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Review

Research progress of galectins in glioma

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Abstract
Galectin, a member of the β-galactoside-binding protein family, is involved in various physiological and pathological processes, including cell adhesion, growth, apoptosis, and immune regulation. Due to its high malignancy, heterogeneity, invasive nature, and resistance to radiotherapy and chemotherapy, no effective treatment has been found for glioma so far. Galectin has been discovered to influence the invasion, migration, angiogenesis, and chemotherapy resistance of glioma, and can also play a significant role in the tumor immunosuppressive microenvironment (TME) by acting on immune cells such as T lymphocytes, macrophages, and myeloid-derived suppressor cells (MDSCs). This review discusses the role of galectin, especially the latest research progress on Gal-1, Gal-3, Gal-8, and Gal-9 in glioma, and proposes the therapeutic potential and challenges of targeting galectin for the treatment of glioma.

Keywords Galectin · Glioma · Therapy · Target · Immune microenvironment

Abbreviations

TME	Tumor immunosuppressive microenvironment
MDSC	Myeloid-derived suppressor cells
GSCs	Glioma stem cells
NK cells	Natural killer cells
DC cells	Dendritic cells
Gal-1	Galectin-1
Gal-3	Galectin-3
Gal-8	Galectin-8
Gal-9	Galectin-9
CRD	Carbohydrate recognition domain
GBM	Glioblastoma multiforme
FAK	Focal adhesion kinase
SPARC	Secreted protein acidic and rich in cysteine
Runx2	Runt-related transcription factor 2
Tregs	Regulatory T cells
VEGF	Vascular endothelial growth factor
IRE1α	Inositol-requiring enzyme 1α
BAEC	Bovine aortic endothelial cells

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EGFR	Epidermal growth factor receptor
TIME	Tumor immune microenvironment
TIM-3	T cell immunoglobulin domain and mucin domain-3
ICI	Immune cell infiltratio
ICP	Immune checkpoint

1 Background

Glioma is a type of neuroepithelial brain cancer originating from glial cells in the central nervous system. It is mainly composed of astrocytes (forming astrocytomas), oligodendrocytes (forming oligodendrogliomas), ependymal cells (forming ependymomas), or mixtures of various glial cells (such as oligoastrocytomas) [1, 2], and it is one of the most common malignant brain tumors in adults [3]. According to the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System, adult-type gliomas are mainly divided into three major categories: IDH-mutated astrocytoma, IDH-mutated and 1p/19q co-deleted oligodendroglioma, and IDH-wild-type glioblastoma. The latest WHO CNS tumor classification directly integrates the molecular characteristics of tumors into the tumor diagnostic decision-making system. This key change directly influences the determination of tumor typing and staging, completely changing the traditional model that relied solely on histopathology for classification in the past [4]. Among gliomas, the most common and most invasive one is glioblastoma (GBM), with a 5-year survival rate of only 2–10% [5]. Although surgical resection, radiotherapy, and chemotherapy have postponed the disease course to some extent, due to the limitations in clinical efficacy and prognosis [6, 7], t there is still an urgent need to explore new diagnostic and treatment methods.

In the metabolism of malignant tumors, carbohydrates serve as crucial energy molecules and play a significant role. Lectins that combine with sugar groups are key functional participants and important regulators in numerous carcinogenic processes [8]. The galectin family, which can specifically bind to β-galactosides, has been shown to play essential roles in glioma pathological processes [9]. Galectins can facilitate the growth of glioma stem cells (GSCs) by enhancing the Warburg effect [10], and influence the invasion, migration, angiogenesis, and chemotherapy resistance of gliomas. They can also play significant roles, such as promoting immune evasion in the tumor immunosuppressive microenvironment (TME), by acting on tumor-associated T lymphocytes, macrophages/microglia, myeloid-derived suppressor cells (MDSCs), natural killer (NK) cells, and dendritic cells (DCs) [9, 11]. This series of complex interactions not only reveals the critical role of galectins in gliomas but also offers a new perspective for exploring their potential therapeutic strategies. Existing research indicates that among the members of the galectin family, only Galectin-1 (Gal-1), Galectin-3 (Gal-3), Galectin-8 (Gal-8), and Galectin-9 (Gal-9) are highly expressed in gliomas, while studies on other family members in gliomas are scarce [9, 10]. This review will systematically introduce the expression status and mechanisms of action of Gal-1, Gal-3, Gal-8, and Gal-9 in gliomas and explore the new prospects of targeting galectins for their diagnosis and treatment.

2 The galectin family

2.1 The discovery and composition of galectins

Galectins are a class of carbohydrate-binding proteins that are widely present in vertebrates [12]. The first member of the family, Galectin-1, was isolated and named by Teichberg et al. from the tissue of electric eels in 1975 [13]. As of now, researchers have discovered a total of 16 members of the Galectin family in mammals, namely Galectin-1 to Galectin-16 [9], which are encoded by the genes LGALS1 to LGALS16. Among them, 12 have been identified in human tissues, namely Galectin-1, -2, -3, -4, -7, -8, -9, -10, -12, -13, -14, and -16 [14].

2.2 The characteristics of galectins

Galectins are a class of small-molecule proteins with characteristics such as the ability to bind β-galactosides independently of divalent cations, a shared primary structure, and a unique structural fold [15]. Almost all members carry at least one highly homologous carbohydrate recognition domain (CRD). Based on the number and structural differences of CRDs, Galectins are classified into three types: prototype Galectins, which contain one CRD and are present as non-covalently linked homodimers (Galectin-1, -2, -5, -7, -10, -11, -13, -14, -15, and -16); tandem-repeat

Galectins, which consist of a single polypeptide chain with two CRDs connected by a linker peptide (Galectin-4, -6, -8, -9, and -12); and chimeric Galectin-3, which has a C-terminal CRD rich in proline and glycine and an N-terminal domain that can mediate oligomerization, mainly trimers and pentamers [16].

Galectin-1, -3, -8, and -9 are widelyed in different tissues and tumor cells [17], but the expression of other Galectins is relatively limited. Galectin-2 and Galectin-4 are mainly expressed in the gastrointestinal tract [18, 19], Galectin-7 is preferentially expressed in the skin [20], Galectin-12 is abundantly expressed in adipose tissue [21]. Galectin-5 is only expressed in rat reticulocytes [22], Galectin-10 is strongly expressed in human eosinophils but not found in mouse eosinophils [23]. Galectin-13, -14, and -16 are mainly present in syncytiotrophoblast cells and have placenta-specific expression [24]. Current studies have indicated that among the members of the Galectin family, only Galectin-1 (Gal-1), Galectin-3 (Gal-3), Galectin-8 (Gal-8), and Galectin-9 (Gal-9) are widely expressed in gliomas and are involved in the occurrence and development of gliomas, while studies on other family members in gliomas are limited [9, 10].

3 The expression and prognosis of galectins in gliomas

Galectin is regarded as a reliable biomarker for the progression of malignant tumors in the central nervous system [25]. Yamaoka et al. [26] conducted the first study and discovered that the mRNA level of LGALS1 in human glioma was significantly higher than that in normal glial cells. It was found that after inhibiting the expression of LGALS1, the growth of 9L/lacZ (rat glioblastoma cells) was significantly retarded. The study also pointed out that ionizing radiation and hypoxia could enhance the expression of LGALS1 in gliomas, suggesting that blocking the expression of this gene before radiotherapy could enhance its therapeutic efficacy [27, 28]. Additionally, it was found that the expression level of Gal-1 in glioblastoma multiforme (GBM) was significantly negatively correlated with patient prognosis [25]. Moreover, in recurrent glioblastoma, Gal-1 expression was significantly higher than in primary tumors [29]. Therefore, there is potential for clinical therapeutic intervention by modulating Gal-1 expression to interfere with glioma development in the future.

Gal-3 is the sole chimeric galectin. Besides being widely expressed in tissues such as the heart, kidney, liver, and immune cells such as activated macrophages [30, 31], studies have indicated that the expression level of LGALS3 is significantly positively correlated with the malignancy as well as the grade of gliomas, but significantly negatively correlated with the survival rate [32]. It has been speculated that Gal-3 may serve as a prognostic biomarker for gliomas [33].

Glioma stem cells (GSCs), a small subset of cells existing in glioma tissue, possess extremely strong self-renewal capacity and are the key cause for the recurrence and treatment resistance of glioblastoma multiforme (GBM). Liu et al. [34] investigated and found that Gal-8 is preferentially present in GSCs under hypoxic conditions, and it can enhance autophagy through the Gal-8-mTOR-TFEB axis to maintain the stem cell characteristics of GSCs. Furthermore, by inhibiting the expression of Gal-8, the proliferative activity of GSCs can be significantly reduced. Additionally, it was discovered that Gal-8 is highly expressed in GBM and is closely associated with poor patient survival rates.

Zhu et al. [33] discovered through immunohistochemical staining that the expression levels of LGALS1, -3, -8, and -9 in glioma tissues were significantly elevated compared to normal brain tissues. This high expression occurred in all grades of gliomas and was significantly positively correlated with the malignancy degree of gliomas. Additionally, the expression level of LGALS9 was negatively correlated with the overall survival rate of patients [35].

The aforementioned studies all indicated that LGALS1, LGALS3, LGALS8, and LGALS9 are expected to become the diagnostic and therapeutic targets for gliomas. We re-evaluated the differential expressions of LGALS1, LGALS3, LGALS8, and LGALS9 in normal brain tissues and gliomas, as well as their associations with prognosis through bioinformatics analysis. Firstly, the mRNA data of gliomas in the TCGA database were analyzed using the "limma", "ggplot2", and "ggpubr" packages in R. The results are shown in Fig. 1A. The mRNA levels of LGALS1, LGALS3, and LGALS9 were upregulated in gliomas, which corroborates what we described above. Since the TCGA database can only reflect the mRNA levels of genes, we analyzed the protein levels using the CPTAC and HPA databases. The results are shown in Figs. 1B andC. Except for the LGALS8 protein being downregulated in glioma tissues, the rest were consistent with the results described above. In the aforementioned studies, researchers have verified that LGALS1, LGALS3, LGALS8, and LGALS9 are related to the survival of glioma patients, which is also consistent with our bioinformatics results (Fig. 1D).

Fig. 1 **A** Based on the TCGA database, the mRNA expressions of LGALS1, LGALS3, and LGALS9 were upregulated in glioma tissues, with statistical significance. **B** Based on the CPTAC samples, the protein expressions of LGALS1, LGALS3, and LGALS9 were upregulated in glioma tissues, with statistical significance, while the expression of LGALS8 was downregulated, with statistical significance. **C** In the HPA database, the protein expressions of LGALS1, LGALS3, LGALS8, and LGALS9 in the cerebral cortex, low-grade glioma, and high-grade glioma tissues. The protein expression of LGALS1 in the tissues of the cerebral cortex (Patient id: 1539), low-grade glioma (Patient id: 34), and high-grade glioma (Patient id: 183) (LGALS1 antibody id: CAB002157), the expression of LGALS1 was higher in tumor samples than in non-tumor samples, and the protein expression level of LGALS1 was higher in high-grade glioma. The protein expression of LGALS3 in the tissues of the cerebral cortex (Patient id: 2521), low-grade glioma (Patient id: 3137), and high-grade glioma (Patient id: 3091) (LGALS3 antibody id: CAB005191), the expression of LGALS3 was higher in tumor samples than in non-tumor samples, and the protein expression level of LGALS3 was higher in high-grade glioma. The protein expression of LGALS8 in the tissues of the cerebral cortex (Patient id: 1582), low-grade glioma (Patient id: 3365), and high-grade glioma (Patient id: 2527) (LGALS8 antibody id: HPA030491), the expression of LGALS8 was higher in tumor samples than in non-tumor samples, and the protein expression level of LGALS8 was higher in high-grade glioma. The protein expression of LGALS9 in the tissues of the cerebral cortex (Patient id: 3732), low-grade glioma (Patient id: 122), and high-grade glioma (Patient id: 38) (LGALS8 antibody id: HPA047218), the expression of LGALS9 was higher in tumor samples than in non-tumor samples, and the protein expression level of LGALS9 was higher in high-grade glioma. **D** Based on the GEPIA database, the high expressions of LGALS1, LGALS3, LGALS8, and LGALS9 were negatively correlated with the prognosis of glioma patients

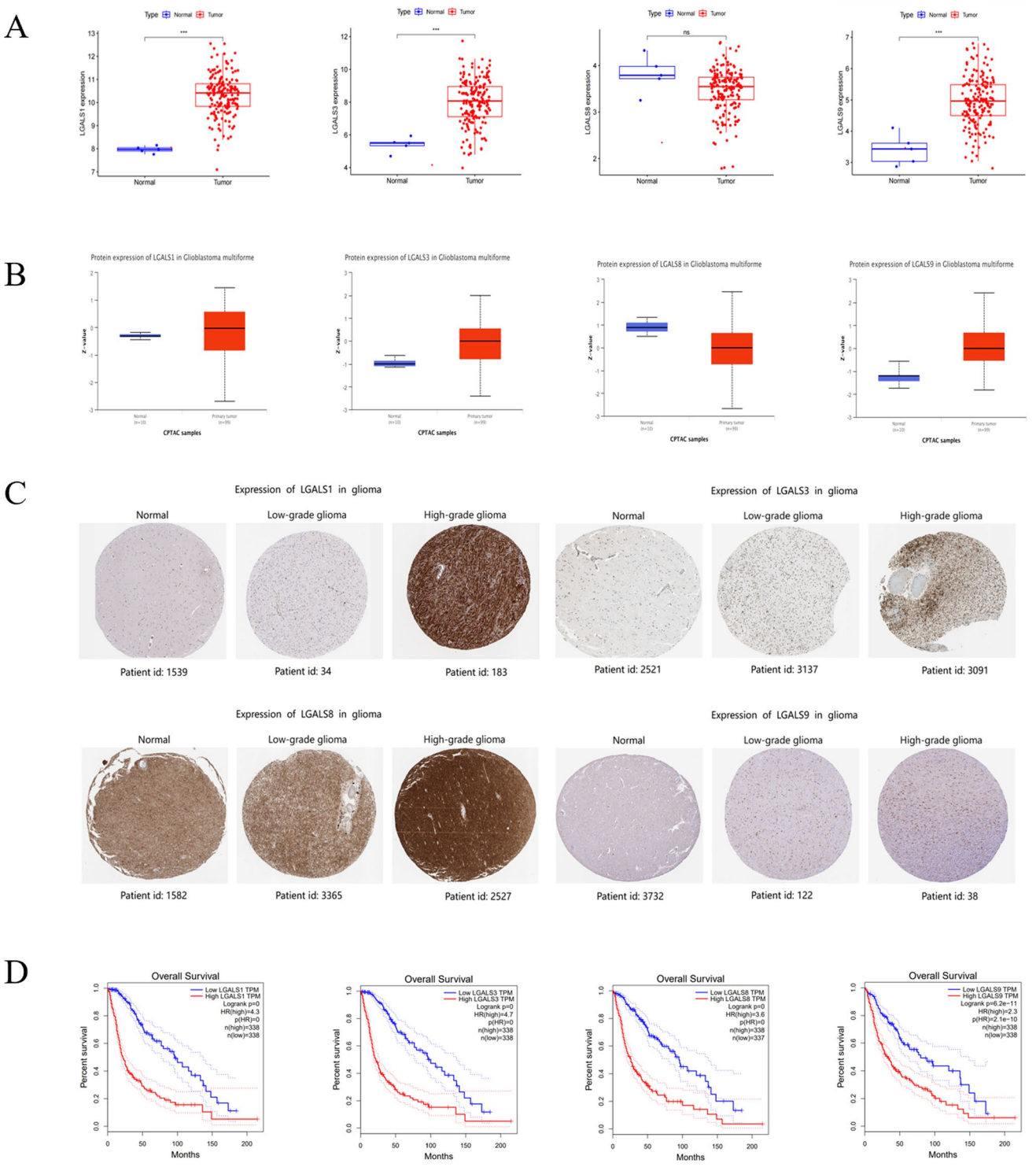
4 Galectin and the proliferation, invasion and migration of gliomas

Numerous studies have indicated that Gal-1 not only facilitates the proliferation of glioma cells but also plays a crucial role in their invasion and migration [36, 37]. For instance, Toussaint et al. [37] demonstrated through in vitro experiments that overexpression of LGALS1 significantly enhanced the invasion and migration capabilities of human astrocytoma U87M cells. Moreover, in an in vivo xenograft mouse model experiment, it was found that mouse models with high expression of LGALS1 had a lower survival rate, which was in accordance with the results of Stike et al. [27] in experiments on human astrocytoma A172 and U118 cells. Camby et al. [38] discovered that Gal-1 promotes glioblastoma cell migration in a lactose-dependent manner. This effect is associated with filamentous actin polymerization and the increased expression of small guanosine triphosphatase RhoA (Fig. 2A). Additionally, multiple studies have shown that Gal-1 can bind to integrin-β1, influence the adhesion function of vascular smooth muscle cells, induce the phosphorylation of focal adhesion kinase (FAK), promote integrin-β1-mediated cell adhesion and movement, and thereby regulate cell migration (Fig. 2A) [39].

Apart from Gal-1, Gal-3, and Gal-8 are also involved in the proliferation, invasion, and migration processes of gliomas. It has been found that in glioma T98G and U251 cells, overexpression of LGALS3 can promote tumor cell proliferation [40]. Secreted protein acidic and rich in cysteine (SPARC) is closely related to the invasion and migration of gliomas. McClung et al. [41] discovered that increased SPARC expression in gliomas can simultaneously upregulate the expressions of MT1-MMP, MMP-2, and Gal-3. These molecules then collaborate to promote tumor cells breaking through extracellular matrix limitations, invading surrounding tissues, and metastasizing to distant locations.

Runt-related transcription factor 2 (Runx2) is highly expressed in glioblastoma and can promote the progression of glioma by mediating the cAMP/PKA signaling pathway [42]. Vladimirova et al. [43] discovered that Runx2 can upregulate the expression of LGALS3, facilitating the malignant progression of glioma. Additionally, Ochieng et al. [44] reported that Gal-3 can promote the migration of glioma cells by regulating Runx2-mediated cytoskeletal reorganization (Fig. 2B). Gal-3 can also combine with integrin α1β1 through a lactose-dependent mechanism, preventing the interaction between integrin α1β1 and extracellular matrix proteins, thereby modulating the adhesion and motility functions of glioma cells (Fig. 2B) [45]. Furthermore, NG2 proteoglycan is a significant component of microvascular pericytes. It was found that Gal-3 can simultaneously form a complex with integrin α3β1 and NG2, and further promote endothelial cell migration through α1β1-mediated transmembrane signal transduction (Fig. 2B) [46].

Metz et al. [47] experimentally discovered that Gal-8, as a soluble stimulant, not only triggers the migration of U87 glioblastoma cells but also facilitates the growth of U87 cells. After transfecting U87 cells with a lentiviral vector carrying a silencing shRNA, the study revealed that these cells express and secrete Gal-8 at only 30–40% of the normal level. They still retain migratory capacity, but their proliferation rate decreases, and apoptosis increases. This indicates that, compared to migratory ability, proliferation is more sensitive to the expression level of Gal-8. Camby et al. [48] also verified the role of Gal-8 in promoting glioblastoma migration through in vitro experiments. Recent research has



found that the binding of Gal-8 to the Ragulator-Rag complex inhibits mTOR and promotes TFEB nuclear translocation, thereby enhancing autophagy and ultimately promoting the proliferation and self-renewal of GSCs (Fig. 2C) [34].

The team from Yuan F analyzed the data from CGGA and TCGA and discovered that, compared with normal brain tissue and low-grade glioma tissue, LGALS9 was significantly upregulated in glioblastoma multiforme. Its expression

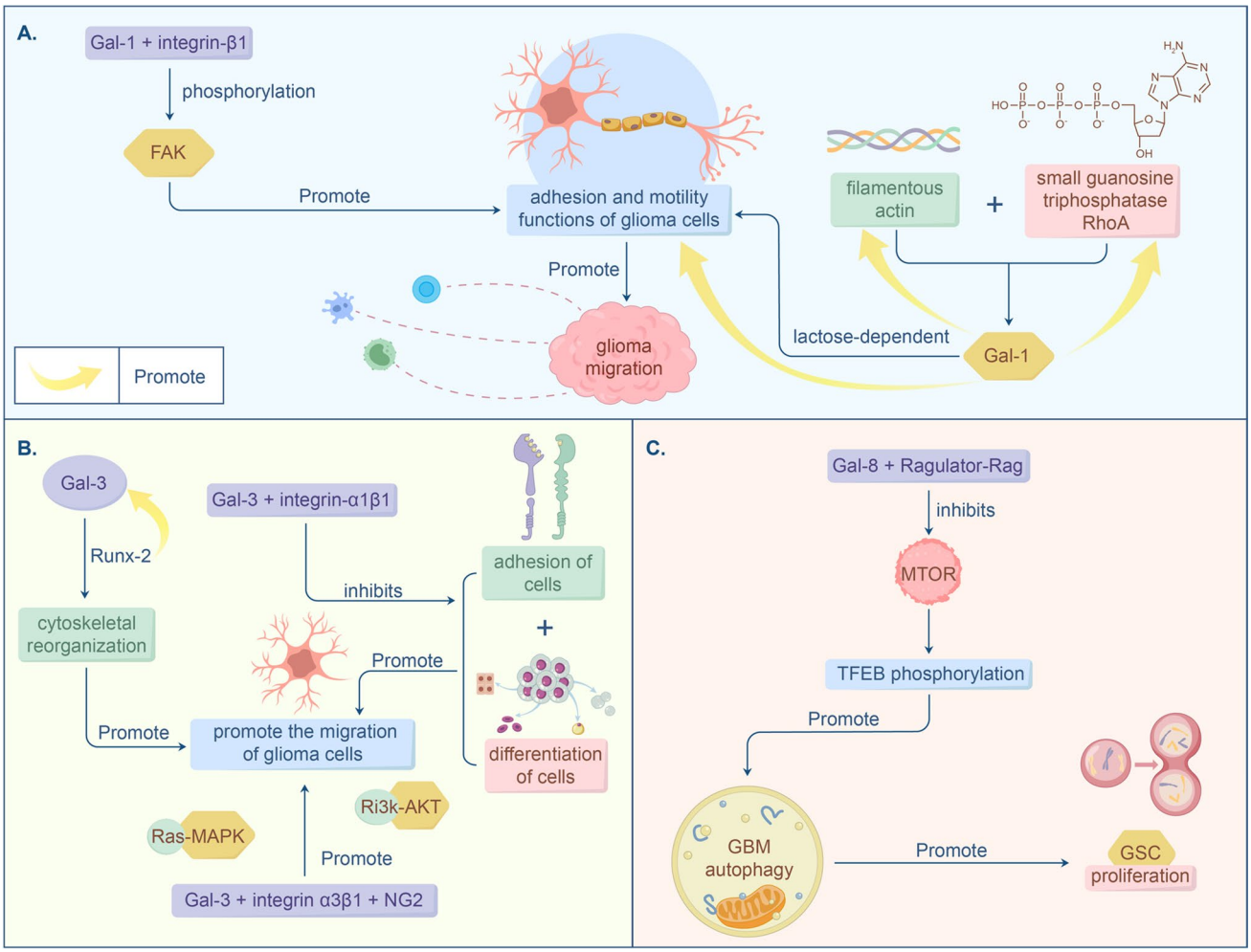


Fig. 2 Mechanisms of action of galactin-1, -3 and -8 on proliferation and migration of glioma cells. **A** The mechanism by which galectin-1 affects the migration of glioma cells by affecting the adhesion and movement of glioma cells. **B** The mechanism of galactin-3 effect on glioma migration. **C** The mechanism of galectin-8 affecting the proliferation of GSC

was higher in the core area of the tumor than in the marginal area [49, 50]. Despite the significant expression of LGALS9 in gliomas, there are currently no relevant reports on its specific roles in proliferation, invasion, and migration.

5 Galectin and angiogenesis in glioma

Tumor-related angiogenesis is a hallmark of tumor growth and an important therapeutic target. Mounting evidence indicates that carbohydrate-binding proteins play a vital role in tumor growth and metastasis. Gal-1 is regarded as a hypoxia-regulated pro-angiogenic factor and exerts a significant role in the angiogenesis of glioma [51]. Mercier et al. [52] demonstrated that Gal-1 promotes the expression of ORP150 protein, which controls the maturation of vascular endothelial growth factor (VEGF), by activating inositol-requiring enzyme 1α (IRE1α), thereby facilitating angiogenesis (Fig. 3A). The latest research points out that the pro-angiogenic effect of Gal-1 in glioma is also associated with the regulation of the X-linked gene BEX2. Additionally, Gal-1 can further promote the formation of new tumor blood vessels by regulating the expression of angiogenesis-related genes, such as CTGF and ATF3.

Gal-3 has also been extensively investigated in the aspect of angiogenesis. Nangia et al. [53] discovered through in vitro and in vivo experiments that soluble Gal-3 can induce endothelial capillary tube formation in vitro and angiogenesis in vivo. This is because carbohydrate recognition events on the surface of endothelial cells trigger a signaling cascade, thereby leading to the differentiation of endothelial cells and angiogenesis. The Gal-3 secreted by tumor cells and macrophages precisely promotes the movement of endothelial cells in the early stage of angiogenesis, which is consistent

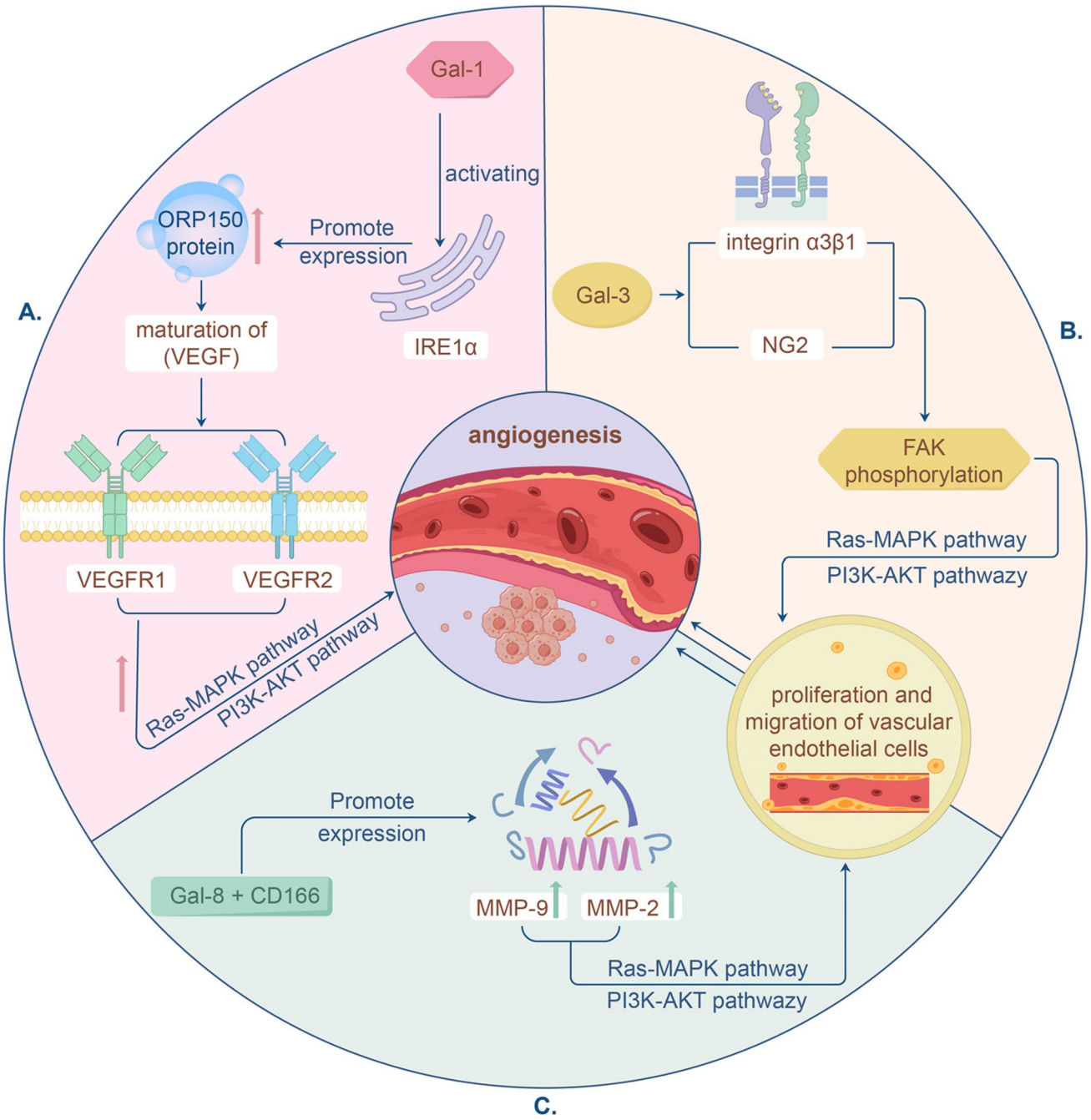


Fig. 3 Galactin-1, -3, and -8 promote angiogenesis. **A** The mechanism of galactin-1 promoting angiogenesis in glioma. **B** The mechanism of galactin-3 promoting angiogenesis in glioma. **C** The mechanism of galactin-8 promoting angiogenesis in glioma

with the findings of Wen Y et al. [54] in glioma studies. Gal-3 promotes the movement of endothelial cells by forming a complex with integrin α3β1 and NG2 and stimulating integrin-mediated transmembrane signal transduction (Fig. 3B).

Troncoso MF et al. [55] discovered that when recombinant Gal-8 was added to Matrigel, it could induce bovine aortic endothelial cells (BAEC) to form extensive capillary networks from large blood vessels. Additionally, in studies of the vascular endothelial cell ligand of Gal-8, it was found that CD166, an important molecule promoting the proliferation and migration of vascular endothelial cells in tumors, participates in the angiogenic effect of Gal-8 on BAEC (Fig. 3C).

The foregoing studies suggest that gliomas are prone to metastasis, which is inseparably associated with the angiogenic characteristics of galectins, and this has pioneered new thinking for targeted therapy to inhibit the angiogenesis of gliomas in the future.

6 Galectins and drug resistance of glioma

Temozolomide, as the first-line chemotherapeutic agent for glioblastoma, the development of resistance to it is highly unfavorable for patient prognosis. It has been discovered that hypoxia, apart from inducing chemoresistance and radioresistance in cancer cells, can also activate the PI3K/Akt signaling pathway to regulate the expression of LGALS1. Moreover, studies have indicated that in glioblastoma cells, cell lines overexpressing LGALS1 exhibit significantly reduced sensitivity to temozolomide, thereby greatly augmenting the risk of drug resistance. Le et al. [56] proved through in vivo and in vitro experiments that reducing the expression of Gal-1 in Hs683 GBM cells using siRNA increased the anti-tumor effects of various chemotherapeutic drugs, particularly the in vivo and in vitro anti-tumor effects of temozolomide. Additionally, low Gal-1 expression also impaired the expression levels of seven genes associated with chemotherapy resistance: ORP150, HERP, GRP78/Bip, TRA1, BNIP3L, GADD45B, and CYR61. Apart from Gal-1, the epidermal growth factor receptor (EGFR) also significantly influences temozolomide resistance. Danhier et al. [57] demonstrated that by jointly using anti-EGFR and anti-Gal-1 siRNA nanocapsules to treat glioblastoma, the chemotherapy resistance of glioblastoma could be significantly reduced, indicating that Gal-1-based combination therapy is more effective in overcoming temozolomide resistance. Furthermore, the transcriptional activity of p53 and its target genes is negatively regulated by Gal-1. p53 can trigger the apoptotic response of cells to chemotherapy. The loss of its function may lead to a reduction in the sensitivity of tumor cells to chemotherapeutic drugs, thereby causing chemotherapy resistance [58].

A number of studies have indicated that Gal-3 participates in the emergence of anti-cancer drug resistance in multiple tumors, such as prostate cancer, breast cancer, and ovarian cancer. This might be associated with its impact on tumor-cell apoptosis. Therefore, Gal-3 is also regarded as a candidate target protein for suppressing anti-cancer drug resistance. However, no research has yet reported its role in glioblastoma drug resistance, which could serve as a promising direction for future studies.[59].

7 The impact of galectins on the immune microenvironment of gliomas

The dynamic interactions between tumor cells and the surrounding microenvironment significantly impact multiple aspects of glioma, including its onset, development, chemotherapy resistance, and immune evasion [60]. Numerous studies have revealed that Gal-1 can interact with various immune cells, such as tumor-associated T lymphocytes, macrophages/microglia, MDSCs, NK cells, and DCs. It plays a pivotal role in the immunosuppressive microenvironment of gliomas by inhibiting T-cell activity, regulating macrophage polarization, affecting the antigen-presenting ability of dendritic cells, and suppressing the immune-surveillance function of NK cells [61, 62].

T cell dysfunction is a salient feature of the immune microenvironment in gliomas. Gal-1 binds to the β-galactoside on the surface of T cells, triggering T cell apoptosis, inhibiting T cell signal transduction, and obstructing their transendothelial migration (Fig. 4A). Consequently, the normal anti-tumor function of T cells is weakened [63, 64]. Gal-1 can also promote the differentiation of $CD4^+$ and $CD8^+$ regulatory T cells (Tregs) and induce the generation of tolerogenic DCs [65, 66]. Moreover, Gal-1 can drive M1 macrophages to polarize into the M2 type (Fig. 4A). M2 macrophages have anti-inflammatory properties, as well as functions in tissue repair and angiogenesis promotion, which significantly facilitate the growth of tumor cells. Experiments have shown that by knocking down LGALS1 to downregulate M2 macrophages and MDSCs, immunosuppressive cytokines can be inhibited, thus reshaping the immunosuppressive microenvironment of GBM [67]. NK cells, which play a crucial role in regulating the immune microenvironment, are linked to the expression of Gal-1. Baker et al. [62] found that glioma cells can suppress the immune surveillance function of NK cells by overexpressing Gal-1. Shah et al. [68] further proposed, through experiments, the Gal-1-regulated miR-1983-TLR7-IFNβ-NK cell signaling pathway against glioma. Experimental studies have indicated that exosomal miR-1983 released by Gal-1-deficient glioma cells can activate TLR7 signal transduction. This leads to the secretion of IFN-β through the downstream signaling of MyD88-IRF5/IRF7, thereby activating NK cells to eliminate glioma cells (Fig. 4A). These studies provide significant insights for the immunotherapy of gliomas.

Gal-3 also plays a significant role in the glioma immune microenvironment. Studies have shown that Gal-3 is involved in microglia activation and can suppress the cytotoxicity and phagocytic function of macrophages [69]. Rivera-Ramos A et al. conducted in vivo and in vitro experiments on Gal-3 knockdown. They found that facilitating

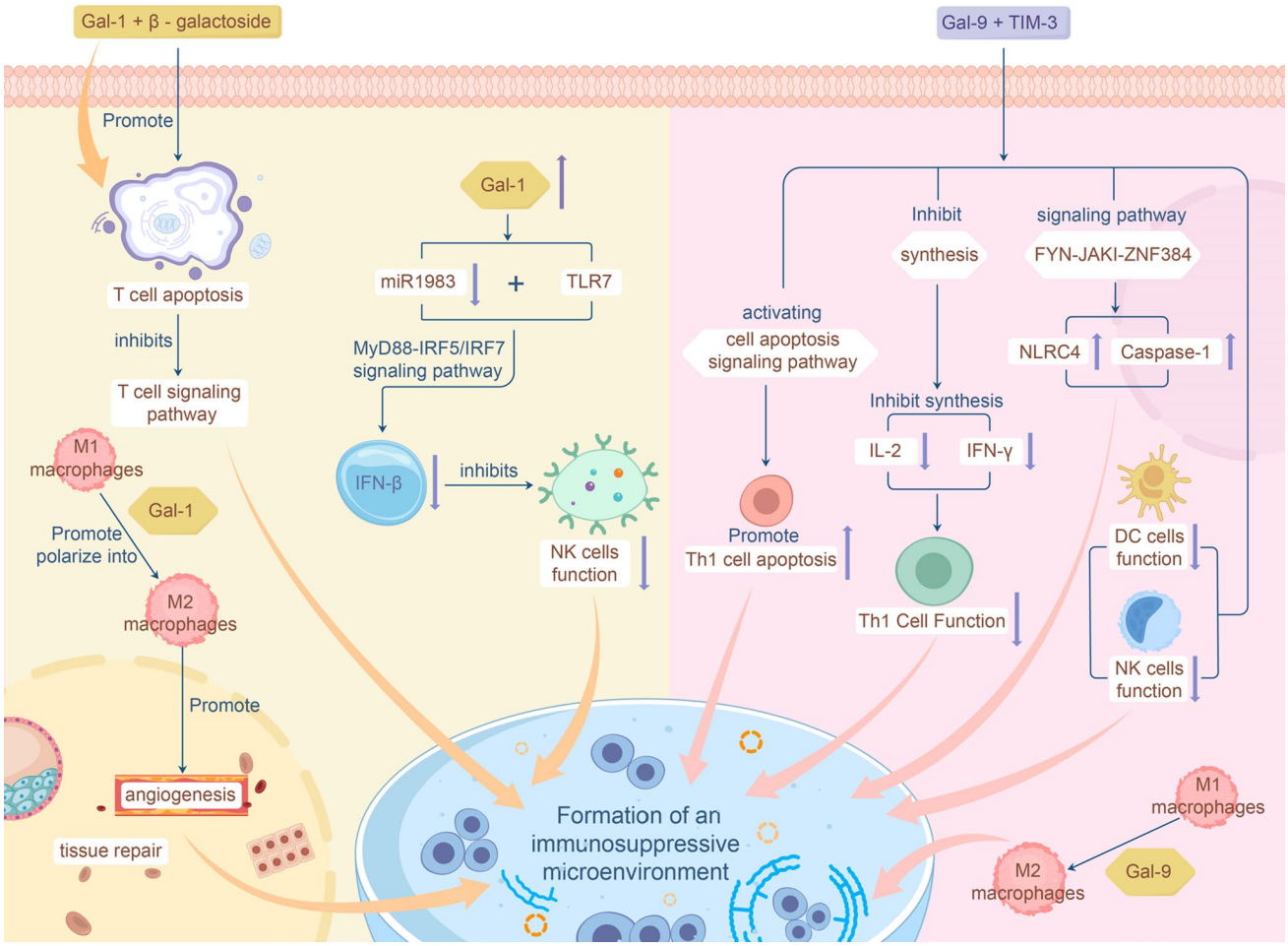


Fig. 4 The role of Galactin-1, -3, and 8 in the tumor immune microenvironment. **A** The mechanism by which galactin-1 affects the formation of tumor-suppressing microenvironment by influencing immune cells. **B** The mechanism by which galactin-9 affects the formation of tumor-suppressing microenvironment by influencing immune cells

microglia activation could transform the anti-inflammatory state in the original tumor microenvironment into a pro-inflammatory, anti-tumor state. This new state was more conducive to NK cell infiltration, inhibited cancer cell migration and invasion, and reduced tumor volume. The study also indicated that using temozolomide in glioblastoma mice with Gal-3 knockdown could significantly inhibit tumor growth, showing a synergistic effect [69, 70].

The immune checkpoint T cell immunoglobulin domain and mucin domain-3 (TIM-3, also known as HAVCR2), as a member of the TIM family of immune regulatory proteins, participates in tumor immune suppression by mediating apoptosis. Studies have revealed that, as a ligand for Gal-9, TIM-3 is a crucial molecule in maintaining T cell dysfunction in the immune microenvironment of gliomas. When Gal-9 binds to TIM-3 on the surface of Th1 cells, it not only activates the intracellular apoptotic signaling pathway, leading to Th1 cell apoptosis, but also inhibits the secretion of cytokines such as IL-2 and IFN-γ, weakening the Th1-type immune response and thereby facilitating tumor immune escape (Fig. 4A) [71, 72]. Gliomas with 1p/19q chromosomal co-deletion are regarded as a specific tumor entity, characterized by relatively weak invasive ability and high therapeutic sensitivity. Li G et al. [73] demonstrated that 1p/19q chromosomal co-deletion can promote anti-tumor immune responses by downregulating the expression levels of TIM-3 and its ligand Gal-9. Furthermore, analyses of databases such as TCGA reveal that the expression of Tim-3/Gal-9 increases along with the increase in glioma grades. Moreover, experiments have discovered that the Tim-3/Gal-9 pathway can activate the NLRC4 inflammasome and the activity of its downstream caspase-1 through the FYN-JAK1-ZNF384 signaling pathway, thereby establishing an immune microenvironment conducive to tumor growth and facilitating the proliferation and invasion of tumor cells (Fig. 4B) [74]. Hence, blocking this pathway could alter the immune microenvironment of glioblastoma and is expected to offer novel ideas for its treatment. Wang et al. [75] likewise indicated in their research on glioblastoma that Gal-9 in the exosomes secreted by glioblastoma cells, by binding to the TIM-3 receptor on DC cells, can inhibit antigen

recognition, processing, and presentation by DC cells, resulting in the loss of the anti-tumor immune response mediated by NK cells (Fig. 4B). The overexpression of Gal-9 can also induce the transformation of M1 macrophages into M2 macrophages, enhance the immunosuppressive function of tumor-associated macrophages, and promote the immune evasion of glioblastoma cells by influencing the activities of TGF-β, IL-10, and Stat3 [76]. All the above studies demonstrate that Gal-9 plays a key role in the immunosuppressive microenvironment of glioblastoma.

Gal-1, Gal-3, and Gal-9 exert significant influences in the immune microenvironment of gliomas. However, the role of Gal-8 in the immune microenvironment of gliomas has not been reported to date. It is anticipated that by targeting the regulation of the expression of key molecules, the immune microenvironment of gliomas can be improved, thereby offering new possibilities for their treatment.

We evaluated the correlations between the gene expressions of LGALS1, LGALS3, LGALS8, and LGALS9 and the levels of immune cell infiltration (ICI) as well as the expressions of immune checkpoint (ICP) genes in glioma through bioinformatics analysis. The ESTIMATE algorithm was employed to predict the contents of stromal cells and immune cells in glioma samples, and in combination with the RNA-seq data from the TCGA database, the stromal score, immune score, and ESTIMATE Score of each sample were calculated. The CIBERSORT algorithm was utilized to estimate the infiltration ratios of 22 immune cells in the immune microenvironment of glioma. Spearman's correlation analysis was adopted to analyze the correlations between the expressions of LGALS1, LGALS3, LGALS8, and LGALS9 and ICI. Furthermore, we also analyzed the correlations between the expressions of LGALS1, LGALS3, LGALS8, and LGALS9 and ICP genes in glioma. The results are shown in Fig. 5. LGALS1, LGALS3, LGALS8, and LGALS9 might play significant roles in regulating the immune responses in the tumor immune microenvironment (TIME) of glioma by influencing ICI and ICP molecules. TIM-3 is the receptor for Gal-9. Their interaction inhibits Th1 immune responses and promotes immune evasion in tumorigenesis [71, 72], which is consistent with our bioinformatics analysis results.

8 Galectins inhibitors and glioma related treatment

A large number of studies have shown that galectins can promote tumor proliferation, migration, and invasion, and can also regulate the tumor microenvironment. Therefore, galectin inhibitors are considered a new and effective immunotherapy method. Currently, the most extensively studied galectin is Gal-3. For example, Gal-3 inhibitors such as GB1107, GB1211, and GR-MD-02 have entered clinical trials and have demonstrated good anticancer effects on melanoma, non-small cell lung cancer, and squamous cell head and neck cancer, with advantages such as minimal side effects [77]. However, there have been no clinical trials using galectin inhibitors in the treatment of glioma, and blood–brain barrier permeability may be one of the reasons hindering treatment. Nonetheless, some relevant studies have explored this area. OTX008, an angiogenesis inhibitor targeting Gal-1, was tested by Zucchetti et al. [78] in vitro experiments, which showed that the glioblastoma U87MG cell line was unaffected by OTX008 either as monotherapy or in combination with sunitinib, possibly due to the low sensitivity of the U87MG cell line to Gal-1 inhibitors. Chauhan K et al. [79] screened 627861, 329090, and 627855 as potential inhibitors of LGAL3SBP from the National Cancer Institute drug database, but further experimental verification is needed. Bousseau et al. [80] found during the evaluation of PST3.1a's effects on angiogenesis and endothelial metabolism that PST3.1a can reduce the interaction between GAL-1 and VEGFR2 in human umbilical vein endothelial cells, resulting in anti-angiogenic effects, and it may be an effective Gal-1 inhibitor for treating GBM. Although many challenges remain in treating glioma with galectin inhibitors, new therapeutic approaches can be developed through combining immunotherapy with galectin inhibition or integrating galectin inhibitors with radiotherapy and chemotherapy.

9 Summary and prospects

We systematically summarized the research progress of the Galectin family in glioma, finding that it plays a vital role in the occurrence and development of glioma, invasion and migration, immune microenvironment, drug resistance, and disease prognosis. We also summarized the research progress of galectin inhibitors in the treatment of glioma. Simultaneously, we have verified its role in glioblastoma through bioinformatics analysis and consider the galactoside-binding lectin family to be an excellent diagnostic and therapeutic target for glioblastoma. Nevertheless, several aspects warrant further investigation, such as the specific mechanism of action of Gal-9 on glioblastoma cells, the role of Gal-8 in the immune microenvironment of glioblastoma, and whether Gal-8 and Gal-9 can be involved in drug resistance in glioblastoma.

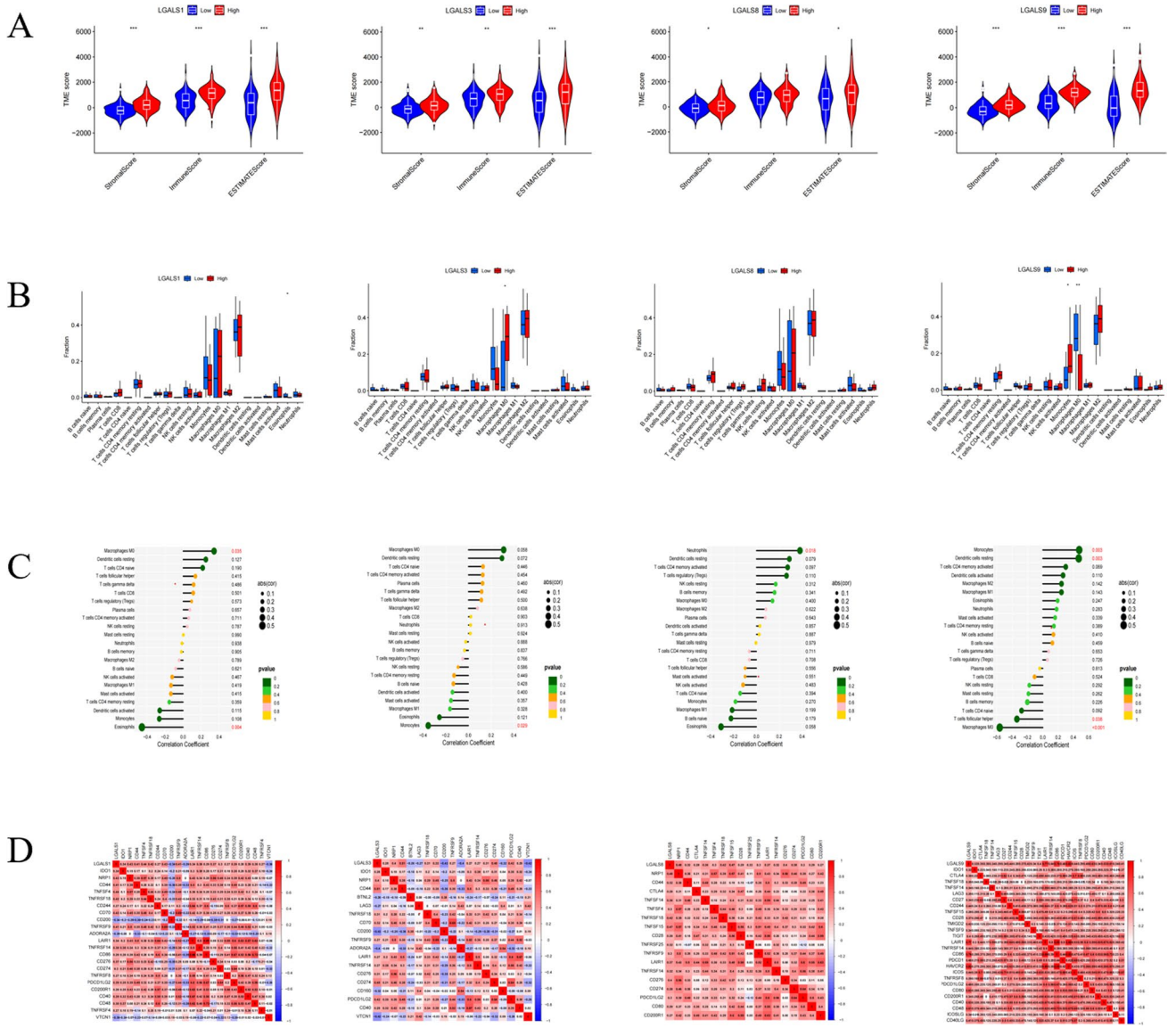


Fig. 5 **a** The expressions of LGALS1, LGALS3, LGALS8, and LGALS9 are associated with the microenvironment of gliomas. There are significant differences in immune and stromal components between the high and low expression groups of LGALS1, LGALS3, and LGALS9. There is a significant difference in stromal components between the high and low expression groups of LGALS8. **b** The infiltration of immune cells between the high and low expression groups of LGALS1, LGALS3, LGALS8, and LGALS9. Eosinophils are differentially enriched in the high and low expression groups of LGALS1. M0 macrophages are differentially enriched in the high and low expression groups of LGALS3. There are no differentially enriched genes between the high and low expression groups of LGALS8. Monocytes and M0 macrophages are differentially enriched in the high and low expression groups of LGALS9. **c** Spearman's correlation analysis was conducted on the expression of LGALS1 and 22 tumor-infiltrating immune cells. The results showed that the infiltration levels of M0 macrophages and eosinophils were significantly correlated with the expression of LGALS1. The infiltration level of monocytes was significantly correlated with the expression of LGALS3. The infiltration level of neutrophils was significantly correlated with the expression of LGALS8. The infiltration levels of monocytes, resting dendritic cells, follicular helper T cells, and M0 macrophages were significantly correlated with the expression of LGALS9. **d** The correlations between the expressions of LGALS1, LGALS3, LGALS8, LGALS9 and immune checkpoint genes. Most ICP genes such as IDO1, NRP1, CD44, TNFSF4, and TNFRSF18 are significantly positively correlated with LGALS1 (all $P < 0.001$), while only CD200, ADORA2A, and VTCN1 are significantly negatively correlated with LGALS1 ($P < 0.001$). ICP genes such as IDO1, NRP1, CD44, and TNFRSF18 are significantly positively correlated with LGALS3 (all $P < 0.001$), while BTNL2, LAG3, and ADORA2A are significantly negatively correlated with LGALS3 ($P < 0.001$). ICP genes such as NRP1, CD44, and CTLA4 are significantly positively correlated with LGALS8 (all $P < 0.001$), while none are significantly negatively correlated with LGALS8 ($P < 0.001$). Most ICP genes such as IDO1, NRP1, and CD44 are significantly positively correlated with LGALS9 (all $P < 0.001$), while CD200, ADORA2A, and VTCN1 are significantly negatively correlated with LGALS9 ($P < 0.001$)

This will enhance our in-depth understanding of the Galectin family in glioblastoma and lay the foundation for developing more efficient immune and targeted therapeutic approaches targeting the Galectin family. Currently, explorations have been made to combine traditional treatment regimens with targeted modulation of Galectin family expression for combined therapy. We anticipate more studies on clinical translational diagnostic and therapeutic schemes based on the Galectin family in the future to further improve the prognosis of glioblastoma patients.

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Data availability All the ideas and illustrations for the figures in this review were conceived and created independently by the authors. The datasets analyzed in this review are available in the TCGA、CTPAC、HPA、GEPIA.

Declarations

Competing interests The authors declare no competing interests.

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