Review

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Inflammatory Mediators and GBM Malignancy: Current Scenario and Future Prospective

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Glioblastoma multiforme is one of the most widespread and dangerous forms of brain tumor with high inflammation. The tumor microenvironment comprises diverse tumor cells, different types of immune cells, and the extracellular matrix. Inflammatory mediators like chemokines, cytokines, and growth factors possibly serve as a capable therapeutic target to quash their tumor-promoting properties in glioblastoma multiforme (GBM). Cytokines are a heterogeneous group of soluble functional proteins which are also associated with the induction and progression of tumors. These are supposed to have both pro-inflammatory (such as tumor necrosis factor-α (TNF-α), interleukin-17A (IL-17A), interferon-γ (IFN-γ), IL-4, IL-2, IL-6, IL-12, IL-13) and anti-inflammatory (such as transforming growth factor-β (TGF-β), IL-10, and granulocyte-macrophage colony-stimulating factor (GM-CSF)) actions and are the crucial communications channels in the tumor microenvironment. In the present minireview we discuss the tumor microenvironment and inflammatory mediators and focus on the involvement of cytokines in establishing communication with the tumor microenvironment. The presented data highlight the possible roles of cytokines in communication between glioblastoma cells and tumor microenvironment. Cytokines formed by immune cells protect the host organs while cytokines secreted by tumor cells are used for their advantage. Though the clinical trials with a number of immunotherapeutic agents are going on around the globe, there is still a requirement for thorough investigation of the regulatory mechanism managing GBM growth, recurrence, and tumor response to the therapy.

Keywords: glioblastoma; microenvironment; inflammatory mediators; cytokines

Background

Glioblastoma multiforme (GBM), as the name suggests (multiforme: having or occurring in many forms), is a tumor characterized by widespread heterogeneity. Structurally, GBM comprises malignant cells and non-malignant cells including endothelial cells, inflammatory cells, cells with stem-like properties as well as cells with neural, glial, or myeloid markers. It is classified as a Grade IV brain tumor by the World Health Organization (WHO) and is still the most common and lethal primary malignant brain tumor in the world. In the United States, it accounts for 14.5 percent of all brain and other central nervous system (CNS) tumors and 48.6% of malignant tumors [1]. As a result, GBM has one of the lowest 5-year overall survival rates (less than 10%) and a high recurrence rate (75–90%) [2]. Similarly, existing GBM treatment, which includes surgical resection, radiation, and temozolomide (TMZ) chemotherapy, has yet to provide satisfactory outcomes, owing to drug resistance [3]. Furthermore, re-emerged tumor cells may have a weakness in DNA mismatch repair following first-line treatment, and roughly 10% of post-TMZ glioblastomas have their own DNA alterations.

A relationship between inflammation and cancer was suggested for the first time by Virchow in 1863, who showed "lymphoreticular infiltrates" in neoplastic tissues, which was further supported by recent experiments [4]. Some workers have defined inflammation as "the seventh hallmark of cancer" [5]. Tumor initiation and progression is a multifaceted course linking inflammatory mediators, genomic mutations, and microenvironmental factors. Different cytokines such as interleukins (interleukin-2 (IL-2), IL-4, IL-6, IL-8, IL-10, IL-12 and IL-13), tumor necrosis factor-α (TNF-α), granulocyte–macrophage colony-stimulating factor (GM-CSF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), interferons, and hypoxia-inducible factors (HIF), play an important role in controlling of the

GBM microenvironment [6]. TNF-α, IL-1α, IL-1β, IL-4, IL-6, IL-8, chemokines (such as CXC chemokine ligand 12 (CXCL-12)), cyclooxygenase-2 prostaglandin (PG) E2, and platelet-derived growth factor (PDGF) are the important inflammatory mediators which may activate the inflammatory cycles in glioblastoma. It has also been reported that concentrations of cytokines are coupled with the infiltration of immune cells like tumor associated macrophage (TAM) [7], which demonstrates that there is an interaction between cytokines and immune cells and between the cerebrospinal fluid (CSF) compartment and tumors. An extensive assortment of cytokines exhibits customized appearances in cancers together with GBM [8,9].

Understanding the interactions in between tumor cells and the tumor microenvironment has become an important aspect in the treatment of glioma [10,11]. Hence, in the present review, we have discussed the role of inflammatory, pro-inflammatory, and anti-inflammatory cytokines and chemokines along with immune cells in the GBM microenvironment and thereby use of these elements in the therapy of glioblastoma.

Inflammatory Microenvironment

Inflammation is an intricate process that works as a biological reaction to injurious stimuli which may generate frequent signs like swelling, pain, and fever [12]. It is an effector of tumor development dependent on its microenvironment in terms of GBM advancement. Malignant cells and non-malignant cells with glial, neural, or myeloid markers; inflammatory cells, endothelial cells; and stem-like cells, as well as soluble inflammatory mediators, make up the tumor microenvironment. The tumor microenvironment is essential for the occurrence, growth, and progression of tumors [13]. Inflammatory markers within the tumor microenvironment are accountable for marked angiogenesis, cell proliferation, tumor invasion and inhibition of immune functions. The response of the body against cancer has several analogies with repair and inflammation; the residing inflammatory cells as well as cytokines released in tumors have a higher probability to enhance the tumor growth, progression, and suppression of immunity. A number of reports have revealed that most tumor tissues are coupled with inflammatory signs. Still, an apparent correlation between cancer and inflammation is lacking and needs to be demonstrated. A number of interconnected elements are involved in this complex mechanism, including tumor cells of various phenotypes, microglia and macrophages, as well as other immune cells, and the microenvironment, which contains a variety of cytokines with both chemotactic and regulatory (autocrine and paracrine) actions. At the same time, the tumor can employ and alter the phenotype of microglia and macrophages, resulting in tumor associated monocytes (TAMs) and tumor associated neutrophils (TANs), which modulate the activity of signaling pathways and ultimately contribute to the tumor's stage of development: tumor cell migration and invasion, immunosuppression, angiogenesis, and so on. In this article, we will look at the most important inflammatory cytokines of glioblastoma involved in the regulation of glioblastoma malignancy.

Bidirectional communication between neoplastic cells and the microenvironment leads to a heterogeneity that boosts tumor immune avoidances allowing cancer cells to permeate and restrain anti-tumor immunity. Soluble factors secreted by glioma cells magnetize a wide range of immune cells in the tumor microenvironment, including glioma associated macrophages, myeloid-derived suppressor cells, dendritic cells, CD4+ and CD8+ T-lymphocytes, T-regulatory lymphocytes, and natural killer cells, which amend and contribute to GBM invasion, proliferation, and resistance against treatment. These important immune cells, which usually control tissue homeostasis, immune surveillance, and wound healing, are repeatedly inhibited, failing to trigger effector T cells and anti-tumor immune responses. Thus, there exists interaction between glioblastoma microenviroment and soluble factors (chemokines and cytokines) with versatile functions which show immunomodulatory effects and hence influence the tumor site. Immunological and GBM cell populations interact in complicated ways with clear contributions from important cytokines and chemokines and maintain these intercellular connections (Fig. 1). Adobe Photoshop-7.0 (Adobe, SAN Jose, CA, USA) and Microsoft Office-2016 (Microsoft, Redmond, WAS, USA) were the softwares used in the preparation of Fig. 1. Apart from this, tumor microenvironment modifies the differentiation and metabolism of myeloid cells to encourage local production of chemokines and cytokines, which further interacts with extracellular matrix components and reprograms immune cells to an inflammatory phenotype and operates host immune reaction in support of cancer growth and metastasis [14–16].

Chemokines and cytokines formed by different types of immune cells protect the host organs and are enhanced by cytokines released by tumor cells.

Nuclear factor kappa B (NF-κB) which is a well established master regulator of inflammatory mechanisms, is recognized as an important participant in various steps of cancer initiation and progression, and hence serves as a significant bond connecting inflammation and cancer [17]. In diverse tumor types, NF-κB signaling might be tumor promoting or anti-tumorigenic in cancerous cells and their inflammatory microenvironment [18]. The effect of IL-33 on NF-κB signaling has been studied using both binding to the promoter of the p65 subunit and physical exposure and sequestration of NF-κB [19].

Inflammatory Mediators

Cancerous and non-cancerous cells present in GBM contribute to tumor development, progression, and resis-

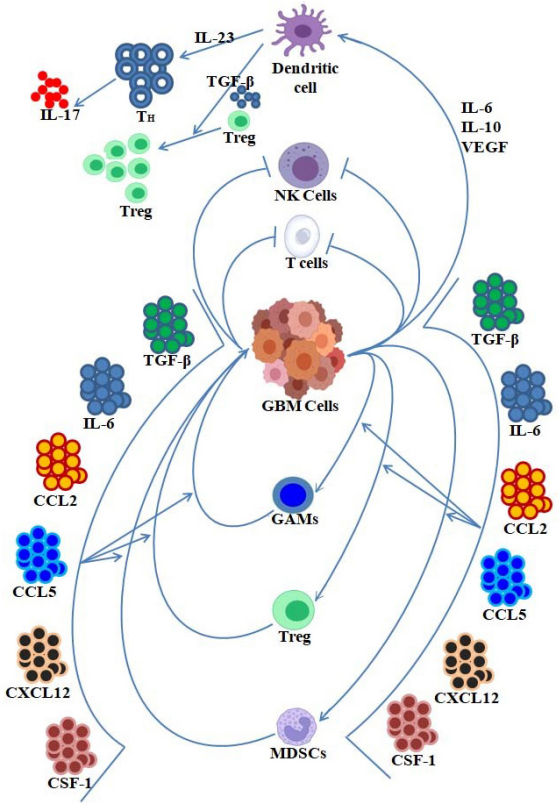

Fig. 1. Schematic presentation showing complicated interactions between Glioblastoma and tumor microenvironment. Different immune cell types such as Glioma-associated microglia/macrophages (GAMs), T-lymphocytes (T cells), myeloid-derived suppressor cells (MDSCs), dendritic cells, T-regulatory lymphocytes (Treg), natural killer cells (NK cells) are distributed throughout microenvironment. This figure also shows complex crosstalk between GBM cell population and different types of immune cells regulated by important cytokines and chemokines maintaining intercellular connections. IL, interleukin; TGF-β, transforming growth factor-β; GBM, glioblastoma multiforme; VEGF, vascular endothelial growth factor; CCL2, C-C Motif Chemokine Ligand 2; CSF, cerebrospinal fluid; CXCL-12, CXC chemokine ligand 12.

tance to the therapeutic regimen. Various soluble inflammatory mediators such as chemokines, cytokines, and chemotactic factors are secreted by GBM cells that help in generating an inflammatory microenvironment which further contributes to the different stages of cancer development, maintenance, and progression. The inflammatory mediators have chemotactic properties and recruit different immune cells to the tumor microenvironment. These mediators encourage tumor cell invasion, proliferation, and metastasis via paracrine signaling [20,21] and inflammatory stromal and senescent cells intensify tumor growth and inflammation. GBM-derived factors like TNF-α, IL-1α, IL-1β, IL-4, IL-6, and IL-8, chemokines (such as CXC chemokine ligand 12 (CXCL-12)), cyclooxygenase-2 (COX-2), prostaglandin-E2, and PDGF are the essential inflammatory mediators which activate the inflammatory cycle in GBM and also encourage carcinogenesis through evading growth suppression, maintaining cancer cell stemness, inducing angiogenesis and metastasis, and opposing apoptosis [22,23].

Cytokines are small proteins secreted by immune cells such as macrophages, B cells, T-lymphocytes (T cells), mast cells, neutrophils, basophils and eosinophils [24]. There are certain inflammatory cytokines present in the dorsal root ganglion, spinal cord, injured skin or nerve and these are known to be linked with pain behaviors and with the production of irregular unprompted action from wounded nerve fibers [24]. Cytokines have diverse pathophysiological functions in GBM and might serve as a capable remedial target by synthetic or natural agents to quash their tumor supporting effects in GBM (Table 1, Ref. [25–45]; Table 2, Ref. [46–61]). It has been reported that blocking the activity of IL-6R by tocilizumab in a glioma cell line (U87MG) prevented cell proliferation by acting through the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) pathways [25]. Inhibiting the proliferation and promoting anti-invasive effects in glioma cell lines is made possible by blocking NF-κB and STAT3. The enhanced NF-κB/IL-6/STAT3 axis associated with the Mes subtype may be relevant to targeted therapeutics. When compared to single treatments, combined NF-κB and STAT3 inhibitors overcame the off-target effect of STAT3 inhibitor alone, maintained low IL-6 and IL-8 levels, and enhanced anti-invasive and cytotoxic effects [62]. Ursolic acid, a bioactive triterpenoid isolated from *Rosmarinus officinalis*, has been shown to downregulate matrix metalloproteinase-9 (MMP-9) and repress IL-1/TNF in rat GBM cells, thereby preventing cancer cell proliferation [63]. The anti-malarial drug chloroquine inhibited glioma cell proliferation by inhibiting TGF activity and the expression of plasminogen activator inhibitor-1 and vascular endothelial growth factor A [64]. Earlier studies have reported a considerable reduction in CXC chemokine receptor 4 (CXCR4) expression by the antagonist PRX177561, which delayed GBM growth [65]. Cyclooxygenases are effective mediators of inflammation and information is available about two COX-isoenzymes, COX-1 and COX-2. COX-2 is an isoenzyme which induces cytokine production in inflammatory cells. The suppression of EP2 receptor was noted to decrease the COX-2/PGE-2-mediated cAMP signaling pathway that resulted in a noticeable reduction in GBM cell proliferation and invasion, encouraging apoptosis, and cell cycle arrest at G_0-G_1 phase [66]. Earlier findings have established the inhibition of chemotherapy-induced cytokines and lipid mediator release from macrophages and consequential tumor growth by COX-2/soluble epoxide hydrolase [67].

Table 1. Expression of inflammatory cytokines and their pathopysiological role.

S.N.	Inflammatory cytokines	Expression of cytokines		Pathophysiology of cytokines	
		Clinical Samples/Cell lines	References	Function	References
1.	IL-1β	GBM clinical samples	[26,27]	↑ ERK activity ↑ proliferation ↑ p38 MAPK/JNK activity ↑ VEGF ↑ JNK and sphingosine kinase-1 activity ↑ proliferation and invasiveness	[28,29]
		GBM cell lines	[30]	↑ p38 MAPK activity ↑ IL-6 ↑ stemness factor genes ↑ invasiveness ↑ drug resistance	[27,31–33]
2.	IL-6	GBM clinical samples	[25,34,35]	IL-6-deficient mice failed to develop GBM ↑ JAK2–STAT3 activation ↑ migration and invasiveness	[36–39]
		GBM cell lines	[30]	↑ JAK2/STAT3 activation ↑ proliferation ↓ apoptosis	[40]
		Plasma of GBM patients	[41]	↑ JAK2–STAT3 and Jagged–Notch activation ↑ stemness ↑ tumor heterogeneity and formation ↑ tumor heterogeneity	[35,42]
3.	IL-8	GBM clinical samples	[43,44]	↑ proliferation and invasiveness ↑ angiogenesis and tumor growth ↑ tumor growth in an autocrine manner	[43–45]

IL, interleukin; GBM, glioblastoma multiforme; ERK, extracellular-signal regulated kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; VEGF, vascular endothelial growth factor; JAK2/STAT3, Janus kinase 2/signal transducer and activator of transcription 3. ↑-increase; ↓-decrease.

Interleukin-1β and GBM

As reported earlier, the inflammasome is a multiprotein complex that triggers the production of IL-1β and IL-18, caspase-1 activation, and pyroptotic cell death to mediate the innate immune response [68]. Pro-caspase-1 is autoprotolyzed into its active form, Caspase 1 (CASP1), by the already-functioning inflammasome [69]. This facilitates the conversion of pro-IL-1β and pro-IL-18 precursors into IL-1β and IL-18, which function to attract inflammatory cells and produce interferon, respectively [70]. In GBM, IL-1β was found to be chronically hyperactive and was highly linked to tumor promotion [71]. Inflammasomes aid in the cleavage and release of IL-1β from myeloid and non-myeloid cells in GBM. The pro-tumor gene *annexin A2*, which is highly expressed in GBM and is in charge of the tumor's invasion, growth, and angiogenesis, also stimulates the manufacture and release of IL-1β. The STAT3 transcription factor is persistently activated by this ongoing generation of IL-1β, which also improves the function of "secretomes" that are in charge of causing neurotoxicity and secreting substances that encourage angiogenesis [71].

The increased expression of IL-1β is directly correlated with IL-6 and IL-8 levels, whereas it is inversely correlated with the level of IL-4. On one hand, IL-1β controls the invasiveness and survival of GBM cells, and on the other hand, anti-IL-1β antibodies inhibit growth and invasion of GBM cells [31]. TGF- and IL-1 have previously been shown to stimulate the glioma stem cell phenotype and contribute to carcinogenesis in glioma cell lines (LN-229) [33]. Reports have also shown increased secretion of cytokines such as IL-6, IL-8 and IL-1β, by glioma cells [27], which are related to the expansion of glioblastoma multiforme. The regulation of levels of IL-1β in GBM cells is dependent on the NF-κB–HIF-1α axis [28].

Interleukin-6 and GBM

IL-6 which is a chief cancer-related inflammatory cytokine and regulates STAT3 activation is overexpressed in GBM patients. The circulatory levels of inflammatory cytokines show a parallel correlation with the capability of tumor cells to produce pro-inflammatory cytokines, and the role of IL-6 in angiogenesis. At the same time, the IL-6 expression is directly linked to IL-1, IL-8, and interferon-γ (IFN-γ) [72]. It has been shown that IL-6 may act as a potential anti-invasion target since it is involved in carcinogenesis by angiogenesis and tumor growth [73]. Augmentation of the IL-6 gene in GBM patients is correlated with their decreased survival [34]. In glioblastoma cell lines (U251, T98G and U87 MG), IL-6 supports vascular endothelial cell migration and assists tumor invasion and angiogenesis [37,74].

Interleukin-8 and GBM

In an experimental study, the circulatory level of IL-8 in GBM patients has been noted to be up-regulated when compared to a control group [72]. Reports also suggest that there is upregulation of IL-8 in gliomas, which promotes angiogenesis. Suppression of IL-8 can reduce proliferation and invasiveness in phosphatase and tensin homolog (PTEN) deficient glioblastoma cells [43]. Findings from murine models also demonstrated enhanced tumor survival

Table 2. Cytokines and their pathopysiological functions in Glioblastoma.

S.N.	Cytokines	Functions	References
1.	TNF-α	• Play significant roles in the growth of GBM • TNF is increased in GBM cells, which also play a significant role in the development of GBM • Increases angiogenesis and glioma cell invasiveness • Demonstrate an anti-tumor impact by causing leukocytes to move	[46,47]
2.	TGF-β	• Promote the invasion ability of GBM cells • Immunosuppressive • Reduces the expression of MHC class II on CD4+ T cells	[48]
3.	IFN-α	• Reduces MGMT expression and, both *in vitro* and *in vivo*, re-sensitizes resistant glioma cells to TMZ	[49]
4.	IFN-β	• Has effective anticancer properties in malignant glioma • In the treatment of gliomas, both GSCs and NSCs are affected	[50]
5.	IFN-γ	• Involved in immune escape of gliomas	[51]
6.	IL-2	• Has been shown to alter Treg responses in GBM	[52]
7.	IL-4	• Involved in the glioma's growth and development • Macrophages to aid in the survival of tumors by fostering an environment that is immunosuppressive	[53]
8.	IL-10	• Play a significant role in regulating the activity of cancer cells and infiltrating immune cells in GBM, mostly by giving an immunosuppressive effect • Can have an immunostimulatory effect	[54]
9.	IL-12	• Increases CAR-T cell cytotoxicity but also changes the TME, causing a rise in proinflammatory CD4+ T cell infiltration, a decline in regulatory Treglevels, and activation of the myeloid compartment	[55]
10.	IL-13	• Excess expression in GBM • 70% of animal experiments that combined IL-13 with the toxin had long-term survival without discernible neurotoxicity • Actions on human GBM cells that are cytotoxic	[56,57]
11.	IL-33	• Control chemokines, when combined, draw in and activate local and circulating innate immune cells, resulting in a pro-tumorigenic milieu	[58]
12.	HIF-1	• Activates angiogenesis, immunosuppression, and metabolic reprogramming, which encourages cell invasion and survival and accelerates tumor progression	[59]
13.	GM-CSF	• Contribute to the characteristic neutrophilia and lymphopenia of glioblastoma	[60]
14.	VEGF	• Role in the angiogenesis of glioma • Levels would significantly increase in glioma, and therefore, could be potentially considered as a biomarker for this cancer	[61]

TNF, tumor necrosis factor; TGF-β, transforming growth factor-β; IFN, interferon; MHC, major histocompatibility complex; T cell, T-lymphocyte; MGMT, O-6-methylguanine-DNA methyltransferase; TMZ, temozolomide; GSCs, glioblastoma stem cells; NSCs, neural stem cells; Treg, T-regulatory lymphocytes; HIF, hypoxia-inducible factors; GM-CSF, granulocyte macrophage-colony stimulating factor.

after transplantation of glioblastoma tumor cells expressing increased IL-2, IL-4, or GM-CSF levels. In addition, GM-CSF expression was found to be high in the U87-MG glioblastoma cell line, which is exclusively over-expressed in astrocytoma cultures [75].

HLA-G and GBM

In glioblastoma, the expression of the non-classical human leucocyte antigen (HLA) class I antigen HLA-G contributes to immune escape mechanisms by inhibiting competent cytotoxic T cells [76]. A number of factors, together with pro-inflammatory cytokines such as TNF-α, IL-17A, IFN-γ, IL-4, IL-2, IL-6, IL-12, IL-13 are involved in HLA-G transcriptional modulation [77]. Earlier studies have shown that the IL-1β-HIF-1α feedback loop gets triggered by the proinflammatory cytokine IL-1β and maintains a pro-inflammatory environment in GBM [28]. As inflammation and HIF-1α are essential components in the progression of GBM, the role of the pro-inflammatory cytokine IL-1β in controlling HLA-G expression in GBM cells and the microenvironment cannot be overlooked. High-mobility group box 1 (HMGB1) is a nuclear protein that acts as a pro-inflammatory mediator and possesses pro-inflammatory activity after combining with pro-inflammatory cytokines such as IL-1β [78]. The association of IL-1β and HMGB1 increases the pro-inflammatory activity of IL-1β [79]. The intimate interaction between HMGB1 and Toll-Like receptors (TLRs) is associated with pathogen recognition and commencement of innate immunity and also shows involvement in tumor progression and chemoresistance [80–82]. It has been noted that HMGB1 discharge is regulated by TLR4 [83]. TNF-

mediated HIF-1-TLR4 feedback loop is also reported to promote inflammatory responses in GBM [84]. The findings show that HMGB1-activated TLR4-dependent inflammatory response causes tumor development [85], whereas HMGB1-mediated cytokine initiation requires TLR4 binding [86]. Still, the mechanisms regulating HLA-G expression via HMGB1-TLR4 signaling in inflammatory conditions are unknown. Human-defensin-3-a is primarily associated with adaptive and innate immune responses, but TLR4 signaling is also targeted for inhibiting transcription of pro-inflammatory genes, primarily those involved in NF-κB regulation [87].

TNF-α and GBM

Recent findings have shown that TNF-α induces the synthesis of IL-6 via the JAK/STAT3 pathway in human glioma cell lines (U373MG and C6), and TNF inhibitors may reduce tumor cell invasion [88,89]. Earlier reports suggest that upregulation of TNF increases metastasis and migration through induction of IL-8, monocyte chemoattractant protein-1 (MCP-1), CXCR4, and MMPs [90,91].

HMGB1-Proinflammatory Cytokines and Inflammation

HMGB1 is a widely expressed intracellular protein which binds to DNA as well as transcription factors and plays a role in chromosomal structure and function [92]. Within the cells, HMGB1 maintains nucleosome dynamics and chromosomal constancy and contributes to DNA repair and telomere protection [93]. Outside of the cells, HMGB1 collaborates with multiple receptors to perform as a cytokine and chemotactic cytokine for regulating inflammation and immunity [94,95]. It can be passively released by dead or dying cells, but it can also be actively released under certain conditions [96]. Its expression has been linked to accelerated glioma progression and angiogenesis [97,98]. It also regulates tumor progression by encouraging cell proliferation, cell migration, and angiogenesis. It is involved in inflammation, where inflammatory cells play a crucial role in tumorigenesis. Augmented cerebral edema may give rise to brain herniation, which is one of the major factors leading to GBM mortality [99]. It is reported that extracellular HMGB1 has pro-inflammatory effects on endothelial cells, marked by enhanced blood vessel permeability and aggregation of leukocytes mediated by upregulated expression of intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and receptor for advanced glycation end product (RAGE) [100]. It is reported that HMGB1 induces the production of CXCL12 and also heterodimerizes with it to trigger CXCR4, which further encourages CXCR4-driven tumor angiogenesis, growth, and invasion [101]. It also supports the recruitment of activated tumor-supportive macrophages, leading to tumor growth and progression [98].

Earlier reports suggest that extracellular HMGB1 activates its receptors on GBM cells through the downstream signaling pathways such as NF-κB, IFN regulatory factor-3 (IRF3), and phosphoinositide 3-kinase (PI3K) and generate functional immune response like activation of CD8+ T cells, tumor-associated dendritic cells (TADC), and macrophages [96]. In addition to the setting of bone marrow-derived macrophages, HMGB1 signaling through RAGE generates NF-κB activation in the inflammatory reaction [102]. Profuse TAM permeation is a general characteristic of GBM, whereas these TAMs lack apparent phagocytic action. Previous studies have demonstrated that, on the basis of polarization status, TAMs in the tumor microenvironment can be grouped into M1 and M2 subtypes [103,104]. In tumor microenvironment, TAM subtypes (M1 or M2) represent tumor-suppressive or tumor-supportive macrophages. Whereas the M1-subtype of TAMs exerts cytotoxic action on tumor cells and brings out tumor-destructive host reactions, the M2-subtype of TAMs is usually immune-suppressive and assists in the malignant behavior of GBM. TAMs are essential players in tumor-host immune communication and cancer development. Cytokines released by tumor cells have been demonstrated to regulate TAMs (M1 or M2) like polarization [105,106].

Interleukin-33 and GBM

According to a recent investigation, IL-33 plays a critical role in the development of the glioblastoma microenvironment, as well as the engagement of TAMs and TANs in the tumor's inflammatory process [58]. TAM migration into the GBM environment is aided by IL-33, which also facilitates the release of a variety of inflammatory cytokines by glioma cells, all of which contribute to the development of malignancy [107]. Both nuclear and soluble IL-33 has been found in a subset of GBMs, and IL-33 expression has been linked to a reduction in survival in GBM patients [58,108]. Nuclear IL-33 was found in endothelial cells and was shown to be linked to chromatin, acting as a transcription factor by binding to the transcription repressor histone methyltransferase (SUV39H1) [109,110]. The broad involvement of IL-33 in causing changes in the structure and rearrangement of chromatin is confirmed by significant alterations in gene expression. IL-33 secretion occurs in necrotic or injured tissue [111–113]. Although IL-33 was detected in interstitial glioblastoma, *in vivo* investigations demonstrate that other processes, not necrosis, are responsible as well [111,114]. It is important to note that glioma cells lack ST2 receptors, and therefore IL-33 does not directly affect glioma development, as evidenced by *in vitro* studies, but instead alters the tumor environment by promoting the release of cytokines that activate local microglia and trigger an immune response [58]. In conclusion, it can be suggested that IL-33 has dual roles as an inflammatory cytokine and a nuclear factor that promotes glioma growth, as well as IL-33's role in microglia phenotype shift.

VEGF-VEGFR and GBM

VEGF-VEGFR2 signaling in glioblastoma is retained by constant production of VEGF ligand and supports tumor invasiveness, expansion, and increased resistance to few treatments [115]. GBM inhibitors and anti-VEGF therapy may halt the progression of GBM, but the mechanism is unknown [116]. Recent reports have shown that stem-cell-like glioma cells produce high levels of VEGF, which is induced by hypoxia, and anti-VEGF therapy cancels the proangiogenic action of GBM [117,118]. FGF-2 is concerned with neoplastic alteration of GBM cells by triggering the Ras/Raf/extracellular-signal-regulated kinase (ERK) signaling pathway and thereby stimulates angiogenesis in GBM [119]. In an experimental study, upregulation in the expression of IL-2, IL-8, VEGF, GM-CSF and FGF-2 was observed and in glioblastoma patients, there was a strong upregulation in the expression for IL-6, IL-10, TNF-α and IL-1β [72]. This study also showed that expression of cytokines was significantly elevated and robustly associated with tumor grade, proliferation markers, and clinical aggressiveness in GBM. It has been reported that significant levels of expression of the IL-1β, CSF3, and TIMP1 proteins, all of which are linked to inflammation, angiogenesis, and improved migratory ability [120]. NF-κB (complex), IL1B, IL-6, Akt, and VEGF were also shown to be possible signaling regulators, which might be key downstream consequences of chr7 gain and chr10 loss related to tumor formation [121].

Chemokines and GBM

4-1BBL is a ligand of the tumor necrosis factor receptor superfamily (TNFRSF), triggering c-Jun N-terminal kinase (JNK)/ERK/PI3K signaling, and this signaling ultimately converges to the main transcription factor NF-κB, significantly enhancing T cell proliferation, cytokine production, and cytolytic effector function. In addition, 4-1BB signaling inhibits activation-induced cell death (AICD) in T cells and promotes long-term survival and immunological memory [122]. 4-1BBL+ B cells show a high level of expression of pro-inflammatory cytokines such as TNF-α and co-stimulatory molecules such as CD86, which have been found to play a key role in the activation of CD8+ T cells [123]. *Ex vivo* functional studies have confirmed that CD8+ T cell activation is associated with 4-1BBL+ B cells, which is also true for GBM cases. Thus, we speculate that 4-1BB is a potential cellular platform for enhancing tumor destruction mediated by CD8+T cells. The introduction of an agonistic antibody against 4-1BB as monotherapy in mouse glioma models resulted in an increase in median survival without affecting long-term survival. However, the introduction of an antibody against 4-1BB in combination with PD-1 blockade not only led to improved survival, but also allowed survival for a long time, reduced exhaustion and improved the functionality of tumor infiltrating lymphocyte (TIL) [122]. A CD70 protein was shown to be overexpressed in 35% of GBMs, compared to 0% in normal tissues. In GBM, high CD70 levels are linked to a worse chance of survival. CD70 has also been linked to the encouragement of tumor migration, which is linked to an increase in M2 macrophage infiltration. It was also found that CD70 expression is characteristic of both primary tumors and recurrent gliomas [124,125], which also demonstrates a CD70-induced compensation mechanism of immunosuppression, makes CD70 an important target for therapy.

The primary inflammatory reaction of the body to the tumor mediates the production of TNF-α. Microglia, macrophages, and dendritic cells secrete cytotoxic and pro-inflammatory factors such as TNF-α and IL-6 during the initiation and primary development of glioma. This leads to an immune response by recruiting CD4+ and CD8+ T cells to the site of tumor localization [126]. As a result, the proinflammatory cytokine IL-1β is released, which changes the expression profile of the tumor, leading to the loss of the integrity of the BBB. This allows the infiltration of myeloid suppressor cells (MDSC) into the volume of the tumor cell colony. In a growing tumor, recruited macrophages initiate an immune response and activate inducible nitric oxide synthase while also secreting IFN-β, IL-12, and MCP-1 [127]. One of the possible scenarios of inflammation inducing malignancy is biopsy-induced inflammation at the wound site, resulting in the migration of immune cells and the secretion of chemokines. C-C Motif Chemokine Ligand 2 (CCL2) causes macrophage recruitment, and its blocking by antibodies reduces the migration of tumor cells in this scenario [128]. It has been established that glioma cells producing CCL2 contribute to the migration of microglia into tumor aggregates, and microglia secrete CCL2 too, which leads to the recruitment of TAMs [126,129,130]. This study shows that there is a positive correlation between the progression of glioma and the expression of not only CCL2, but also its C-C motif chemokine receptor 2 (CCR2) receptor. Coupled with the information that radiation increases the level of CCL2 in brain tissues, according to the scenario of inflammation associated with injury [131], indicates that the role of CCL2 is being formed as a malignancy-induced inflammatory chemokine in conditions of damage to brain tissues and glioblastoma.

In addition to the microglia-recruiting ability of CCL2, the chemokine CXCL16 is involved in the phenotypic alteration of microglia. In the context of the glioma microenvironment, CXCL16 is able to redefine the type of inflammatory action of microglia, which can be both harmful and neuroprotective in nature, which makes special sense in the context of stage-by-stage tumor development. The presence of auto- and paracrine effects on glioma cells through CXCL16 has also been shown, in which CXCL16 significantly induces proliferation, migration, and invasion of cancer cells. CXCL12 has a similar effect on GBM

cells [132]. Moreover, it is shown in the original GBM tissues, acutely dissected from patients, that they contain high values of CXCL16 and its CXCR6 receptor in comparison with the control. At the same time, it is known about the transmission of the CXCL16 signal along the signaling pathway without the CXCR6 receptor, which indicates the broad influence of chemokine. The CXCL16/CXCR6 bundle is a critical guide for the polarization of the vector of immunological and inflammatory activity of microglia and macrophages inside the microenvironment of gliomas, particularly glioblastoma [133]. Thus, for example, polarized GBM M2-like macrophages secrete anti-inflammatory, immunosuppressive cytokines TGF-β1, CCL2 and IL-10 [134], which in turn, in conjunction with integrin (avβ3)-dependent EC-macrophages, interact with EC (endothelial cells) macrophages and promote angiogenesis. Moreover, it has been shown that anti-inflammatory cytokines, in particular TGF-β1, are capable of reversing M1 macrophage-dependent suppression of angiogenesis in an immunosuppressive microenvironment [135]. Along with this, IL-10 secreted by M2 macrophages is able to induce the development of glioma via the JAK2/STAT3 pathway [136].

TGF-β induces proliferation, differentiation, and invasion [135,137–139] and its high level contributes to TMZ cell GBM resistance via the K-homology splicing regulator protein (KSRP)/mir-198/O-6-methylguanine-DNA methyltransferase (MGMT) signaling pathway, leading to hypermethylation via regulation of H19 and HOXD-AS2 levels and binding to KSRP and mir-198 [140]. TGF-β can also interfere with suppressor of mothers against decapentaplegic (SMAD) signaling [141,142]. TGF-β1 stabilizes the tumor state by forming radioresistance [140,142]. Furthermore, TGF-induced autophagy-dependent resistance to TMZ in glioblastoma cells may be of this type [143]. Moreover, TGF-β3 is able to induce invasion of glioma cells through phosphorylation of SMAD [141]. It is also worth mentioning that a number of cytokines control the most important signaling pathways in terms of glioblastoma survival and malignancy. These include CXCL8 and, to a lesser extent, CXCL1/2, which are involved in the regulation of NF-κB and AKT pathways. It was shown that these chemokines are promoted by AKIP1 [144]. In confirmation, clinical trials were conducted in which a correlation of A-kinase interacting protein 1 (AKIP1) and CXCL1/2/8 expressions was found, and their increased expression was shown in samples obtained from patients with low-grade glioma [144]. Previously, data showed that the IL-11 gene is hypermethylated in glioblastoma cells [145]. Recently, it has been noted that IL-11 is secreted by microglia and surrounding macrophages via the STAT3-*MYC* signaling pathway [146].

The action of *MYC* is induced, which is responsible for the regulation of the main transcription factors regulating the malignancy of glioblastoma: OLIG2, SOX2, and POU3F2 [147,148]. Thus, IL-11 is able to promote the transition of glioblastoma cells to the stem state [146], in which resistance to TMZ is acquired. Moreover, its hypermethylation may indicate a developed mechanism of self-regulation through a change in the phenotypes of microglia and surrounding macrophages. GBM cells do not express IL-22, but express IL-22R and IL-10R2 receptors for it, while GBM cells respond to exogenous IL-22, responding with increased proliferation and survival. This regulation is mediated by phosphorylation of STAT3 and activation of Akt and ERK1/2 pathways. It is assumed that the cellular environment due to proinflammation can secrete IL-22 [149]. As reported, bioinformatic analysis of sc-RNA seq, OSM is also secreted mainly by microglial cells surrounded by glioblastoma tissues [150]. Simultaneously, differential expression analysis and subsequent KEGG enrichment revealed that OSM activation is mediated by JAK/STAT and NF-κB signaling, which play a key role in cancer regulation [150].

Immunotherapy and Clinical Trials in GBM Malignancy

The selectivity of the blood-brain barrier to immune cells [151], draining of antigens into the cervical lymph nodes through lymphatic vessels [152] and functioning of microglia as antigen presentation cells [153] suggest that the brain is immune advantaged, but blood-derived immune cells are not completely prohibited from entering the brain [154]. GBM cells can act as immunosuppressant since these can secrete a range of protumor cytokines or chemokines which in turn can control polarization of macrophage, encourage recruitment regulatory T cell, and inhibit maturation and function of dendritic cell and natural killer cell. Immunotherapy happens to be a promising tool for cancer treatment, but current approaches against solid tumors including GBM remain a significant challenge and needs to be surmounted with the development of immunotherapy for GBM. The checkpoint blockade therapy becomes refractory due to extensive infiltration of immunosuppressive macrophages. However, preclinical studies on combination immunotherapy demonstrated encouraging results. Reports suggest that permutation of IL-6 inhibition with CD40 stimulation reverses macrophage-mediated tumor immunosuppression and sensitizes tumors to checkpoint blockade leading to extended animal survival in GBM models [155]. Immunotherapeutic agents such as peptides, dendritic cells, antigen receptor T cells, checkpoint inhibitors and oncolytic viruses have shown promising results in preclinical as well as clinical trials.

A good number of frequently used cytokines in cancer therapy are interferons and interleukins. The combined therapy with herpes simplex virus type 1 thymidine kinase genes and IL-2-encoding genes shows that the treatment is well accepted and tumor responses are noticed in 50% of patients suffering from recurrent GBM [156].

Table 3. Consolidated number of clinical trials as per database of privately and publicly funded clinical studies conducted around the world on website, https://clinicaltrials.gov/.

S.N.	Status of clinical trials	Total no. of trials	Study with result	Study without result	Study phase					
1.	Completed	787	208	579	EP = 15 WR = 1	P1 = 354 WR = 56	P2 = 385 WR = 169	P3 = 41 WR = 10	P4 = 1 WR = 1	NA = 47 WR = 0
2.	Withdrawn	68	0	68	EP = 2 WR = 0	P1 = 22 WR = 0	P2 = 34 WR = 0	P3 = 5 WR = 0	P4 = 0 WR = 0	NA = 7 WR = 0
3.	Terminated	189	71	118	EP = 5 WR = 0	P1 = 85 WR = 22	P2 = 96 WR = 57	P3 = 10 WR = 4	P4 = 1 WR = 0	NA = 13 WR = 6
4.	Suspended	15	0	15	EP = 0 WR = 0	P1 = 4 WR = 0	P2 = 6 WR = 0	P3 = 2 WR = 0	P4 = 0 WR = 0	NA = 2 WR = 0
5.	Active & not recruiting	155	8	147	EP = 8 WR = 0	P1 = 68 WR = 1	P2 = 73 WR = 5	P3 = 7 WR = 2	P4 = 0 WR = 0	NA = 9 WR = 0
6.	Enrolling by invitation	6	0	6	EP = 1 WR = 0	P1 = 4 WR = 0	P2 = 1 WR = 0	P3 = 0 WR = 0	P4 = 0 WR = 0	NA = 1 WR = 0
7.	Recruiting	329	0	329	EP = 24 WR = 0	P1 = 128 WR = 0	P2 = 126 WR = 0	P3 = 18 WR = 0	P4 = 1 WR = 0	NA = 47 WR = 0
8.	Not recruiting	79	0	79	EP = 5 WR = 0	P1 = 28 WR = 0	P2 = 27 WR = 0	P3 = 4 WR = 0	P4 = 2 WR = 0	NA = 11 WR = 0
9.	Unknown	128	0	128	EP = 4 WR = 0	P1 = 45 WR = 0	P2 = 53 WR = 0	P3 = 10 WR = 0	P4 = 0 WR = 0	NA = 18 WR = 0

EP, Early Phase-1; P1, Phase I; P2, Phase II; P3, Phase III; P4, Phase IV; NA, Not Applicable; WR, With Result.

In a clinical study (phase I), significant clinical responses were noted in adult patients with HGG after treatment with two vaccinations (autologous fibroblasts retrovirally transduced with herpes simplex virus thymidine kinase (HSV-TK) and IL-4-encoding genes) along with irradiated autologous glioma cells [157]. Two clinical trials (phase II) showed that efficacy of TMZ in recurrent GBM patients was improved after treatment with IFN-α, when compared to control group of patients [158]. Further, in preclinical studies, IFN-β has been reported to enhance the chemosensitivity towards TMZ by reducing transcription of MGMT [159]. It was also reported that the addition of IFN-β to standard chemoradiotherapy with TMZ (phase I clinical trial) was well tolerated and enhanced the survival of GBM patients [160], but no meaningful efficacy in cases of GBM or pediatric HGG, was noted after combined therapy with IFN-γ and radiotherapy or chemoradiotherapy [161].

Dendritic cell vaccines (DCV) comprise efficient antigen-presenting cells that are proficient of provoking immune responses. Immune and clinical responses to a DCV in GBM were reported in a phase II clinical study of GBM, it was shown that 17 of 34 patients attained a significant enhancement in median survival [162]. When DCV was used in newly diagnosed GBM patients whose median PFS time was 18 months it was found that 3 patients survived for more than 34 months [163]. Results from other studies showed no benefit in newly diagnosed GBM patients when treated with a tumor lysate DCV [157]. Also, results from a phase II clinical trial using tumor lysate DCV in patients with recurrent GBM showed no significant increase in survival [164]. Seven GBM patients when with treated with DCV primed against transfected tumor mRNA showed a median OS time of 759 days when compared to control group who had a median OS time of 585 days [165]. In a different study with pp65-transfected DCV mixed with GM-CSF and dose-intensified TMZ for treatment of newly diagnosed GBM patients, eleven patients showed a median OS time of 41.1 months when compared to controls that had 19.2 months [166].

Earlier findings have suggested that TAM infiltration and M2 macrophages lead to an immunosuppressive TME and assist the progression of gliomas [167]. A number of reports have established bigger facts of TAMs in higher-grade gliomas as compared to the lower-grade tumors [168]. It has been noted that macrophage genes expression is coupled with tumor pathology, response to treatment as well as OS in glioma patients [169]. There are evidences which show that TAMs contribute significantly to the development and maintenance of immunosuppression and migration of tumor cell and also promote angiogenesis in glioma [170] and this suggests that immunotherapy targeting TAMs might be potential in glioma treatment. As TAMs depend on CSF for differentiation and survival, BLZ945 which is a CSF-1 inhibitor, has been applied to target TAMs in mouse glioblastoma models. The findings from the study suggest that the inhibition of CSF-1 could reduce the M2 macrophage oc-

Table 4. List of representative immunotherapeutic agents under clinical trials according to the website https://clinicaltrials.gov/ directory of clinical studies that have been privately and publically sponsored and carried out around the world.

Immunotherapeutic agents	Registration ID	Molecules	No. of patients	Phase	Outcome	Status
Checkpoint inhibitors	NCT02337491	Pembrolizumab	80	II	• Maximum Tolerated Dose (MTD) • Dose Limiting Toxicity • 6-Month Progression-Free Survival	Completed
	NCT03367715	Ipilimumab	10	II	• 1-year Overall Survival • Median Overall Survival • Median Progression Free Survival	Completed
	NCT02017717	Nivolumab	529	III	• Percentage of Participants With Adverse Drug Events That Caused Discontinuation, by the Worst CTC Grade • Percentage of Participants who Experienced Adverse Events • Percentage of Participants With Serious Adverse Events	Active, not recruiting
Vaccine	NCT01480479	CDX-110	745	III	• Overall Survival • Progress-Free Enduring • Security and Acceptability	Completed
	NCT03615404	CMV pp65 DCs	11	I	• Percentage of Patients for Whom 3 or More Vaccines Can be Made • Percentage of Patients Who Experience Unacceptable Toxicity	Completed
	NCT02366728	DCs	64	II	• Median Overall Survival • Percentage of 111In-labeled Dendritic Cells Migrating to the Inguinal Lymph Nodes • Median Overall Survival in CMV Positive Participants	Completed
	NCT01480479	Rindopepimut	745	III	• Overall Survival • Progress-Free Enduring • Security and Acceptability	Completed
	NCT01222221	IMA950	45	I	• The Connection between Each Negative Occurrence and the IMA950 Multiform, Multiantigen Vaccination for Glioblastoma • Total Number of Patients Displaying Patient-Specific T-cell Reactions to One or More Tumor-Associated Peptides in the Study Vaccination IMA950 • Assessment of Progression-Free Survival at 6 and 9 Months Following Surgery	Completed
	NCT02455557	SurVaxM peptide	66	II	• Progression-free Survival • Immune Reactions to SurVaxM and Response Predictors • Occurrence of Toxicities in Grades 3 or 4	Active, not recruiting
	NCT03018288	HSPPC-96	90	II	• In Order to Ascertain whether Newly Diagnosed MGMT Unmethylated GBM Patients Treated with RT + TMZ + Pembrolizumab Followed by Pembrolizumab + TMZ +/– HSPPC-96 (X) 6 Cycles Have Enhanced One-Year Overall Survival	Active, not recruiting

Table 4. Continued.

Immunotherapeutic agents	Registration ID	Molecules	No. of patients	Phase	Outcome	Status
Adaptive T cells	NCT00693095	CMV specific T cells	23	I	• To determine if administering CMV-DCs to adult patients with newly discovered GBMs while they are recovering from TMZ-induced lymphopenia treated with ALT in CMV seropositive individuals improves the T-cell response • To assess the safety of ALT with CMV pp65-activated T cells in adult patients with newly-diagnosed GBMs while they are recovering from TMZ-induced lymphopenia for therapeutic purposes	Completed
	NCT01109095	HER.CAR CMVspecific CTLs	16	I	• Number of individuals after CTL infusion who experienced dose-limiting toxicity • Tumor shrinkage with CTL injection • T cell frequency area under the growth curves (AUC) throughout time • Effect of CTL with gene modifications on CMV-specific T cell immunity	Completed
	NCT04003649	IL13Ra2-CART cells	60	I	• Incidence of adverse events • Dose-limiting toxicity (DLT) • Feasibility (neoadjuvant therapy)	Recruiting
	NCT00807027	INNOCELL immuncell-LC	180	III	• MRI • EORTC QLQ-C30, treatment response, overall survival, and Karnofsky Performance Status	Completed
	NCT00990496	CMV Specific Cytotoxic T Lymphocytes	25	I	• To find out how frequently tumor responses-defined as stable illness, partial or full responses following the injection of CMV CTL occur. • To use micro chimerism assays to gauge the strength and length of donor chimerism after infusion. to use micro chimerism assays to gauge the strength and length of donor chimerism after infusion • The frequency of elevations in CMV pp65 or IE-1 T cells following the injection of allogeneic CMV CTL into GBM patients • To evaluate the safety of infusions of allogeneic CTL in this patient population	Terminated

currence in the TAM populations which further leads to increased survival and tumor regression [171]. The permutation of a PI3K or IGF-1 inhibitor along with a CSF-1 inhibitor in recurrent tumors considerably enhances OS which provides a novel solution to resistance against CSF-1 inhibitor [172]. PLX3397 is a CSF-1 inhibitor which may cross the blood-brain barrier in animals and can decrease the number of tumor-associated microglia and boost tumor invasion in glioblastoma mouse models [173].

PD-L1 is an immune checkpoint molecule related to program cell death that can suppress the functioning of T lymphocytes and intervene immune evasion by cancer cells [174]. PD-L1 expression has been noted in human glioma tissues and can be related to glioma grade. In a study conducted to evaluate PD-1-inhibited natural killer cells, it was noted that the blockade of PD-1 could promote the cytotoxicity of NK cells against GSC [175]. The combined immunotherapy of PD-1 inhibitors with other therapeutic agents is a further attractive alternative. The combination of anti-PD-1 immunotherapy and stereotactic radiosurgery in a GL261 cell implanted mouse model lead to the prolonged median survival to 52 days as compared with 27 days which was achieved with radiotherapy-alone and 30 days that was achieved with anti-PD-1-immunotherapy alone [176]. Also, the combined immunotherapy of a PD-1 inhibitor and VEGF inhibitor was noted to be acceptable and promising in clinical trials and animal models. Further, triple-combination immunotherapy using GVAX, anti-PD-1 monoclonal antibody, and an anti-OX40 monoclonal antibody is very much effective against gliomas [177].

Considering the success of combination immunotherapy in GBM preclinical studies and other cancers, the application of immunotherapeutic agents aiming diverse arms of the immune system has been started to be largely tested in GBM clinical trials. There are many ongoing and completed clinical trials (phase I/II/III) studying the combination of multiple ICBs for GBM treatment (Table 3). At present, novel immunotherapeutic strategies have been quite well studied in several preclinical and clinical studies. Dramatic responses have been detected during clinical trials, in which immune checkpoint inhibitors, vaccines, dendritic cells and cytokines exhibit promising efficacy (Table 4). However, further studies are required to conclude whether immunotherapy can be implemented as part of standard therapy for glioma.

Future Opportunity for GBM Treatment

Though there has been substantial development in recent years towards advancement in the field of GBM pathophysiology and its microenvironment and the expansion of preclinical studies and clinical trials, there is no absolute drug for GBM patients. Until now, the FDA (USA) approved drugs TMZ and bevacizumab have been the only options available to medical science for the treatment of GBM patients. A number of studies are going on where researchers are looking at the efficiency of chimeric antigen receptor T cell therapy, tumor vaccination therapy, and immune checkpoint inhibitors. It has been suggested that the pro-inflammatory and tumorigenic mediators and their linked signaling pathways could be a potential strategy for GBM treatment. Recent findings from some studies also designate combination therapy as an effective gradient in the treatment of GBM [178–180].

Some preclinical and clinical studies have also suggested that treatment with TLR agonists could open a new venue in GBM management. However, a few studies state that an improper course of administration of TLR agonists influences the pharmacokinetics and pharmacodynamics of the ligands. It has been reported that intravenously administered agonists are distributed and may cause supplementary side effects and decrease the therapeutic efficiency of the active compound [181]. Earlier findings also show that the use of TLR modulators might result in chronic inflammation and autoimmune diseases [182]. It is also suggested that chronic inflammation might be a critical factor for the growth of malignant tumors, together with GBM. It is also noted that TLR agonists produce immunosuppressive effects by regulating Tregs, IL-10 and PD-L1 expression and finally favoring oncogenesis [183]. Thus, route of administration, dose, and delivery system should all be considered for better performance and less toxicity of TLR agonists in GBM treatment [181,183]. At the same time, TLR-4 antagonists like TAK-242 and CXC195, which have anti-inflammatory, anti-proliferative, and induce apoptosis and cell cycle arrest, might be tested as anticancer agents in GBM treatment [184,185].

Conclusions

In this minireview, we have tried to bring GBM, tumor microenvironment, inflammatory mediators, clinical trials throughout the world and concerned agents in immunotherapy at the same platform. From literature survey and data analysis, we may conclude that there exists a complicated interaction between inflammatory mediators and tumor microenvironment. We reviewed the participation of cytokines and chemokines in regulatory pathways of glioblastoma malignancy. It is crucial to remember that the mechanisms involve bidirectional cytokine connection in between tumor cells and immune cells and are also influenced by the tumor microenvironment and the local immune response profile. Thus, the operating pathways are linked to the processes of invasion, migration, proliferation, angiogenesis, and immunological modulation. All the key elements of glioblastoma malignancy are regulated through the systems of autocrine and paracrine control by extracellular cytokines through membrane receptors, which have a persistent and ongoing influence on all cellular and extracellular protein structures.

In this minireview we have also tried to excavate current approaches to immunotherapy for GBM. We have results of many clinical trials with us and still there are a number of clinical trials going on around the world which involve different kind of immunological agents. It may be noted that GBM-mediated immunosuppression is a result of factors other than the inherent characteristics of tumor cells, but also as a result of different kinds of signaling pathways operating in the microenvironment. Immunotherapy for GBM needs integrated efforts with balanced permutation of cell therapy, vaccine therapy, radio therapy and chemotherapy. Thus, in future, better understanding of interaction between GBM cells and brain microenvironment is required to develop effective anti-GBM immunotherapies.

Author Contributions

IU, AL, RKK, and VS designed the study; IU, AL, RKK, and VS collected and analyzed the data. PT conceptualized and supervised the study and also compiled the data and prepared figures. IU, AL, RKK, VS, and PT have been involved in drafting the manuscript. All the authors revised the manuscript critically for important intellectual content and accept responsibility for every aspect. The final manuscript was read by all authors and approved for publication.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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