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The Role of ICAM-1 on Immune Cells in Glioblastoma: A Literature Review

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Abstract

Introduction: Glioblastoma (GBM) is an extremely aggressive brain tumor that poses significant challenges to clinical oncology. Previous research has discovered that intercellular adhesion molecule-1 (ICAM-1) is expressed in immune cells and is one of the most common molecules in the tumor microenvironment. However, the entire scope of ICAM-1 functions on immune cells in glioblastoma is still under investigation. This literature review aims to synthesize existing knowledge about the role of ICAM-1 on immune cells in GBM progression.

Methods: This review summarizes research from 1980-2024 using PubMed, OVID Medline, Web of Science, and Google Scholar. The following keywords were used to identify the articles focusing on the role of ICAM-1 on immune cells in glioblastoma: "glioblastoma", "ICAM-1", "CD54", "macrophages", "lymphocytes", "dendritic cells", and "natural killer cells". Studies that primarily focus on ICAM-1 expression and function within the tumor microenvironment were selected.

Results: Immune cell expression of ICAM-1 in the GBM microenvironment may exhibit both pro- and anti-tumor effects. In tumor-associated macrophages, ICAM-1 upregulation regulates polarization and immunosuppression. In dendritic cells, decreased ICAM-1 expression may hinder anti-tumor responses by limiting T cell activation. The role of ICAM-1 in tumor-infiltrating lymphocytes remains unclear. In neutrophils, ICAM-1 upregulation may promote immune suppression by reducing T-cell activity. The decreased ICAM-1 levels on NK cells in GBM may lead to NK cell exhaustion.

Discussion: The radio-chemotherapy has differential effects on ICAM-1 functions and, to some extent, affects the interpretation of findings. In turn, the alteration of ICAM-1 expression also influences the effectiveness of GBM radio-chemotherapy and the composition of the tumor microenvironment. The corticosteroid administration and tumor types are also factors affecting immune cell activity and composition.

Conclusion: This review inspires innovative therapeutic strategies to improve treatment outcomes and patient prognosis for glioblastoma, as well as provides potential directions for future research on ICAM-1 for glioblastoma.

Keywords: glioblastoma, ICAM-1, immune cells, macrophages, microglia, tumor-infiltrating lymphocytes, dendritic cells, neutrophils, natural killer cells

Introduction

Glioblastoma (GBM) is a highly aggressive malignant brain tumor, accounting for approximately 16% of primary malignant brain tumors [1–3]. The median progression-free survival of patients is only 7 months, and the median overall survival is 14 months, with a five-year survival rate of less than 5% [3–5]. The current standard care for GBM is the surgical removal of tumor sites as safely and extensively as possible, followed by radiotherapy and chemotherapy [3]. Nevertheless, it fails to prevent the postoperative recurrence of GBM [6]. Therefore, it is essential to comprehensively understand the factors influencing treatment and their mechanisms to develop targeted therapeutic approaches for GBM.

There are various challenges in GBM treatment. Increasing research evidence suggests that the tumor microenvironment (TME) plays a significant role in immune evasion, and tumor progression [7]. TME refers to the dynamic ecosystem surrounding the tumor that constantly interacts with tumor cells, including immune cells, non-immune cells, extracellular matrix, signaling molecules, etc. [8]. The GBM TME is highly immunosuppressive, with immune cells being a crucial contributor to immune suppression. The immune cells of TME are composed of tumor-associated microglia/macrophages (TAMs), tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells, neutrophils, and dendritic cells (DCs) [8]. TAMs constitute the majority of immune cell components in GBM TME, accounting for approximately 30% [9]. TILs are less abundant in GBM, and the proportion of anti-tumor CD8+ T cells is lower and exhibits an exhausted phenotype [10]. NK cells recognize and kill tumors by cytotoxicity, but their activity is

largely suppressed in GBM [8]. Neutrophils are associated with tumor progression and treatment resistance [11,12]. Finally, the role of DCs in GBM remains unclear, but they are thought to mediate T cell activation through antigen presentation, possibly in the brain or draining cervical lymph nodes [13].

One of the most common molecules participating in cell adhesion expressed in the TME is intercellular adhesion molecule-1 (ICAM-1, also called CD54) [14]. ICAM-1 is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily [14]. ICAM-1 is typically expressed at low concentrations in epithelial cells, endothelial cells, and immune cells at baseline, with upregulation by pro-inflammatory cytokines [14]. The binding of endothelial ICAM-1 and its ligands lymphocyte function-associated antigen-1 (LFA-1) and macrophage-1 antigen (Mac-1) on leukocytes triggers transendothelial migration, promoting the recruitment of immune cells [14]. In addition, ICAM-1 regulates the effector functions of immune cells by involving the formation of immunological synapses to assist T cell activation and acting as a signaling molecule to regulate macrophage phagocytosis and NK cell cytotoxicity [15–17]. In the GBM microenvironment, ICAM-1 has a dual role. For instance, GBM cells express ICAM-1 to recruit tumor-associated macrophages to produce cytokines that enrich the tumor microenvironment and accelerate tumor invasion [18]. ICAM-1 expressed by vascular endothelial cells in TME increases the infiltration of effector lymphocytes, yet angiogenesis factors downregulate its expression in GBM [19]. However, as it stands today, there is very limited research that explores how ICAM-1 in immune cells participates in the progression of GBM despite its expression and functionality in immune cells. Therefore, this review will focus on the potential role of ICAM-1 expressed in immune cells in glioblastoma and how it might influence tumor progression.

Methods

PubMed, OVID Medline, Web of Science, and Google Scholar were the four databases used to conduct this literature review. PubMed and OVID Medline cover peer-reviewed journals in biomedicine and life sciences. Web of Science and Google Scholar serve as interdisciplinary databases to ensure the inclusion of literature that was not retrieved by the first two. The search strategy for the literature review included combinations of keywords and synonyms with Boolean operators such as “glioblastoma,” “ICAM-1,” “CD54,” “macrophages,” “lymphocytes,” “dendritic cells,” and “natural killer cells.” The inclusion criteria were peer-reviewed publications written in English and dated between 1980 and 2024 to secure quality and coverage. 64 results were found. The exclusion criteria were publication in conference abstracts, research protocol, comment articles, etc., which did not provide experimental data. In addition, by carefully reading the abstracts and main text, publications that did not primarily focus on the expression of ICAM-1 on immune cells in the context of GBM were also excluded to ensure relevance. Additional relevant sources were identified by reviewing the bibliography. The literature review ultimately included six articles. Table 1. shows a summary of search results.

Table 1. Summary of the articles focusing on ICAM-1expression on immune cells in glioblastoma

Study	Immune cell type	Type of study	Role of ICAM-1
Bunonfiglioli et al. [20]	Microglial cells	In vivo and in vitro	● let-7 helps to activate anti-tumor lymphocytes by increasing antigen-presenting molecules, including ICAM-1. ● In GBM, let-7 was downregulated, as was the expression of ICAM-1 and the antigen-presenting ability of microglia.
Ogden et al. [21]	Monocytes and monocyte-derived dendritic cells	In vitro	● ICAM-1 participated in antigen presentation and assisted T cell activation. ● Circulating monocytes in GBM patients expressed decreased ICAM-1 levels and were less able to differentiate into mature DCs.
Cheng et al. [22]	Dendritic cells	In vitro and in vivo	● ICAM-1 participates in antigen presentation and assists T cell activation. ● Decreased ICAM-1 levels would lead to immune-tolerant DCs to inhibit T cell activation.
Wang et al. [23]	Dendritic cells	In vitro and in vivo	Increased expression of ICAM-1 on DC nanovaccines enhances the migration of DCs to draining lymph nodes.
Kuppner et al. [25]	Tumor-infiltrating lymphocytes	In vitro	No ICAM-1 expression was found on TILs.
Roussel et al. [26]	Tumor-infiltrating lymphocytes	In vitro	ICAM-1 expression might relate to Th2 differentiation.

Results

Tumor-Associated Macrophages/Microglia

TAMs comprise monocyte-derived macrophages and central nervous system-resident microglia originating from the yolk sac [9]. The literature search reveals limited studies on TAM ICAM-1 in the context of GBM, among which there is only one study related to microglia expressing ICAM-1. In this study, Bunofilioli et al. cultured microglial cells from wildtype and Toll-like receptor 7 knockout mice with lethal-7 (let-7) microRNAs (miRNAs), which was abundant in normal brains but downregulated in GBM [20]. Subsequently, they used fluorescence-activated cell sorting to analyze the expression of major histocompatibility complex (MHC) I, MHCII, and ICAM-1 [20]. The expression of ICAM-1 was upregulated by let-7 miRNAs with reduced tumor size [20]. ICAM-1 was considered to aid in antigen presentation to lymphocytes in the facial nerve transection model [26]. Therefore, ICAM-1 may activate T and NK cells to promote anti-tumor responses.

For macrophages in GBM TME, no literature was found on the role of macrophage ICAM-1 expression in GBM. However, in other cancer and disease models, the expression of ICAM-1 has been shown to regulate the polarization of macrophages. There are two macrophage polarization states, including classical M1 phenotype and alternative M2 phenotype [9]. The former promotes host defense and tumor rejection, whereas the latter displays an anti-inflammatory phenotype favoring immune suppression and tumor progression [9]. Gu et al. discovered that siRNA transfection downregulated the expression of ICAM-1 in mouse macrophage line RAW264.7, which indicated a shift towards M1 polarization [15]. The pathways related to such an alteration included the regulation of miR-124 by ICAM-1 and the direct regulation of MCP-1 by miR-124 [15]. They also found that miR-124 was most abundant in the brain tissues of ICAM-1 wildtype mice [15]. Some evidence suggests that the downregulation of miR-124 in GBM promotes tumor invasion, whereas miR-124 upregulation inhibits tumor cell proliferation [27,28]. In this case, the expression of ICAM-1 on macrophages is involved in regulating miR-124, which affects macrophage polarization and GBM invasion. On the contrary, in the study by Yang et al., the absence of ICAM-1 in mice with colorectal cancer led to increased efferocytosis in macrophages, which induced M2 polarization and increased macrophage infiltration, as well as the secretion of cytokines such as interleukin 13 (IL-13), IL-10, and transforming growth factor-beta (TGF-β), promoting metastasis [29]. Therefore, ICAM-1 appears to regulate macrophage polarization through distinct mechanisms.

Dendritic Cells

DCs are antigen-presenting cells crucial for activating T cells and anti-tumor responses within the GBM microenvironment. DCs in TME capture exposed tumor antigens, migrate to draining lymph nodes, and present processed antigenic peptides via the MHCI and II molecules [30]. With the assistance of co-stimulatory and accessory molecules, naive T cells recognizing the peptide-MHC complexes are activated and differentiated into cytotoxic T lymphocytes (CTLs) and helper T (Th) cells, which elicits anti-tumor responses and trigger tumor cell lysis [30].

In other disease models, ICAM-1 promotes T cell priming, migration, survival, and effector memory by binding to LFA-1 on T cells and is critical for the formation of the immunological synapse [31-33]. The search results uncovered three articles related to DC ICAM-1 expression and its contribution to the effector function of DCs as well as the efficacy of DC vaccines in GBM background. Ogden et al. measured the proportion of circulating immune cells in GBM, brain metastasis, and healthy controls, then characterized the expression of surface molecules on peripheral monocytes and monocyte-derived dendritic cells using antibodies [21]. The researchers found a significantly increased percentage of circulating monocytes in GBM patients, characterized by decreased expression of antigen-presenting molecules, including ICAM-1, and DC differentiation molecules [21]. These separated peripheral monocytes displayed a lower ability to differentiate into mature DCs [21]. There was a reduction of antigen-presenting molecules, including ICAM-1, on immature DCs, which might lead to decreased functional DCs and dampened T cell activation and proliferation [21]. Therefore, in GBM, the reduction in ICAM-1 expression may be associated with weakened DC effector functions. In the study of Cheng et al., they co-cultured DCs isolated from the bone marrow of transgenic EGFP-BALB/c nude mice with RFP-expressing human glioma stem cell (GSC) line in vitro using dual fluorescence tracking [22]. After co-culturing with GSCs, DCs exhibited a malignant phenotype that promoted tumor growth, indicating the reprogramming of DCs by GSCs [22]. These DCs expressed lower levels of ICAM-1 and other co-stimulatory molecules [22], which decreased the functions of DCs and led to an immune-tolerant phenotype [22]. Immune-tolerant DCs may lead to the induction of anergy T cells and differentiation of Tregs, promoting immunosuppression [34]. The immune-tolerant DCs may indicate that in GBM, ICAM-1 on DCs would facilitate antigen presentation and T cell activation, while reduced ICAM-1 on DCs is likely to be a mechanism of GSC reprogramming to enhance immunosuppressive TME and inhibit T cell-mediated anti-tumor responses.

Additionally, in a recent study, Wang et al. developed a novel DC-based nanovaccine [23]. They used Cu2-xSe nanoparticles to trigger apoptosis of tumor cells and the exposure of tumor-associated antigens (TAAs) [23]. The TAA-loaded nanoparticles induced the expression of ICAM-1 and other surface molecules on mature DCs [23]. The prepared nanovaccine combined TAA-loaded nanoparticles with the mature DC membranes [23]. The Dil-traced nanovaccines improved homing ability and accumulated in

the lymph nodes of mice bearing the GL261 glioma cell line, which promoted tumor rejection and delayed the progression of GBM [23]. The above evidence shows that elevating ICAM-1 molecules on the DC surface promotes DC abilities in antigen presentation and homing to lymph nodes, which better activates anti-tumor T cells and effectively improves the efficacy of DC vaccines. Therefore, increasing DC ICAM-1 expression during the generation of DC vaccines is likely to be helpful for GBM treatment.

Tumor-Infiltrating Lymphocytes

TILs are an immune cell population less abundant in GBM than other immune cell types [35]. The activation and differentiation of CD4+ T and CD8+ T cells mediate anti-tumor responses and are associated with improved prognosis [19]. In other cancers, enhanced expression of ICAM-1 promoted the cytotoxicity of T cells and tumor lysis. In thyroid cancer, CD4+ lymphocytes after OK-432/fibrinogen treatment showed high expression of ICAM-1 and high cytotoxicity, while anti-ICAM-1 antibodies suppressed interferon gamma (IFN-γ) secretion and inhibited tumor cell lysis mediated by T cells [36]. Besides, in mice bearing with tumor cells from colorectal carcinoma or melanoma, ICAM-1 on CD8+ T cells facilitated CD8+ T cells activation, proliferation, and effector functions, which boosted systematic anti-tumor reactions during radiotherapy [37]. These pieces of evidence demonstrated that the expression of ICAM-1 on T lymphocytes could induce cytotoxicity and tumor lysis. However, whether ICAM-1 plays the same role in GBM remains unknown, and the search results showed inconsistent results. Kuppner et al. collected brain tissue samples from patients with GBM, healthy individuals, and patients with brain metastasis [24]. The monoclonal antibodies followed by immunoperoxidase staining were used to characterize the expression of surface molecules on TILs. The results did not find significant changes in ICAM-1 expression on TILs [24]. In another research by Roussel et al., TILs extracted from the tumor tissues of GBM patients without receiving chemo- or radiotherapy were analyzed by monoclonal antibodies and flow cytometry [25]. The results suggested elevated levels of ICAM-1 on TILs in GBM tumor tissue were associated with increased IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) production and may skew the differentiation of the TIL population to anti-tumor phenotype [25].

Neutrophils

As a part of innate immunity, neutrophils capture and kill invading pathogens via phagocytosis, degranulation, and secretion of neutrophil extracellular traps consisting of DNA and serine proteases [11]. Although only a small proportion of neutrophils infiltrated into the tumor tissue of GBM, it indeed plays an important role [11]. However, the search results reveal that the role of neutrophils expressing ICAM-1 in the context of GBM is a blank area. Other disease models suggest that the expression of ICAM-1 on neutrophils may be related to suppressed T cell activity. In human gastric cancer, the upregulation of ICAM-1 in tumor-associated neutrophils was associated with activation of GM-CSF-mediated Janus kinase (JAK)-signal transducer and activator of transcription protein 3 (STAT3) signaling pathway transduction [38]. In GBM, GM-CSF synthesized in the brain decreased lymphocyte proportion but increased neutrophil proportion [39]. Therefore, neutrophil ICAM-1 may inhibit the infiltration of T lymphocytes via GM-CSF mediated JAK-STAT3 pathway activation. Additionally, in a mouse endotoxemia model, upregulation of ICAM-1 on neutrophils enhanced phagocytosis through increased interaction with ICAM-1-fibrinogen and activation of the tyrosine-protein kinase signaling pathway [40], which might help clear apoptotic tumor cells and promote tumor development [41]. Furthermore, the upregulation of ICAM-1 increases reactive oxygen species (ROS) production [40]. ROS is believed to decrease T cell NF-kB activation, downregulate surface T cell receptor/CD3ζ, and inhibit T cell proliferation, leading to T cell exhaustion in GBM, thus contributing to an immune-suppressive tumor environment [42]. Therefore, in GBM, ICAM-1 expression on neutrophils may reduce tumor antigen exposure and facilitate tumor progression by promoting the clearance of apoptotic tumors; it may also increase ROS production, thereby reducing the activity of anti-tumor T cells and favoring immunosuppressive microenvironment.

Natural Killer cells

NK cells are important cytotoxic lymphocytes in the innate immune system. They kill virus-infected cells and tumor cells by releasing perforin and inducing cell apoptosis through death receptor signaling. They also promote inflammation and anti-tumor responses by releasing the pro-inflammatory cytokine IFN-γ [8]. The interaction between ICAM-1 and its receptors LFA-1 and Mac-1 is considered as co-stimulatory signals driving NK cell cytotoxicity to tumor cells in other disease models [17]; thus, NK cell ICAM-1 may mediate the cytotoxicity of NK cells in GBM. Research done by Schierloh et al. demonstrated that under inflammatory conditions, IL-2 stimulation led to upregulation of ICAM-1 expression on NK cell surfaces, and NK cells with high ICAM-1 expression were the primary producers of IFN-γ [43]. Additionally, ICAM-1 expression on NK cells serves as a co-stimulatory molecule mediating T cell activation and expression of Th1 gene profiles [43]. In the immunosuppressive microenvironment of GBM, NK cells produce lower levels of IFN-γ and display exhausted functions, which may be related to the downregulation of NK cell ICAM-1 [44].

Discussion

The role of ICAM-1 on immune cells in GBM remains unexplained. The present review suggests that ICAM-1 on immune cells may be a double-edged sword. The

dysregulation of ICAM-1 expression would be a potential mechanism underlying the immunosuppression and allowance of progression in GBM. On the one hand, the dysregulation of ICAM-1 on TAMs is associated with TAM polarization and efferocytosis. M2 polarized TAMs are the primary immunosuppressive immune cells in GBM; they secrete anti-inflammatory cytokines, such as IL-10 and TGF-β from M2 TAMs, exhaust CTL functions, and favor differentiation of Tregs to enhance the immunosuppressive nature of the GBM microenvironment, thus allowing for immune evasion [45]. Other M2 TAM secretory molecules can maintain GSC proliferation, support angiogenesis, increase invasiveness, and facilitate the epithelial-mesenchymal transition of tumor cells, all contributing to GBM progression [45]. Moreover, the ICAM-1 expression on neutrophils might promote immune evasion by reducing antigen-presenting ability and inducing the production of ROS to inhibit T cell-mediated antitumor responses. On the other hand, microglial ICAM-1 may activate T lymphocytes and NK cells to promote antitumor responses, and GBM perhaps hampers antigen presentation by decreasing ICAM-1 on microglial cells. The reduction of ICAM-1 on DC by GBM reprogramming might decrease the antigen presentation, affect migration to lymph nodes, and induce immune-tolerant DCs to inhibit CTL activation and skew to Treg differentiation, thereby promoting immune evasion of GBM and allowing tumor growth. Furthermore, the downregulation of ICAM-1 on NK cells may be associated with depleted cytotoxicity, which is likely also a mechanism of immune evasion in GBM.

In the two studies on the ICAM-1 expression on TILs, there was inconsistency in the results. One showed no presence of ICAM-1 on TILs [24], while the other demonstrated a subset of TILs expressing ICAM-1 [25]. A possible explanation is the methodology difference. Kuppner et al. used immunohistochemistry to visualize the expression of surface molecules [24], but Roussel et al. applied flow cytometry for immunophenotyping [25]. Compared to the former approach, flow cytometry has higher sensitivity in detecting low-expressing surface molecules, thus it would be advantageous to detect the presence of ICAM-1 on immune cell membranes [46]. Additionally, compared to other cancer models, the results from Roussel et al. suggest that TILs in GBM exhibit a phenotype with lower antitumor efficiency [25]. One possible explanation is the difference in whether radio- and chemotherapy are administered. Furthermore, Lecoultre et al. demonstrated that radiotherapy-temozolomide treatment increased macrophage phagocytic activity and efferocytosis in GBM, which might promote pro-tumor reactions [47]. The effects of radio- and chemotherapy on immune cells seem consistent with ICAM-1, and the study by Kesanakurti et al. highlights the effects of ICAM-1 expression induction by radiotherapy [48]. These pieces of evidence suggest that ICAM-1 on immune cells might influence the effectiveness of radio-chemotherapy, and selectively targeting the expression of ICAM-1 could synergize the standard treatment of GBM.

In Ogden et al.'s study on monocyte-derived dendritic cells, corticosteroids influenced immune cells [22]. During perioperation and treatment, corticosteroids are a kind of drug commonly used to relieve cerebral edema and unpleasant symptoms induced by radio-chemotherapy, such as nausea and headache [49]. However, much literature suggests that chronic administration of corticosteroids is associated with shortened survival and poorer prognosis in patients with GBM [49-51]. This reveals that we should carefully monitor corticosteroid administration during GBM treatment. In addition, corticosteroids induce downregulation of endothelial ICAM-1 while enhancing the endothelial barrier, and this may be the mechanism of decreasing lymphocyte infiltration and dampening inflammation [52]. However, in GBM, the decreased lymphocyte infiltration, especially CD8+ T lymphocytes, is not helpful for tumor rejection. ICAM-1 on immune cells is essential for shifting between immunosuppression and immune activation, involving antigen-presenting, T cell activation, TAM polarization, etc. Although the existing evidence is not sufficient to prove that downregulation of ICAM-1 by corticosteroids aggravates immunosuppression in GBM, the potential adverse effects of steroids suggest that the dose of steroids applied should be carefully considered and the immune status should be closely monitored in the treatment of GBM patients. At the same time, specifically targeting immune cell ICAM-1 to enhance the anti-tumor function and inhibit pro-tumor response may be more effective in assisting GBM therapy and improving prognosis, but this needs to be further tested through experiments.

In addition, the impact of ICAM-1 in the regulation of macrophage polarization may vary across different microenvironments, which could activate different pathways and have varying effects on the functions of immune cells, leading to differences in outcomes in various disease models [15,24]. For example, lipopolysaccharides and pro-inflammatory cytokines such as IL-1β, tumor necrosis factor-alpha, and IFN-γ induce ICAM-1 expression, potentially promoting M1 polarization in endotoxemia [9,14]. Conversely, secretion of growth factors like vascular endothelial growth factor upregulates ICAM-1 expression but may contribute to M2 polarization [53,54]. GBM models with ICAM-1 deficiency, specifically in TAMs, neutrophils, and NK cells, are still lacking. The existing evidence is based on other cancer models involving colorectal cancer (macrophages), thyroid cancer (CD4+ T lymphocytes), melanoma (CD8+ T lymphocytes), and gastric cancer (neutrophils). Although the types of infiltrating immune cells in other cancers are similar, their proportions are entirely different. For example, Tregs and TAMs are the most abundant infiltrating immune cells in digestive tract tumors [55]. Melanoma and its brain metastasis exhibit abundant infiltration of T cells and neutrophils and relatively less

macrophage infiltration, making melanoma have a better response to immunotherapy than other cancers. In contrast, in GBM, macrophages and microglia account for the highest proportion of immune cells in GBM TME, and they are responsible for poor immunotherapy efficacy and strong drug resistance to immune checkpoint inhibitors and CAR-T therapy [56]. The differences also suggest that inhibiting M2-polarized TAM functions, increasing CTL and NK cell infiltration, and reducing neutrophil infiltration may be a more appropriate strategy conducive to GBM immunotherapy. Additionally, compared with peripheral tumors, the blood-brain barrier (BBB) is a major obstacle in the treatment and drug delivery of brain diseases. Although the BBB is partially destroyed in GBM, it maintains integrity in most areas [57]. Therefore, the BBB is a factor that needs to be considered when designing drugs for GBM therapy.

Furthermore, the present literature review has some limitations. Firstly, in the six retrieved articles, the types of immune cells investigated skew to dendritic cells and lymphocytes, while there is a lack of exploration of other immune cell types. In addition, some studies need more functional experiments and more direct and robust evidence to demonstrate the significant role of immune cell ICAM-1 in GBM, which, to some extent, limits the interpretation of the results. Furthermore, the administration of radio-chemotherapy and heterogeneity of the microenvironment may also partially restrict the generalization of findings from other disease models to GBM. Therefore, it is necessary to experimentally validate the role of immune cell ICAM-1 in the context of GBM.

Nevertheless, the current literature review integrates the existing relevant studies to discuss the effects of ICAM-1 expressed on various immune cells in the context of GBM, contributing to a deeper and more comprehensive understanding of the GBM immune microenvironment. ICAM-1 may be a biomarker of GBM immune status. The differences between GBM and other cancers suggest that developing more targeted treatment strategies for GBM may help amplify treatment effects and extend patient survival. The dual role of ICAM-1 on immune cells also reveals that assistance of immunotherapy specifically targeting immune cell ICAM-1 may be more effective when applying standard management to treat GBM. For instance, enhancing ICAM-1 on lymphocytes, DCs, or NK cells to strengthen their effector functions and to boost the impacts of immune cell therapy in GBM; it is also possible to regulate the expression of ICAM-1 on TAMs to alleviate the immunosuppression in GBM TME. Furthermore, the potential negative effects of corticosteroids in treating GBM suggest the need to monitor immune status and develop safer drugs to prevent excessive immune suppression.

Conclusions

This literature review elucidates the complex role of ICAM-1 on immune cells in GBM, which could facilitate tumor remission by enhancing antigen presentation, T cell activation, and NK cell cytotoxicity and contributes to immune evasion by regulating TAM M2 polarization and neutrophil functions. For future directions, we should further validate the dual role of ICAM-1 by using CRISPR-Cas-9 or Cre-Lox technology to generate ICAM-1 knockout in specific immune cell types and examine the effects on GBM progression in vivo, which could help further define the appropriate therapeutic strategies. Moreover, it is necessary to explore the impact of selective targeting of immune cell ICAM-1 on GBM development and whether it would enhance radio-chemotherapy. In addition, when studying models of brain tumors including GBM, considering the administration of corticosteroids and the effects of targeting ICAM-1 may more reasonably mimic the context of TME in patients with GBM. Moreover, the upregulation of ICAM-1 helps to enhance the tumor rejection by DC vaccine, and whether increasing ICAM-1 expression would assist immune cell therapies, such as CART-T therapy and NK vaccine in GBM, is also worth verifying in animal models. The development of additional options for GBM treatment potentially helps improve patient management and prognosis, provide alternatives for patients resistant to current therapy, and develop personalized treatment.

List of Abbreviations Used

GBM: glioblastoma
TME: tumor microenvironment
TAM: tumor-associated microglia/macrophages
TIL: tumor-infiltrating lymphocytes
NK: natural killer
DC: dendritic cell
ICAM-1: intercellular adhesion molecule-1
LFA-1: lymphocyte function-associated antigen-1
Mac-1: macrophage-1 antigen
let-7: lethal-7
miRNA: microRNA
MHC: major histocompatibility complex
miR-124: microRNA-124
IL: interleukin
TGF-β: transforming growth factor-beta
CTL: cytotoxic T lymphocyte
Th: helper T
GSC: glioma stem cell
TAA: tumor-associated antigen
IFN-γ: interferon-gamma
GM-CSF: granulocyte-macrophage colony-stimulating factor
JAK: Janus kinase
STAT3: signal transducer and activator of transcription protein 3
ROS: reactive oxygen species

Conflicts of Interest

The author declares that there is no conflicts of interest.

Ethics Approval and/or Participant Consent
Since this article is a literature review, it does not require ethics approval and participant consent.

Authors' Contributions
XC: made substantial contributions to the design of study, drafted the manuscript, and gave a final approval of the version to be published.

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