, facilitating tumor progression, proliferation and migration through multiple well-understood signaling pathways. Notably, TAAs also influence GBM cell behaviors via suppressing immune responses and enhancing the chemoradiotherapy resistance of tumor cells. These new activities are closely linked with the treatment and prognosis of GBM. In this review, we discuss recent advances regarding new functions of reactive astrocytes, including TAA-cancer cell interactions, mechanisms involved in immunosuppressive regulation, and chemoradiotherapy resistance. It is expected that these updated experimental or clinical studies of TAAs may provide a promising approach for GBM treatment in the near future.

1. Introduction

Glioblastoma (GBM) has continued to be the most lethal devastating tumor arising in the brain [1]. While multiple studies have aimed to explore potential treatments through molecular mechanisms, radiotherapy combined with chemotherapy is still the standard treatment for postoperative GBM patients and has dismal outcomes [2,3]. The median survival remains less than approximately 15 months after diagnosis [4].

Given the poor efficacy of TMZ, researchers have been dedicated to

Abbreviations: AEG-1, Astrocyte elevated gene-1; AQP4, Aquaporin 4; BBB, Blood brain barrier; BDNF, Brain derived neurotrophic factor; BNCT, Boron neutron capture therapy; CCL2, C-C motif chemokine ligand 2; CCR6, Chemokine C-C motif receptor; cGAMP, 2′3′-cyclic GMP-AMP; CNS, Central nervous system; CSPG4, Chondroitin sulphate proteoglycan 4; CX43, Connexin 43; DSBs, Double-strand breaks; ECM, Extracellular matrix; ECs, Endothelial cells; EGFR, Epidermal growth factor receptor; EMT, Epithelial to mesenchymal transition; EVs, Extracellular vesicles; FGF, Fibroblast growth factor; GABA, Glutamate and γ- aminobutyric acid; GAMs, Glioma-Associated Microglia/Macrophages; GBM, Glioblastoma; GDF-15, Growth/differentiation factor 15; GFAP, Glial fibrillary acidic protein; GFR1, Glial cell line-derived neurotrophic factor family receptor 1; Gln, L-Glutamine; GSCs, GBM stem cells; HA, Hyaluronic acid; HGF, Human growth factor; HH, Hedgehog; HIFs, Hypoxia-inducible factors; Hyal 1/2/3, Hyaluronidases 1/2/3; IAPs, Increasing inhibitors of apoptosis; IGF-1, Insulin growth factor-1; IKKa, Inhibitor ofNFκB kinase subunit alpha; IFN, Interferon; IKKs, IkappaB kinases; IL-6, Interleukin 6; ILs, Interleukins; LPS, Lipopolysaccharide; MDM2, Mouse double minute 2 homolog; MDSCs, Myeloid-derived suppressor cells; MHC, Major histocompatibility complex; MMP, Matrix metalloproteases; NF-κB, Nuclear factor kappa-B; NG2, Neural glial antigen 2; NK, Natural killer; NO, Nitric oxide; PCDH7, Protocadherin 7; PD1, Programmed cell death protein-1; PD-L1, Programmed death ligand-1; PTCH, Patched; PTEN, Phosphatase and tensin homolog deleted on chromosome ten; RANKL, Receptor activator of nuclear factor kappa-B ligand; RET, Receptor tyrosine kinase; RT, Radiation therapy; SDF1, Stromal cell-derived factor-1; SMO, Smoothened; TAA, Tumor associated astrocytes; TET, Tetrandrine; TGF-β, Transforming growth factor β; Th17 cells, T-helper17 cells; TME, Tumor microenvironment; TMZ, Temozolomide; TNF-α, Tumor necrosis factor alpha; Treg, Regulatory T; uPA, Urokinase plasminogen activator; uPAR, Urokinase plasminogen activator receptor; VEGF, Vascular endothelial growth factor; α-SMA, α-smooth muscle Actin; OS, overall survival; FDA, the united stated food and drug association; TTF, Tumor treating field

* Corresponding author at: Department of Oncology, Xiangya Hospital, Central South University, Changsha, 410008, Hunan, China.
** Corresponding author at: Department of Neurosurgery, Xiangya Hospital, Center South University, Changsha 410008, Hunan, China.
E-mail addresses: zhixiongliu@csu.edu.cn (Z. Liu), hongshen2000@csu.edu.cn (H. Shen).
[1] These authors contributed equally to this work.

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finding new therapeutic strategies using new substances against GBM. However, most of these substances are not capable of crossing the blood–brain barrier (BBB). This complex barrier receives support from glial cells such as astrocytes [5]. The compromised BBB during GBM progression promotes neuroinflammation by permitting the entrance of immune cells from the blood, inducing the activation of astrocytes. The subsequently released interleukins (ILs) consequently disrupt the astrocyte–BBB junctions [6].

Notably, stromal cells in the GBM tumor microenvironment (TME) have been found to promote tumor progression and growth [7,8]. Among the various cells of the GBM TME, astrocytes are the most common cells that interact with GBM cells [9] and manipulate GBM behaviors via diverse mechanisms. The biology and functions of astrocytes have long been well established, with more details regarding their role in the immunosuppressive microenvironment of GBM coming to light [10].

Thus, studying the correlation between astrocytes and GBM is crucial in understanding additional targets for therapy optimization. Targeting astrocytes within the TME as a means of inhibiting GBM progression is an attractive and revolutionary idea with regard to patient treatment and outcome [11].

2. The microenvironment of glioblastoma

The TME is composed of both the noncancerous cells and biomolecules inside the tumor as well as the extracellular matrix (ECM). Noncancerous cells constituting the TME include normal and reactive astrocytes, GBM stem cells (GSCs), fibroblasts, vascular pericytes, immune cells, microglia/macrophages and endothelial cells (ECs) (Fig. 1). Biomolecules produced by noncancerous cells include cytokines, chemokines, hormones, and nitric oxide (NO). The TME is thought to regulate everything in the GBM and the brain tissue adjacent to the tumor, and the close interaction between GBM and the TME in the CNS is essential for tumor development [12]. The concept of niches in GBM was originally developed to describe the primary location of GSCs in the tumor and where the TME exerts its maximum influence [13]. Consequently, niches are the main source for the detection and demonstration of the TME.

One notable characteristic of GBM is hypoxia occurring in the whole tumor with variable intensity within the TME. Hypoxia is considered to be an efficient hallmark of GBM [14] that activates and upregulates hypoxia-inducible factors (HIFs) that induce the expression of oncogenes and transcription factors, as well as proangiogenic factors such as angiopoietins, transforming growth factor β (TGF-β), and vascular endothelial growth factor (VEGF), which are involved in GSC self-renewal, maintenance, expansion and invasion properties [15]. Hypoxia also contributes to metabolic programming and recruitment of macrophages and microglia, which form the inflammatory niche, in which macrophages secrete TGF-β and IL-6, facilitating the expansion of the GSC population [16]. Maintaining the stemness of GSCs also relies on biomolecules such as NO and cyclic guanosine monophosphate released by ECs [17]. Recent studies have revealed that fibroblast growth factor (FGF-2) plays a significant role in regulating GBM and is important in preserving the stemness of GSCs, eliciting one promising area for further exploration on the influence of basic FGF-2 on GSCs [18]. Studies have assumed that GSCs represent a rare subset of cells within GBM with the ability to generate new tumors [19], which is highly responsible for the cellular heterogeneity of GBM [20].

The number of glioma-associated microglia/macrophages (GAMs) is almost equal to the number of tumor cells. Compelling evidence has proven that GAMs favor tumor progression, since GAMs together with other myeloid cells are strictly related to the immunological features of gliomas [21]. For instance, GAMs secrete TGF-β that promotes GBM cells release of versican, MMP2 and MMP9, the matrix metalloproteases critical for the degradation of ECM components such as collagen and elastin to enhance the invasiveness of GBM [22]. On the other hand,

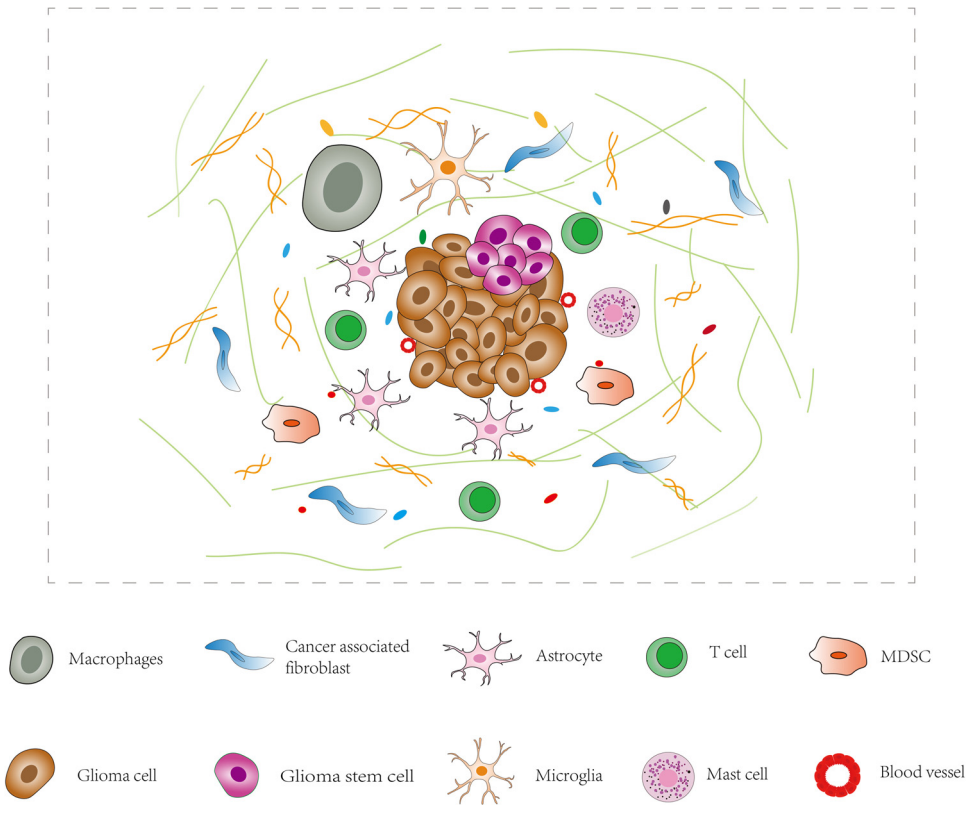

Fig. 1. TAAs and desmoplastic TME. During oncogenesis, TAAs largely contribute to the fibrotic microenvironment, which is a major characteristic of GBM. The desmoplastic TME consists of glioma cells and numerous stromal components, such as MDSCs, microglia, and macrophages.

TGF-β promotes the polarization of microglia/macrophages into an immunosuppressive M2 phenotype, promoting tumor progression via enhancing the capacity of GAMs to inhibit T cell proliferation [23].

The interaction between pericytes, ECs and GSCs forms the signaling networks that contribute to tumor angiogenesis [24]. Specifically, pericyte-EC interactions are responsible for the formation of endothelial junctions, which recruit macrophages that are closely associated with the tumor vasculature [25]. Pericytes promote vascular maturation by expressing neural glial antigen 2 (NG2), chondroitin sulfate proteoglyacan 4 (CSPG4) and α-smooth muscle actin (α-SMA). NG2/CSPG4, serving as a component of both tumor and stromal cells, promotes tumor growth [26]. In GBM neoangiogenesis, the increased pericytes, which are an essential element of the neovascular unit, together with the disruption of the BBB are regarded as a good marker of neovascularization [27].

ECM constitutes the noncellular component of the microenvironment and functions as a source of biochemical signals, contributing to the normal physiology of the CNS [28]. The dynamic ECM makes up approximately 20 % of brain volume [29]. During development, interactions between GBM cells and the ECM regulate tumor cell invasion, malignancy and migration. Under pathological conditions in GBM, ECM agrin is partially lost from the basal lamina of blood vessels and is then replaced with tenascin [30]. ECM-binding proteins such as hyaluronic acid (HA), CD44, MMP9 and hyaluronidases 1/2/3 (Hyal 1/2/3) all have a direct impact on ECM remodeling, which facilitates the invasiveness and infiltration of GBM.

3. The function of astrocytes

Astrocytes account for approximately half of the cells in the human brain and play an important physiological role in the CNS (Table 1).

3.1. Roles in physiology

Astrocytes express both potassium and sodium channels, which exhibit evoked inward currents [31]. Astrocytes are not physiologically silent, since regulated increases in intracellular calcium concentration are exhibited in astrocytes, and the regulated increases in calcium are functionally significant in the communication between astrocytes and neurons [32]. Notably, calcium signaling enables astrocytes to directly play a role in synaptic transmission [33]. Furthermore, astrocytes are essential in maintaining fluid homeostasis in the healthy CNS via densely clustered aquaporin 4 (AQP4) water channels [34]. Different means of proton shuttling located on the astrocyte membranes, such as the Na^+/H^+ exchanger and the vacuolar-type proton ATPase, play a critical role in regulating ion homeostasis in the healthy CNS [35].

It is noteworthy that astrocyte processes at synapses also maintain transmitter homeostasis of the synaptic interstitial fluid by expressing high levels of transporters for neurotransmitters, including glutamate, GABA, and glycine, serving to clear the neurotransmitters from the synaptic space [36].

Additionally, Astrocytes exert functions during the development of neurons in many CNS regions, including forming molecular boundaries guiding the migration of developing axons and certain neuroblasts [37]. Moreover, Astrocytes produce various molecular mediators that can increase or decrease blood vessel diameter in the CNS. Moreover, in response to changes in neuronal activity, astrocytes serve as the primary mediators of alterations in CNS blood flow [38].

3.2. Roles in synaptic activity and plasticity

As mentioned above, astrocytes regulate the release of gliotransmitters, such as GABA, in response to changes in synaptic activity, which involves astrocyte excitability [39]. Astrocytes are also able to efficiently remove neurotransmitters from the synaptic cleft [40]. Therefore, astrocytes play a pivotal role in regulating the balance between inhibitory and excitatory transmission, which is the basis of normal brain function [41]. Growing evidence also indicates that astrocytes are essential in the development and maintenance of neural circuits [42], in which astrocytes promote cell-cell communication with other neural cells through membrane processes, allowing for the recycling of neurotransmitters [43]. Astrocytes are responsible for the formation of developing synapses by releasing thrombospondin [44]. In addition, astrocytes can potentially exert long-term influences on synaptic function and synaptic remodeling through the release of growth factors and related cytokines such as tumor necrosis alpha (TNFα) [45–47].

3.3. Roles in metabolism

Compelling evidence has demonstrated that neuronal activity during hypoglycemia and periods of high neuronal activity can be maintained via astrocytic glycogen utilization [48], in which the astrocyte glycogen content is modulated by transmitters [49]. Furthermore, glucose metabolites pass across gap junctions that are regulated by transmitters as well as neuronal activity [50]. Other research indicates that astrocyte glycogen breaks down to lactate, which is transferred to adjacent neural synapses and axons to meet the demand for energy during hypoglycemia [49,51].

3.4. Astrocytes in the blood brain barrier

The BBB is mainly formed by its two central units, the endothelial cells and pericytes [52], lining cerebral microvessels and maintaining a precisely regulated microenvironment for the central nervous system (CNS).

Endothelial cells, forming tight junctions and surrounded by a basal lamina, perivascular pericytes, and astrocyte end-feet, control the

Table 1
Biological comparison of quiescent astrocytes and reactive astrocytes.

	Biological behaviors or functions	Specific biomarkers
quiescent astrocytes	-maintaining the fluid homeostasis	AQP4 [34]
	-maintaining the transmitter homeostasis	GABA [39]
	-developing synapse	Thrombospondin [44]
	-exert long-term influences on synaptic function and synaptic remodeling	TNFa [45,46,47]
	-play a role in BBB maintenance by interacting with both endothelial cells and pericytes	
	-forming molecular boundaries guiding the migration of developing axons and certain neuroblasts	Albumin [56]
	-primary mediators of alterations in CNS blood flow	Insulin [56]
	-regulating the balance between inhibitory and excitatory transmission	
	-maintaining high neuronal activity via astrocytic glycogen utilization	
reactive astrocytes	-exacerbating the neuroinflammatory responses	CCL2, IL-6
	-forming a functional barrier termed as “glial scar”	GFAP [58]
	-support tissue repair	nestin, vimentin, c-MET, STAT-3, BDNF, GDF-15, CD44 [57]

transport of essential molecules such as energy metabolites from the blood into the brain and the transport of metabolic waste products from brain into the blood by expressing multiple substrate-specific transport systems, indicating that BBB serves as a key homeostatic site connecting the CNS and systemic circulation. Pericytes share a basement membrane with endothelial cells and also contribute to the integrity of the BBB [53].

Astrocytes directly interact with both endothelial cells [52] and pericytes [54], contributing to a variety of dynamic regulations in the nervous system. Astrocytes are also necessarily associated with endothelial cells and pericytes in vitro, indicating that astrocytes can induce BBB properties in cerebral as and related epithelial cells [55]. Astrocytes and endothelial cells mutually influence each other by secreting a wide range of chemical agents, such as albumin and insulin, leading to a two-way induction that enhances the growth and differentiation of astrocytes and endothelial cells [56].

Therefore, given that astrocytes play a role in BBB maintenance, additional studies are needed to identify potential molecular mediators that induce BBB properties and clarify the related roles of astrocytes in BBB function.

4. Astrocyte in glioblastoma

4.1. Astrogliosis in CNS pathologies

In certain CNS pathologies, such as GBM, astrocytes undergo molecular, cellular, and functional changes and are transformed into reactive astrocytes through a process called astrogliosis that is characterized by hypertrophy, as well as activation of cell proliferation at the lesion site. Most importantly, astrogliosis is associated with the upregulation of intermediate filaments composed of nestin, vimentin, signaling receptors (c-MET), transcription factors (STAT-3), growth factors (brain derived neurotrophic factor (BDNF) and growth/differentiation factor 15 (GDF-15)), cell adhesion proteins (CD44), and extracellular matrix components (collagens and versican) and supports tissue repair [57]. Furthermore, reactive astrocytes release inflammatory cytokines (C-C motif chemokine ligand 2 (CCL2) and interleukin 6 (IL-6)) and NO, thereby exacerbating neuroinflammatory responses (Table 1).

Notably, reactive astrocytes in acute brain injuries promote the upregulation of glial fibrillary acidic protein (GFAP), forming a functional barrier termed a “glial scar” [58], which restricts and regulates inflammation, isolating the lesion from the surrounding tissues [59], facilitating the regulation and repairment of the BBB [60], enhancing synaptic plasticity, and initiating neuronal circuit reorganization. Consequently, reactive astrocytes may increase clinical stabilization and improve patients survival [61].

4.2. Tumor-associated astrocytes in the GBM microenvironment

Using an intersectional fluorescence-activated cell sorting-based strategy, astrocytes have been proven to consist of five heterogeneous subpopulations with distinct morphological, molecular, and functional properties from three CNS regions [62].

Brain region-specific gene signatures revealed by distinct astrocyte subpopulations were found to be linked to glioma that harbor distinct genomic alterations, suggesting that astrocytes play specific roles in the interactions with the surrounding GBM microenvironment [63]. In a similar study, the results identified unique gene expression patterns between populations of tumor-associated astrocytes (TAAs), in which certain stromal astrocytes in the tumor microenvironment expressed a GBM-specific gene signature and the majority of these stromal astrocyte genes predicted survival in the human disease [64].

One recent study also demonstrated that intrinsic astrocyte heterogeneity significantly contributes to glioma pathogenesis [65]. The diverse subpopulations of astrocytes have different functions, and different astrocyte phenotypes are also separately correlated with different GBM subtypes, providing new insights for understanding GBM progression dynamics [62].

5. The Crosstalk between glioma and astrocytes

As mentioned above, the GBM microenvironment is crucial in the progression of tumors, and the parenchymal and non-malignant cells adjacent to the mass facilitates the development and growth of GBM [25].

Astrocytes, one main component of the GBM microenvironment, display a reactive phenotype when they contact tumor cells. A large amount of growth factors, chemokines, cytokines and other soluble substances secreted by reactive astrocytes serve as essential intermediators orchestrating continued astrocyte activation and signaling transfer between stroma and epithelial GBM cells. For instance, the astrocyte phenotype triggered by glioma-astrocyte interactions expresses a high concentration of GFAP and connexin 43 (CX43), favoring a more permissive environment for glioma cell invasion [66].

The upregulation of MMP2 expressed by GBM via the TGF-β1 signaling pathway and reactive astrocytes during glioma-astrocyte interactions aid the parenchymal infiltrative capacity of GBM cells [22]. Furthermore, stromal cell-derived factor-1 (SDF1) secreted by reactive astrocytes stimulates uncontrolled proliferation of GBM cells [67]. Therefore, reactive astrocytes are an important source of secretions in the TME of GBM, augmenting GBM malignancy by causing aberrant cell proliferation and triggering a malignant transformation in the tumor microenvironment [11]. Several pathways involved in the interaction between GBM and reactive astrocytes will be discussed below (Table 2).

Table 2
TAAs mainly involved pathways and their functions.

Signaling pathways	Mediators	Functional roles
NF-κB signaling pathway	RANKL, LPS	• Activating astrocytes to secret various factors regulating glioma cell invasion and progression [68,69] • Enhancing the proliferation of GBM [70,71]
SHH signaling pathway	SHH protein	• Sustaining TAAs activation and proliferation [74,75] • Tumor migration and invasion [77]
P53 signaling pathway	p53	• Modulating the expression of tumor cells’ secreted proteins [81] • Leading to an increased expression of laminin, fibronectin, N-cadherin and vimentin, facilitating apoptosis evasion [82,83] • Favoring cancer malignancy and proliferation [83,84]
IL-6/JAK/STAT signaling pathway	IL-6	• Increasing aggressive behavior of GBM [87] • Enhancing the invasiveness of GBM through the degradation of extracellular matrix [89,90] • Facilitating angiogenesis in GBM [86]
PI3K/Akt signaling pathway	GDNF	• Enhancing the proliferation and the invasiveness of GBM [25,97,99] • Favoring cancer malignancy and migration [93] • Enhancing the invasiveness of GBM through the degradation of extracellular matrix [101] • Inhibiting the apoptosis of GBM cells [98]

5.1. NF-κB signaling pathway

The number of activated astrocytes is markedly increased in the periphery of invasive tumors that highly express receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL, produced by GBM cells, activates astrocytes through nuclear factor kappa-B (NF-κB) signaling, and these astrocytes in turn secrete various factors regulating glioma cell invasion. Among them, TGF-β signaling is markedly increased [68]. Similarly, fibulin-3 released by GBM cells drives oncogenic NF-κB and increases NF-κB activation in peritumoral astrocytes, which is linked to tumor progression [69].

Lipopolysaccharide (LPS), another activator of NF-κB signaling, is suppressed by tetrandrine (TET), whose suppressive effects might result from the inhibition of NF-κB activation through downregulating phosphorylation of IkappaB kinases (IKKs) [70]. Thus, targeting RANKL and LPS can prevent the transformation of astrocytes into the reactive phenotype.

Additionally, astrocyte-derived chemokine C-C motif ligand 20 (CCL20) combines with chemokine C-C motif receptor (CCR6), stimulating the NF-κB signaling pathway, which reinforces the upregulation of HIF-1α under hypoxia and further enhances the proliferation of GBM [71].

5.2. Sonic hedgehog (SHH) signaling pathway

Neuron-derived SHH regulates the molecular and functional profile of astrocytes [72]. Two populations of SHH-producing stromal cells, namely, astrocytes and endothelial cells, are highly concentrated in the perivascular niche of gliomas [73].

It is clear that SHH protein, which is secreted by GBM cells, serves as a hedgehog (HH) pathway ligand. SHH signaling is mediated by HH ligand binding to the membrane-localized receptor patched (PTCH) on TAAs, which relieves the inhibitory effect on the smoothened (SMO) receptor. Derepressed SMO then leads to a cascade of cytoplasmic events in TAAs that facilitates the activation of GLI family zinc finger transcription factors, modulating targeted gene expression and eventually resulting in TAA activation [74,75]. One previous study showed that deregulation of SHH-Gli signaling resulted in hyperproliferation of precursor cells and may initiate brain tumors [76]. Furthermore, another study demonstrated that suppression of the SHH-Gli pathway markedly inhibited glioma cell migration and invasion [77]. Analysis of nonstem glioblastoma cells revealed that glioma stem cells differentially respond to SHH ligand, demonstrating a highly efficient single-cell killing therapeutic strategy for targeting glioma stem cells.

Consequently, SHH-Gli signaling facilitates the activation of astrocytes in the perivascular niche surrounding gliomas, which in turn favors the invasion of gliomas.

5.3. p53 signaling pathway

An important intermediator in the crosstalk between GBM and astrocytes is the tumor suppressor gene p53, mutated in 87 % of GBM cases [78], which missense mutation has been demonstrated to be the main mutation type [79].

The primary function of p53 is to be activated in the nucleus, initiating cell death or growth arrest and maintaining homeostasis under healthy conditions. However, the apoptosis mechanism is completely inhibited in cancerous p53-/- cells. p53 also regulates the expression of proteins that are secreted to stimulate adjacent cells [80]. Particularly in the ECM of GBM, p53 modulates the expression of tumor cell-secreted proteins [81].

Thus, p53 can potentially modulate the ECM composition. The ECM of p53+/- astrocytes had a greater presence of laminin and fibronectin, which are known to trigger the epithelial to mesenchymal transition (EMT), compared to that of the ECM of p53+/+ astrocytes [82], through which tumor cells acquire a more migratory and invasive phenotype that can facilitate apoptosis evasion and promote the survival of GBM cells [83].

One similar study demonstrated an increased expression of N-cadherin and vimentin when GBM cells were cultured in the ECM of p53+/- astrocytes, and these two markers are responsible for a mesenchymal phenotype associated with increased resistance to apoptosis [84].

Culturing the U87 GBM cell line on ECM from p53+/- astrocytes reduced their apoptotic rate, which further confirmed that the specific TME formed by the neighboring p53+/- astrocytes promotes GBM survival. Additionally, compelling evidence has proven that GBM cells inhibit astrocytic p53 expression, favoring cancer malignancy [83]. Thus, a synergistic relationship exists between GBM cells and the cells in the TME, in which GBM cells hinder p53 expression in astrocytes to predispose cells to aberrant cell proliferation, while dysfunctional p53 induces a permissive environment for GBM cells.

Recent targeted therapy based on p53 reactivation reduced both GBM cell growth and resistance to temozolomide, indicating a promising role for p53 in the future treatment of GBM [85].

5.4. IL-6/JAK/STAT signaling pathway

Recent findings demonstrated that tumor-associated astrocytes secrete IL-6 to promote the progression and increase the malignancy of GBM in an astrocyte-glioma coculture system [86].

In particular, IL-6 in the TME activates downstream JAK/STAT signaling via binding to cognate surface receptors, which dimerize and thereby activate the receptor-associated tyrosine kinase JAK, which phosphorylates the receptor cytoplasmic portion. Tyrosine-phosphorylated receptors provide docking sites for the recruitment of cytoplasmic monomeric STAT3 protein, and the activation of STAT3 is linked with clinically more aggressive behavior of GBM [87,88]. IL-6 increases MMP2 and MMP9 expression through the activation of the IL-6/STAT3 mechanistic pathway, enhancing the invasiveness of GBM through the degradation of extracellular matrix [89,90]. Additionally, IL-6 also induces the upregulation of MMP-14, further enhancing the invasiveness of GBM [86].

STAT3 is also a direct transcriptional activator of the VEGF gene, which is the most potent angiogenesis-inducing signal, facilitating angiogenesis in GBM [91]. Suppression of apoptosis is mediated through the expression of various survival genes that are regulated by STAT3, such as Bcl2l1, Bcl-2, and Mcl-1. Thus, inhibition of STAT3 in GBM cells leads to downregulation of survival-related genes and apoptosis [92].

5.5. PI3K/Akt signaling pathway

Reactive astrocytes secrete glial cell line-derived neurotrophic factor (GDNF), which binds to the receptor tyrosine kinase (RET)/glial cell line-derived neurotrophic factor family receptor 1 (GFR1) receptor and activates the PI3K/Akt pathway to induce GBM migration [93]. In human glioma, PI3K/Akt pathway activation is often associated with (phosphatase and tensin homolog deleted on chromosome ten) PTEN alterations such as mutation, promotor methylation [94] and loss of heterozygosity, and PTEN has been proven to be a significant tumor suppressor [95].

Following activation of the PI3K/Akt pathway, Akt positively regulates the survival gene Mcl-1 [96]. Akt also leads to the activation of the NF-κB pathway by mediating phosphorylation of the inhibitor of NF-κB kinase subunit alpha (IKKa), increasing inhibitor of apoptosis (IAP) gene transcription and further enhancing GBM cell survival [97]. Akt phosphorylates mouse double minute 2 homolog (MDM2) and induces the translocation of MDM2 into the nucleus, inhibiting p53 apoptosis functions [98]. Moreover, Akt directly phosphorylates the apoptotic protein caspase-9 and decreases its protease activity, favoring GBM survival [99].

Activation of the PI3K/Akt pathway also increases epidermal

growth factor receptor (EGFR) expression. Mutant receptors, especially the EGFRvIII variant, which is constitutively activated in GBM and induces radioresistance in GBM, can give rise to constitutive activation of the Akt pathway [100]. MMPs, particularly MMP-9 that promotes invasiveness, are also regulated through the Akt pathway [101]. Moreover, astrocyte elevated gene-1 (AEG-1) enhances the proliferation and invasiveness of GBM by modulating the PI3K/Akt [25].

Activation of the PI3K/Akt pathway has been correlated with the grade of malignancy according to WHO classification, suggesting that high pAkt expression is associated with a poor prognosis in GBM patients [102].

6. Astrocytes are involved in GBM proliferation

Multiple studies have demonstrated that reactive astrocytes secrete high levels of factors such as TNF-α, TGF-β, IL-6, and insulin growth factor-1 (IGF-1) in response to CNS injury. Apart from brain-metastatic breast or lung cancer cells [103], these factors also significantly increase the in vitro proliferation of primary brain tumors such as GBM [104]. Exposure of astrocytes to extracellular vesicles (EVs) derived from GBM generate a medium loaded with fibroblast growth factor (FGF), human growth factor (HGF), VEGF, chemokines, and ILs that stimulate the proliferation of GBM cells [105].

Other potent substances in the medium, such as Cx43, are upregulated by astrocytes and modulate the levels of Bcl-2 and Bax2 in GBM cells, inhibiting the mitochondrial apoptotic response. Cx43 expression further prevents GBM cells from undergoing apoptosis via blocking cytochrome C release from mitochondria [106]. GBM cells express protocadherin 7 (PCDH7) to favor the assembly of GBM-TAA gap junctions composed of Cx43, which allows the transfer of the second messenger 2′3′-cyclic GMP-AMP (cGAMP) from GBM cells to TAAs. cGAMP further stimulates the STING pathway, an innate immune response pathway, promoting GBM cell production and the resulting astrocyte production of factors such as TNF and interferon (IFN)-α in the GBM microenvironment. The release of these two factors in turn activates NF-κB and STAT-1 in GBM cells, consequently supporting tumor cell proliferation and invasion [107,108].

L-glutamine (Gln) is involved in the balance of carbon and nitrogen requirements of neural tissue. Gln starvation, which is considered one type of metabolic dysfunction, hinders GBM cell proliferation. Gln produced by GBM cells themselves is not sufficient to satisfy the metabolic needs of the tumor cells. Interestingly, one astrocyte-glioma coculture system showed that astrocytes synthesize and secrete Gln to facilitate this requirement, and the Gln supplemented by the astrocytes was subsequently taken up by the GBM cells [109].

Similarly, GDF-15, a divergent member of the TGF-β superfamily, is overexpressed in reactive astrocytes. Initially, GDF-15 has antitumor properties because it induces the phosphorylation of Smad3 (a tumor suppressor protein) and apoptosis via the intrinsic mitochondrial pathway, inhibiting tumor cell division [110,111]. As the tumor progresses, GDF-15 no longer phosphorylates Smad3 [112]. GDF-15 also increases the activation of the PI3K-PKB pathway, which increases the viability of GBM cells [110]. In addition, GDF-15 disrupts p53 function in vascular cells and increases HIF-1α and VEGF expression, causing angiogenesis in GBM under hypoxia [113]. GDF-15 increases GBM cell proliferation in vitro, and the depletion of GDF-15 inhibits GBM cell growth in vivo [114]. Overexpression of GDF-15 in GBM patients seems to correlate with poorer survival of patients [112].

Overall, astrocytes surrounding GBM are responsible for the overexpression of multiple factors that are conducive to the proliferation of tumor cells (Fig. 2).

7. Astrocytes are involved in the invasion and migration of GBM

The major obstacle to curing malignant tumors such as GBM is diffuse invasion, which enables tumors to escape complete surgical resection and chemoradiotherapy. GBM uses the extracellular routes of migration that are travelled by immature neurons and stem cells and frequently uses blood vessels as guides, taking advantage of the ECM to support the invasive process. GBM cells repurpose ion channels to dynamically adjust their cell volume to accommodate narrow spaces and breach the blood-brain barrier through disruption of astrocytic endfeet.

As discussed above, astrocytes facilitate the remodeling of ECM by releasing IL6, which activates the expression of MMPs, including MMP2, MMP9 and MMP14, consequently favoring GBM invasion. The interaction between GBM cells and the surrounding astrocytes also activates MMP2 via the uPA-plasmin cascade [115]. Astrocytes also directly induce the interaction between the urokinase plasminogen activator (uPA) and its receptor uPAR in GBM cells in vitro, which in turn enhances the activation of plasmin, a serine protease that cleaves and activates MMP2 [115]. GDF-15 induces an increase in uPA and uPAR [116]. Additionally, the adhesion of GBM cells is mediated by integrins [117], and GDF-15 may interfere with integrin activation [118].

Moreover, IL-6 secreted by astrocytes promotes the in vitro invasive property of GBM cells by upregulating the expression of fascin-1, an actin-bundling protein that is involved in forming cellular protrusions that support cell migration [89]. Astrocytes also directly increase the expression of VEGF or induce the upregulation of VEGF through the STAT signaling pathway, and VEGF is responsible for angiogenesis and further invasion of GBM.

As a part of the neuron-glial network, astrocytes also facilitate interactions with GBM in the TME via ion channels and ion transporters. Astrocytes can participate in two-way communication with other cells by receiving and sending neurotransmitters such as glutamate and γ-aminobutyric acid (GABA) [119]. Various mechanisms involved in gliotransmission include Ca^{2+}-regulated vesicular exocytosis and release via plasma membrane ion channels, and exosomes transport miRNAs and proteins that promote the progression and invasion of GBM [120]. Proinflammatory cytokines such as IL-6, IL-10, STAT, TGF-β, bFGF, EGF, and MMP secreted by glioma cells stimulate astrocyte reactivity, disrupt ion homeostasis and regulate the expression of ion channels in glioma-associated stromal cells such as microglia [121,122].

Furthermore, reactive astrocytes release abundant chemokines into the tumor microenvironment, which further promote the tumorigenesis, aggression, and invasion of GBM. Ion channels in the plasma membrane of reactive astrocytes are involved in regulating secretion. For instance, activation of Ca^{2+} channels induces the secretion of endothelin-1 by astrocytes [123]. Therefore, ion transporters play dual roles in communication between astrocytes and glioma, as well as in glioma invasion (Fig. 2).

8. The astrocyte-mediated immunosuppressive microenvironment in anticancer immunity

Despite continuous progress in understanding the immune regulation of GBM and the development of immunotherapies [124], therapeutic advances have been insufficient. Elucidating a method to enhance antitumor immunity and develop promising immunotherapy seem to be huge challenges in GBM treatment. It has been thoroughly illustrated that the immune system becomes immediately activated as cancer cells develop and can fight the developing tumor with the activation of natural killer (NK) cells and T lymphocytes [125].

However, cancer cells become easily resistant to the natural immune reaction via immune evasion. Immune evasion and T lymphocyte dysfunction are a major hurdle for immune responses and are mediated by various mechanisms, including the immunosuppressive microenvironment in GBM patients, in which GBM cells interact with infiltrated immune cells and stromal components [9,126].

Currently, although there is no direct evidence that astrocytes are involved in the GBM immunosuppressive microenvironment, reactive

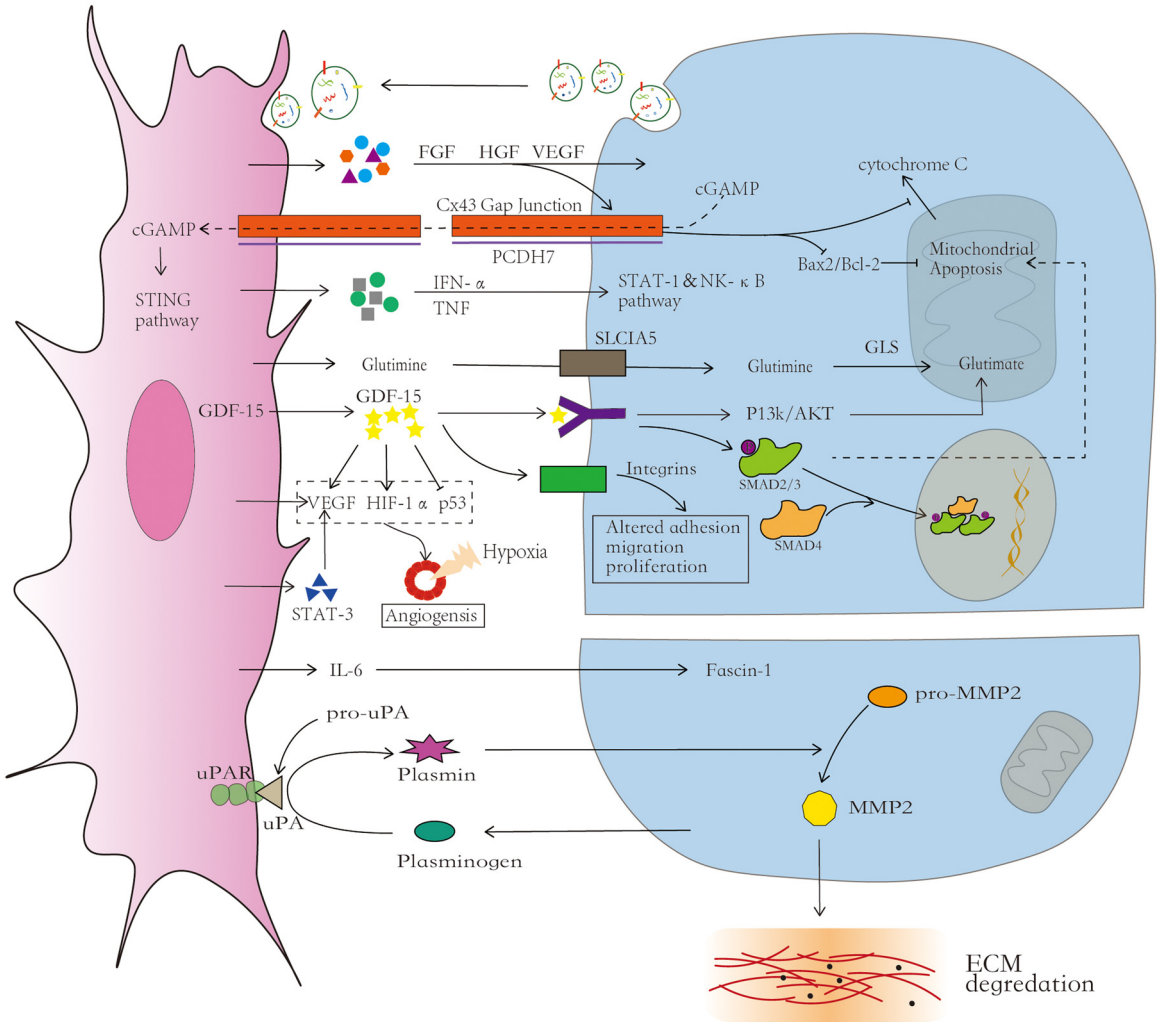

Fig. 2. TAAs in the proliferation and invasion of GBM. Exposure of astrocytes to EVs derived from GBM generates FGF, HGF, VEGF, chemokines, and ILs, stimulating the proliferation of GBM cells. Cx43 modulates the levels of Bcl-2 and Bax2 in GBM cells, inhibiting the mitochondrial apoptotic response. Gln metabolism is a major carbon source for tumor cell survival. GDF-15 induces phosphorylation of Smad3 and apoptosis via the intrinsic mitochondrial pathway, inhibiting tumor cell division. Astrocytes facilitate the remodeling of ECM by releasing IL6, which activates the expression of MMPs, favoring the invasion of GBM. Astrocytes induce the interaction between uPA and uPAR, which in turn enhances the activation of plasmin to activate MMP2.

astrocytes secrete factors such as tenascin-C, which has been linked to mechanisms implicated in immune protection of GBM cells by paralyzing T cell migration [127]. In addition, IL-10, an immunomodulatory cytokine secreted by astrocytes with anti-inflammatory properties, has also been shown to promote tumorigenesis via inhibiting the expression of proinflammatory mediators, including Class II (major histocompatibility complex) MHC and IFN-γ [128]. Class II MHC is involved in the antigen-presenting ability of monocytes, and IFN-γ induces the synthesis of IL-6, which further induces alternative macrophage activation to facilitate the immune eradication of GBM cells [129,130].

Moreover, STAT-3 is upregulated in reactive astrocytes and is essential in inducing angiogenesis, immunosuppression, and tumor invasion [87,131]. STAT-3 expression recruits and promotes the proliferation of regulatory T (Treg) cells [132], which in turn have suppressive activity toward CD8+ effector T cells [133]. The upregulation of STAT3 has also been associated with the expansion of T-helper 17 cells (Th17 cells), which are characterized by the expression of IL-17 [134,135]. Emerging evidence has suggested that the T-helper cell response toward Th17 differentiation silences the antitumor Th1 response, facilitating tumor progression [136]. STAT3 also promotes the expansion of tumor-associated myeloid-derived suppressor cells (MDSCs) [137] which inhibit CD4+ and CD8 + T cell activation as well as innate immune responses [138]. Several astrocyte-regulated factors associated with the STAT signaling pathway, including IL-6 and VEGF, regulate tumor-associated MDSC accumulation [139].

Notably, an extensive study showed that STAT-3 inhibits the activation of microglia and macrophages both in vitro and in vivo, inducing tumor growth [140]. The STAT-3-expressing subpopulation of reactive astrocytes has been shown to modulate the immune process in the CNS during GBM metastasis, thus promoting tumor cell survival [141].

GDF-15, which is elevated in reactive astrocytes, also causes tumor immune evasion. GDF-15 reduces IL-2 synthesis and increases the synthesis of immunosuppressive IL-10. A study showed that GDF-15 impairs NK cell function and reduces the infiltration of macrophages and T cells in GBM [114]. In addition, GDF-15 causes dendritic cell function abnormalities. It reduces the synthesis of IL-12 and increases the synthesis of TGF-β, which strongly disrupts immune function [142].

As a recent research hotspot, programmed death ligand-1 (PD-L1) leads to cancer immune evasion via inhibition of T cell function through binding to programmed cell death protein-1 (PD1) [143]. Astrocytes govern the activity of brain-infiltrating CD8 + T lymphocytes through the upregulation of PD-L1 expression, which is mediated by EVs derived from GBM [144]. One recent study indicated that a distinct reactive astrocytic subtype marked by JAK/STAT pathway activation and PD-L1 expression is mediated by high concentrations of anti-inflammatory IL10 and TGFβ, contributing substantially to the properties of an

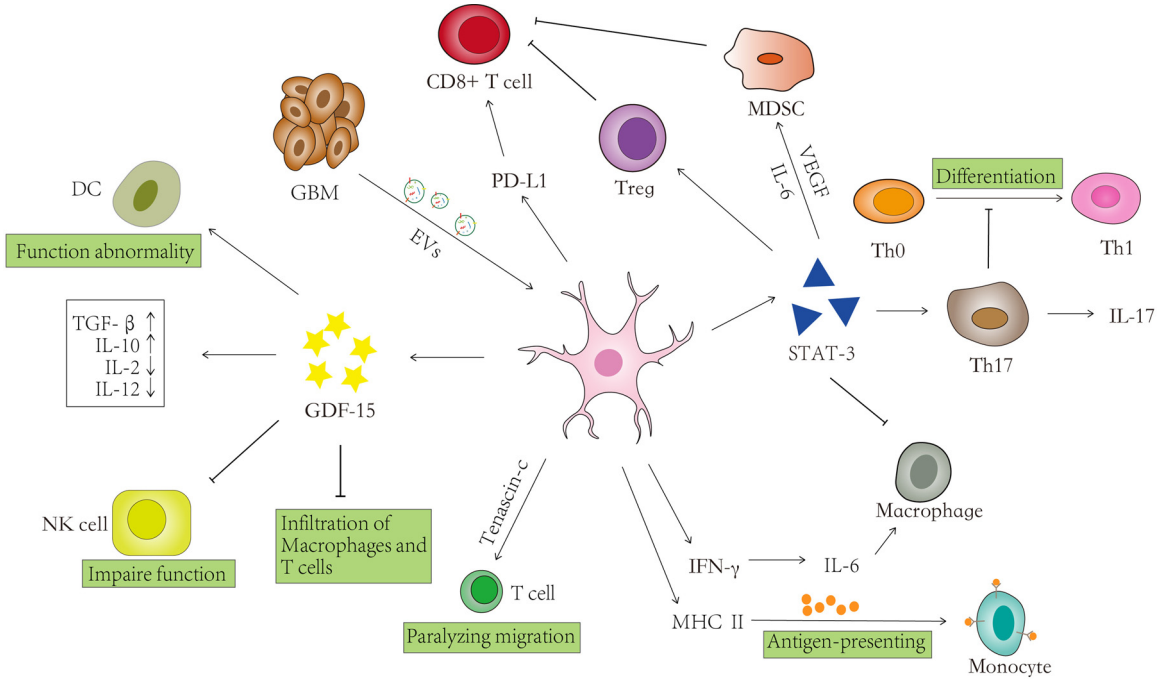

Fig. 3. The immunosuppressive modulator role of TAAs. Astrocytes secrete multiple factors with immunosuppressive effects, such as paralyzing T cell migration, inhibiting the expression of proinflammatory mediators and suppressing CD4 + and CD8 + T cell activation. GDF-15 causes tumor immune evasion by regulating the expression of ILs and impairs the function of NK and dendritic cells.

immunologically "cold" tumor environment [11].

Altogether, these reports highlight the potential of reactive astrocytes to protect GBM cells against anticancer immune reactions by secreting several well-described immunomodulatory factors (Fig. 3).

9. Reactive astrocytes and resistance to chemoradiotherapy treatment

Traditional clinical treatment modalities include surgery, radiation therapy (RT), and chemotherapy. Concomitant adjuvant temozolomide (TMZ) chemotherapy and radiotherapy with the median overall survival (OS) of 16 months is the current standard care for GBM patients [145]. Tumor treating field (TTF), approved by the United States Food and Drug Administration (FDA), could significantly increase the median OS of GBM patients by 2.8 months [146]. Although promising in preclinical experiments, the therapeutic effects of other novel treatments, including boron neutron capture therapy (BNCT), antiangiogenic therapy, immunotherapy, epigenetic therapy, oncolytic virus therapy and gene therapy are still either uncertain or have discouraging clinical results [124].

Thus far, no monotherapy for GBM is sufficient to prevent tumor recurrence. Compelling evidence has suggested that the interaction between tumor cells and their microenvironment triggers the tumor cell resistance to therapy, and astrocytes are thought to play an essential role in this interaction [104,147].

It has been suggested that gap junction communication (GJC) between glioma cells and astrocytes decreases the sensitivity of tumor cells to TMZ chemotherapy [148]. The glioma-astrocyte gap junctions modulate the invasive property of glioma by mediating microRNA signaling, and microRNAs transferred between glioma cells and astrocytes may enhance the chemoresistance of glioma cells [149]. Moreover, the gap junction protein Cx43 in glioma cells, which is upregulated by astrocytes during the glioma-astrocyte interaction, is responsible for TMZ resistance [106]. Moreover, knockdown of Cx43 in astrocytes increases TMZ-induced apoptosis of glioma cells [150]. In combination with the Cx43 property of promoting proliferation and migration of glioma cells, TMZ could potentially increase its effectiveness in combating GBM via artificially downregulating Cx43 protein.

Another standard option for the treatment of GBM is radiotherapy. After coculturing GSCs with astrocytes, researchers discovered that the presence of astrocytes diminished the sensitivity of glioma cells to radiotherapy. The initial level of radiation-induced γH2AX foci, which indicate breaks double-stranded DNA in GSCs, was reduced, suggesting that astrocytes influence the induction and repair of DNA double-strand breaks (DSBs) caused by radiotherapy. The study further identified significantly different gene expression profiles, including STAT3 in GSCs grown in astrocyte-mediated coculture, suggesting several potential targets for GSC radiosensitization. Consistent with these results, the JAK/STAT3 inhibitor WP1066 enhanced the radiosensitivity of GSCs [151]. Moreover, expression of active Akt accelerates DNA repair, suggesting that the PI3K/Akt pathway is also involved in the radioresistance of GBM cells [152]. Importantly, targeting Akt resulted in increased residual unrepaired DNA DSBs following irradiation of U251 GBM cells [153].

Given the pivotal role of astrocytes in GBM resistance to chemoradiotherapy treatment [154], more studies are needed to further elucidate the potential mechanisms involved in the interactions between astrocytes and glioma cells that induce GBM resistance to treatment.

10. Conclusion

As a powerful tumor contributor, there is accumulating evidence supporting the multiple roles of TAAs in the establishment of the TME, such as regulating environmental homeostasis and supporting tumor survival, proliferation, immune evasion, invasion and therapeutic resistance. The interplay between tumor cells and TAAs is increasingly recognized as a main driver for GBM progression. Although the development of basic studies and therapeutic strategies targeting TAAs have been revealed, more details on TAAs and GBM treatments remain to be illustrated. Further understanding of mechanisms involved in the crosstalk between TAAs and GBM will open new avenues for translational medicine and more meaningful clinical therapies for GBM.

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Availability of data and materials

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Authors' contributions

HZ, YZ, ZL and HS designed and drafted the manuscript; BC wrote figure legends and revised the article; HZ, YZ and BC drew the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Declaration of Competing Interest

All authors declare that they have no competing interests.

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