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Critical View of Novel Treatment Strategies for Glioblastoma: Failure and Success of Resistance Mechanisms by Glioblastoma Cells

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According to the invasive nature of glioblastoma, which is the most common form of malignant brain tumor, the standard care by surgery, chemo- and radiotherapy is particularly challenging. The presence of glioblastoma stem cells (GSCs) and the surrounding tumor microenvironment protects glioblastoma from recognition by the immune system. Conventional therapy concepts have failed to completely remove glioblastoma cells, which is one major drawback in clinical management of the disease. The use of small molecule inhibitors, immunomodulators, immunotherapy, including peptide and mRNA vaccines, and virotherapy came into focus for the treatment of glioblastoma. Although novel strategies underline the benefit for anti-tumor effectiveness, serious challenges need to be overcome to successfully manage tumorigenesis, indicating the significance of developing new strategies. Therefore, we provide insights into the application of different medications in combination to boost the host immune system to interfere with immune evasion of glioblastoma cells which are promising prerequisites for therapeutic approaches to treat glioblastoma patients.

Keywords: glioblastoma, immunotherapy, immune evasion, tumor microenvironment, peptide and mRNA vaccines

INTRODUCTION

Glioblastoma is the most invasive and therapy-insensitive type of glial tumor. The subpopulation of glioblastoma cells is disposed to proliferate quickly and in an uncontrolled manner, where alternative subsets infiltrate into nearby healthy tissue making an entire resection impossible. The high heterogeneity of glioblastoma contributes to tumor progression and recurrence which causes resistance from therapeutic drugs (Vieira de Castro et al., 2020; Zhang and Liu, 2020). On the molecular level, glioblastoma cells, for instance, often fail the proper regulation of pro- and anti-apoptotic proteins leading to apoptotic resistance (Vengoji et al., 2018). Additionally, glioblastoma stem cells (GSCs), using altered signaling pathways, do not only play a critical role in resistance to conventional therapies and tumor recurrence, but also in tumor initiation and progression (Dean et al., 2005; Vengoji et al., 2018; Bhaduri et al., 2020; Vieira de Castro et al., 2020). Hypoxia is a prominent microenvironmental factor that results from a rapid growth of glioblastoma and the

need for oxygen, provoking angiogenesis as well as anaerobic glycolysis. This, in turn, generates a local accumulation of lactate with a decreased pH environment and encourages glioblastoma cells for migration (Xie et al., 2014).

The aim of the review is to provide a critical overview of the common as well as novel treatment strategies of glioblastoma based on the resistant mechanisms developed by glioblastoma cells and to ascertain combination therapies to improve the failure of monotherapies.
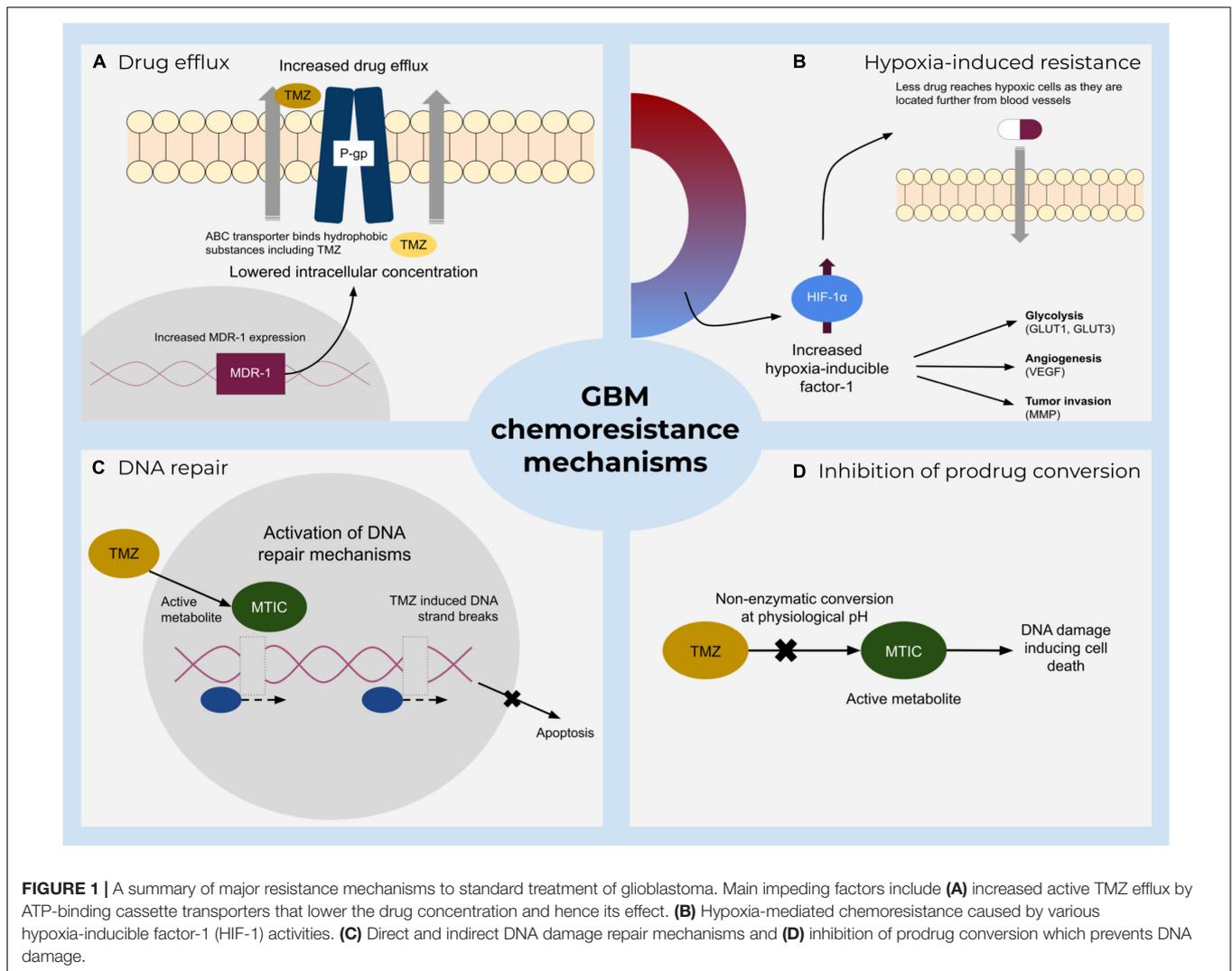
Standard Care Therapies for Glioblastoma

Standard of care therapies for glioblastoma include resection, radio- and chemotherapy with the administration of temozolomide (TMZ) or nitrosoureas components. Chemoresistance during medication is a major drawback and includes several mechanisms (**Figure 1**), such as drug metabolic inactivation, increased DNA-repair mechanisms, inhibition of prodrug conversion, and lowering the intracellular

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Abbreviations: ACE2, angiotensin-converting enzyme 2; ADCs, antibody-drug conjugates; AIF, apoptosis-inducing factor; AIM-2, absent in melanoma 2; APCs, antigen-presenting cells; ARG1, arginase; B7-H1, B7-homolog 1; Bak, Bcl-2 antagonistic killer; Bax, Bcl-2 associated X protein; Bcl-2, B cell lymphoma-2 protein; Bcl-Xl, Bcl-extra-long; BBB, blood-brain barrier; BH3, Bcl-2 homology domain 3; CAR, chimeric antigen receptor; CCR2, C-C chemokine receptor type 2; CD, cluster of differentiation; CNS, central nervous system; CRS, cytokine release syndrome; CSCs, cancer stem-like cells; CTLs, cytotoxic T lymphocytes; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCR4, C-X-C chemokine receptor type 4; DCs, dendritic cells; DNA, deoxyribonucleic acid; DNRII, dominant-negative TGF-beta receptor II; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; ECM, extracellular matrix; FcRn, neonatal Fc receptor; FDA, US Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; GAMs, glioma-associated microglia/macrophages; GDNF, glial-derived neurotrophic factor; GLUT, glucose transporter; GM-CSF, granulocyte-macrophage colony-stimulating factor; GSCs, glioblastoma stem cells; HER2/neu, human epidermal growth factor receptor 2; HGF/SF, hepatocyte growth factor/scatter factor; HIF-1, hypoxia-inducible factor 1; HSP, heat shock protein; HSV, herpes simplex virus; IAPs, inhibitors of apoptosis; IDO, indolamine 2,3-dioxygenase 1; IFN-γ, interferon-gamma; IKK, IκB kinase; IL, interleukin; IL-13Rα2, interleukin-13 receptor alpha 2; ILT/LIR, Ig-like transcript/leukocyte Ig-like receptors; KIR, killer-cell Ig-like receptors; mAb, monoclonal antibody; mTOR, mammalian target of rapamycin; mTORC2, mTOR complex 2; M-CSF, macrophage colony-stimulating factor; Mcl-1, myeloid cell leukemia factor 1; MCP-1, monocyte chemotactic protein 1; MDSCs, myeloid-derived suppressor cells; MDR-1, multidrug resistance protein 1; MGMT, methyl guanine methyl transferase; MHC I, major histocompatibility complex class I; MHC II, major histocompatibility complex class II; MMP, matrix metalloproteinase; MTIC, 3-methyl-(triazen-1-yl) imidazole-4-carboxamide; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOS2, nitric oxide synthase 2; NSCLC, non-small cell lung cancer; OS, overall survival; P-gp, permeability glycoprotein; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PDK1, pyruvate dehydrogenase lipoamide kinase isozyme 1; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog; RNA, ribonucleic acid; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; STAT3, signal transducer and activator of transcription 3; TAA, tumor-associated antigens; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor-β; Th, T helper; TILs, tumor-infiltrating lymphocytes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; TME, tumor microenvironment; TMPRSS2, transmembrane protease serine subtype 2; TMZ, temozolomide; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; Treg, T regulatory cell; TRP-2, tyrosine-related protein 2; UCB, umbilical cord blood; VEGF, vascular endothelial growth factor.

drug concentration by enhanced drug efflux via enhanced expression of transporters (Wee et al., 2016; Sharifzad et al., 2019; Pessina et al., 2020). TMZ is frequently described as a DNA alkylating prodrug that induces double-strand breaks of the DNA which eventually lead to apoptosis (Karachi et al., 2018; Sharifzad et al., 2019). Recently, a debate has emerged casting doubt on the precise molecular function of this component (Strobel et al., 2019; Kaina, 2019; Stepanenko and Chekhonin, 2019; Westhoff et al., 2020; Herbener et al., 2020). According to the traditionally proposed model, TMZ alkylates bases that are present in the DNA, leading to a mismatch during replication and induces futile rounds of DNA repair, finally ending in DNA strand breaks and apoptosis (Kaina, 2019). The O^6-methylguanine-DNA-methyltransferase (MGMT) can resolve some of the TMZ-induced alterations and thus mediate survival, but is frequently found not to be expressed in approximately half of all glioblastoma cells, i.e., about 45% of patients considered to benefit from TMZ (Karachi et al., 2018; Miyauchi and Tsirka, 2018; Arora and Somasundaram, 2019). The standard practice, however, is still to prescribe TMZ treatment notwithstanding a patient's methylation level (Kamson and Grossman, 2021), although studies show no statistically significant difference in survival between the groups controlling for TMZ in the absence of MGMT methylation (Hegi et al., 2005). Indeed, even the predictive value of MGMT promotor methylation with regards to tumor response to TMZ is not uncontroversial (Stepanenko and Chekhonin, 2019; Yu et al., 2020). Overall, TMZ treatment extends patient survival from 12.1 to 14.6 months (Strobel et al., 2019), i.e., modulating its therapeutic potency is unlikely to be curative, but might further extend the therapeutic window.

MGMT inhibitors are therefore considered to be of interest to improve the clinical response to TMZ treatment (Karachi et al., 2018; Arora and Somasundaram, 2019). However, systemic inhibition of MGMT might lead to increased apoptosis or even the accumulation of mutations in healthy tissue, so that localized application of inhibiting pseudo-substrates or tumor-specific delivery of blocking peptides have been considered as strategies to increase the efficiency of TMZ treatment while not concurrently sensitizing healthy tissue to the alkylating agent (Yu et al., 2020; Wängler et al., 2020, respectively). Some of these strategies are currently being evaluated clinically and are showing rather promising results (Yu et al., 2020). Alternatively, metronomic application of TMZ might suffice to sensitize relatively resistant glioblastoma cells to this drug, as MGMT is a suicide enzyme that is destroyed upon de-alkylating a base (Karachi et al., 2018; Miyauchi and Tsirka, 2018; Arora and Somasundaram, 2019; Le Rhun et al., 2019; Strobel et al., 2019).

The treatment of recurrent glioblastoma encompasses nitrosourea compounds, namely lomustine (Brandes et al., 2016; Le Rhun et al., 2019). Nitrosoureas are alkylating reagents which are able to cross the blood-brain barrier due to their high lipophilicity, causing cell damage and apoptosis. However, lomustine implies severe adverse reactions (prolonged thrombocytopenia and dose-limiting pulmonary toxicity was determined) (Brandes et al., 2016). The small increase of overall survival (OS) while the progression-free survival (PFS) for newly diagnosed as well as recurring glioblastoma denotes the need for
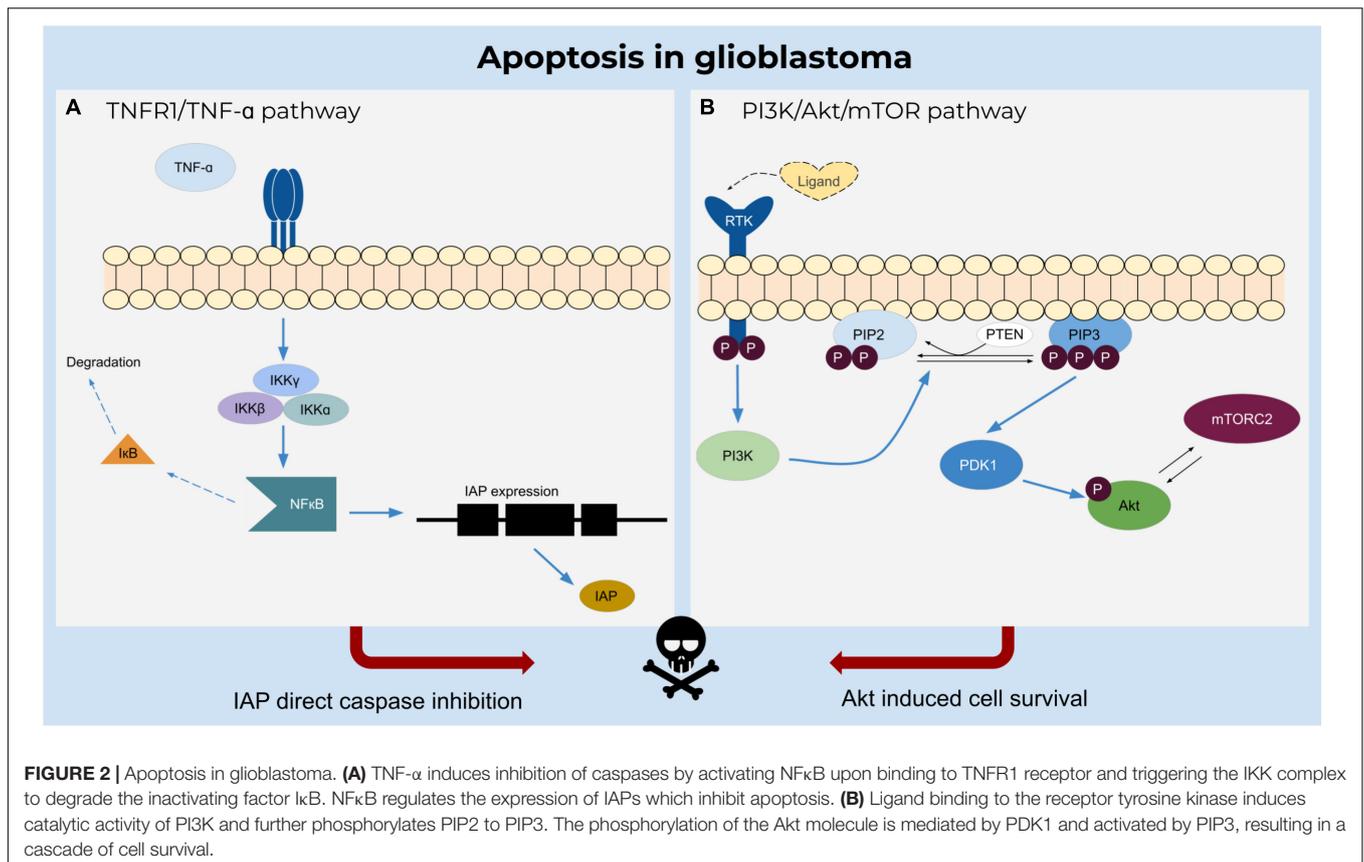
FIGURE 1 | A summary of major resistance mechanisms to standard treatment of glioblastoma. Main impeding factors include **(A)** increased active TMZ efflux by ATP-binding cassette transporters that lower the drug concentration and hence its effect. **(B)** Hypoxia-mediated chemoresistance caused by various hypoxia-inducible factor-1 (HIF-1) activities. **(C)** Direct and indirect DNA damage repair mechanisms and **(D)** inhibition of prodrug conversion which prevents DNA damage.

better management of the disease by reducing severe side effects and preventing resistance.

Glioblastoma Cells Are Resistant to Apoptosis

Apoptosis plays an important role in the elimination of damaged cells in multicellular organisms to sustain normal biological processes (**Figure 2**). A dysregulation of apoptosis can lead to cancer and other pathophysiological disorders. In the case of preventing apoptosis or establishing resistance, anti-apoptotic proteins (e.g., B cell lymphoma-2 protein family members Bcl-2 or Bcl-xL) bind to pro-apoptotic family members (e.g., Bcl-2 homologous antagonist/killer (Bak) or Bax) resulting in the neutralization of their activity (Tsujimoto, 1998; Ola et al., 2011).

Another attractive target for sensitization to therapy is the Bcl-2 family, including Bcl-2, Bcl-xL and Bcl-w, which inhibit the release of mitochondrial apoptogenic factors by sequestering Bak and Bax (Strik et al., 1999; Wick et al., 2004; Stegh et al., 2007). Apart from overexpression of anti-apoptotic proteins, the

downregulation of pro-apoptotic proteins (Bak, Bax, Box, and NOXA) has been described for glioblastoma (Strik et al., 1999; Tyagi et al., 2002; Steinbach and Weller, 2004). Low protein levels in glioblastoma patients have been detected for Apaf-1 and procaspase-9 (Blahovcova et al., 2015). Consequently, the initiation of apoptosis is circumvented and therapeutic response is poor (Tagscherer et al., 2008). The Bcl-2 family proteins act as a critical regulator of life-death decisions within the apoptotic pathway and especially the inactivation or downregulation of anti-apoptotic Bcl-2 family members, represent an interesting target for anticancer therapies. The expression and activity of the Bcl-2 protein can be decreased by using antisense oligonucleotides, small molecules, or peptides (Ola et al., 2011). Antisense oligonucleotides, for instance Genasense (not approved by FDA), lead to the degradation of *bcl-2* mRNA or incites a steric hindrance of translation, which reduces Bcl-2 expression (Julien et al., 2000; Frankel, 2003). Small molecule inhibitors, such as ABT-737, ABT-263 (navitoclax), or more recently the FDA approved alternative ABT-199 (venetoclax), BH3 mimetics, were designed to block the BH3 domain binding

FIGURE 2 | Apoptosis in glioblastoma. **(A)** TNF-α induces inhibition of caspases by activating NFκB upon binding to TNFR1 receptor and triggering the IKK complex to degrade the inactivating factor IκB. NFκB regulates the expression of IAPs which inhibit apoptosis. **(B)** Ligand binding to the receptor tyrosine kinase induces catalytic activity of PI3K and further phosphorylates PIP2 to PIP3. The phosphorylation of the Akt molecule is mediated by PDK1 and activated by PIP3, resulting in a cascade of cell survival.

site on the surface of Bcl-2 and/or Bcl-xL, preventing inhibition of pro-apoptotic Bak or Bax (An et al., 2004; Kouri et al., 2012; Singh et al., 2019). Interestingly, in the context of glioblastoma, navitoclax has been the more promising substance, suggesting that modulation of Bcl-xL is needed for therapeutic efficacy (Hlavac et al., 2019; Nguyen et al., 2019), unfortunately navitoclax is also associated with serious, but manageable side effects, such as thrombocytopenia and neutropenia, severely limiting its therapeutic value (Wilson et al., 2010; Kuter, 2015). Additionally, the anti-apoptotic Bcl-2 family member myeloid cell leukemia factor-1 (Mcl-1), which interferes in early cascade events by suppressing cytochrome c release from mitochondria, is highly expressed in human glioblastoma (Michels et al., 2005; Karpel-Massler et al., 2017). High levels of Mcl-1 mediate BH3-mimetic resistance, suggesting that a dual inactivation of Bcl-2/Bcl-xL and Mcl-1 is necessary for apoptosis of glioblastoma cells (Kouri et al., 2012; Karpel-Massler et al., 2017; Shang et al., 2020). AT-101, a small molecule targeting Mcl-1, is presently being examined in a clinical trial (Xiang et al., 2018). Although inhibition of Mcl-1 has received certain attention as a potential drug target, only slowly implemented in clinical applications and poses challenges in glioblastoma treatment due to high molecular weight and the blood brain barrier. With the aim to overcome such drawbacks the use of combinatory approaches is further explored (Tron et al., 2018; Shang et al., 2020).

In order to circumvent apoptosis resistance of glioblastoma, inhibitor of apoptosis (IAP) proteins can also be targeted by small

molecule inhibitors resulting in enhanced sensitivity to radiation and TRAIL (Vellanki et al., 2009; Lincoln et al., 2018).

Regarding the death receptor-mediated pathways, gene expression of several members of the TNF receptor family as well as FAS and FADD but also caspase-8 and caspase-7 was found to be reduced in human glioblastoma tissue. Subsequently, DISC formation and initiation of apoptosis by both the death receptor and mitochondrial pathway are affected favoring resistance to apoptosis and different therapies (Blahovcova et al., 2015; Wang et al., 2017). As an approach to sensitize glioblastoma cells to TRAIL-induced cell death, lanatoside C has been shown to upregulate expression of TRAIL-R2 as well as to activate a necrosis-like and caspase-independent cell death pathway. Low doses of lanatoside C demonstrated significant anti-glioblastoma activity in cell culture and glioblastoma xenografts when combined with low doses of TRAIL (Badr et al., 2011). However, even if the expression of TRAIL-R1 and TRAIL-R2 is increased in glioblastoma cells, resistance to TRAIL-induced apoptosis can be caused by low levels of caspase-8 and FADD (Knight et al., 2001).

THE TUMOR MICROENVIRONMENT PROVOKES RESISTANCE

Advances in immunotherapies are promising approaches for an efficient management of glioblastoma. However, resistance

mechanisms to immunotherapy and poor understanding of the glioblastoma microenvironment are still a major drawback for the development of novel therapies (Razavi et al., 2016; Adhikaree et al., 2020).

The Immune System in the Brain

The idea of an immune privileged location of the brain is challenged by the facts that the CNS possesses a lymphatic vessel network, which can attract leukocytes to migrate from the cerebrospinal fluid to the cervical lymphatics and back. These leukocytes can traverse to the CNS even with an intact blood-brain barrier (Li et al., 2001; Razavi et al., 2016), which offers new perspectives for immunotherapy. Besides that, inflammation increases the permeability of the blood-brain barrier enabling the intrusion of circulating monocytes and lymphocytes into the brain (Sharifzad et al., 2019; Adhikaree et al., 2020). In particular, the blood-brain barrier is disrupted in glioblastoma, increasing the numbers of immune cells in the CNS (Amin et al., 2012) by compromised tight junctions and degradation of proteoglycans of the extracellular matrix by proteases (Schneider et al., 2004). Furthermore, glioblastoma is known as a highly vascularized tumor with vessels having a larger diameter. Pericytes, which normally surround endothelial cells, are sparse along these vessels, thereby expanding the leakiness of the blood-brain barrier (Miyauchi and Tsirka, 2018).

Professional antigen-presenting cells (APCs), like dendritic cells (DCs), can display exogenous tumor antigens on major histocompatibility complex class I (MHC I) or II molecules, priming CD8^{+} T cells (cytotoxic T lymphocytes, CTLs) or CD4^{+} T cells (T helper cells, Th), respectively. IFN-γ signaling is responsible for the upregulation of MHC I and MHC II molecules on target cells, allowing an increased ability to present antigenic peptides on MHC for T cell inspection and amplify an anti-tumor specific immune response by migrating into the brain parenchyma (Engelhardt and Ransohoff, 2012; Candeias and Gaipl, 2016). Contrastingly, reduced levels of MHC I molecules are found on glioblastoma cells, depending on the patient sample or cell lines investigated, which represents an immune evasion mechanism of glioblastoma cells (summarized in Burster et al., 2021).

The Tumor Microenvironment and Immune Evasion

The tumor microenvironment is surrounded by cytokines, chemokines, and growth factors to recruit immune cells to enable tumor growth and progression, seriously affecting the therapeutic cure (**Figure 3**). Examples for cells in this niche are B cells and T cells, such as T regulatory cells (Tregs), so-called tumor-infiltrating lymphocytes (TILs), tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and blood-brain barrier cells, which communicate by secreted mediators to facilitate cell growth, invasion, therapeutic resistance, and immune evasion (Ou et al., 2020).

Glioblastoma is characterized by the growth of new capillaries from existing blood vessels, containing hyperpermeable vessels with an enlarged diameter. The vasculature in solid tumors

ensures tumor growth and sufficient oxygen and nutrient supply (Weathers and de Groot, 2015; Ahir et al., 2020). The high vascularization is caused by the expression of angiogenetic factors, including VEGF, interleukin 6 (IL-6), IL-8, and transforming growth factor-β (TGF-β). Clinical studies demonstrated that the abundance of glioma-associated microglia/macrophages (GAMs) is higher in high-grade gliomas compared to low-grade gliomas (De et al., 2016). GAMs are polarized into an immunosuppressive state by TGF-β, periostin, versican, macrophage colony-stimulating factor (M-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Immunosuppressive mediators, such as IL-10 and B7-homolog 1 (B7-H1), are highly expressed in glioblastoma. Chemoattractants [*inter alia*, hepatocyte growth factor (HGF), TGF-β, and granulocyte-colony stimulating factor (G-CSF)] attract different cell populations to the tumor microenvironment and lead from a decreased pro-inflammatory to an amplified anti-inflammatory state (Hanahan and Weinberg, 2011; De et al., 2016). Macrophages and microglia are able to switch between two distinctive phenotypes, the M1 pro-inflammatory and the M2 cytoprotective and immunosuppressive subpopulation, contributing to tumor cell proliferation, migration, and invasion. M2 are subdivided to M2a, M2b, and M2c due to the functional activation state. Of these, the M2c subset is dominant in gliomas (Gabrusiewicz et al., 2016). M2 macrophages produce immunosuppressive cytokines (TGF-β and IL-10), activating M2c (Gieryng et al., 2017), and are well-known to regulate T cell function (Wu et al., 2010). GAMs are recruited to the tumor site and being polarized into the M2 phenotype by different mediators, for instance, M-CSF and GM-CSF (Pyonteck et al., 2013). In addition, TGF-β isoform 1 and 2, prostaglandin E2, and the extracellular matrix protein periostin are involved in M2 polarization (Strepkos et al., 2020). Accordingly, TGF-β2 stimulates the synthesis of the proteoglycan versican by glioblastoma cells, which promotes GAM-induced inflammatory cytokine production to enhance glioma invasion (Arslan et al., 2007; Strepkos et al., 2020). GSCs also secrete factors to polarize GAMs to M2 and impede phagocytosis of M1 (Wu et al., 2010). Accordingly, targeting the interaction of cytotoxic and apoptotic effects of M2 receptor activation, several preclinical and phase I studies are currently on the way to promote GAM M1-like polarization or alter the microglia polarization, including emactuzumab, plerixafor, and maraviroc (Di Bari et al., 2015; Mercurio et al., 2016; Laudati et al., 2017). Nevertheless, the sophisticated crosstalk of tumor microenvironment and tumor heterogeneity of glioblastoma significantly contribute to therapy resistance (Strepkos et al., 2020).

The heterogenous population of immune cells from the myeloid lineage, MDSCs, are important for tumor survival within the tumor microenvironment. The amount of these cells is higher in the glioblastoma tumor microenvironment and suppress cytotoxic NK cell, CD4^{+}- and CD8^{+} T cell function (Marvel and Gabrilovich, 2015; Gieryng et al., 2017). Two subsets of MDSCs exist: Polymorphonuclear- and mononuclear-MDSCs. Both use different mechanisms to suppress CD8^{+} T cells. Polymorphonuclear-MDSCs, predominantly found in glioblastoma, produce high levels of reactive oxygen species,

FIGURE 3 | Glioblastoma and the tumor microenvironment. A summary of main components of the tumor microenvironment in glioblastoma.
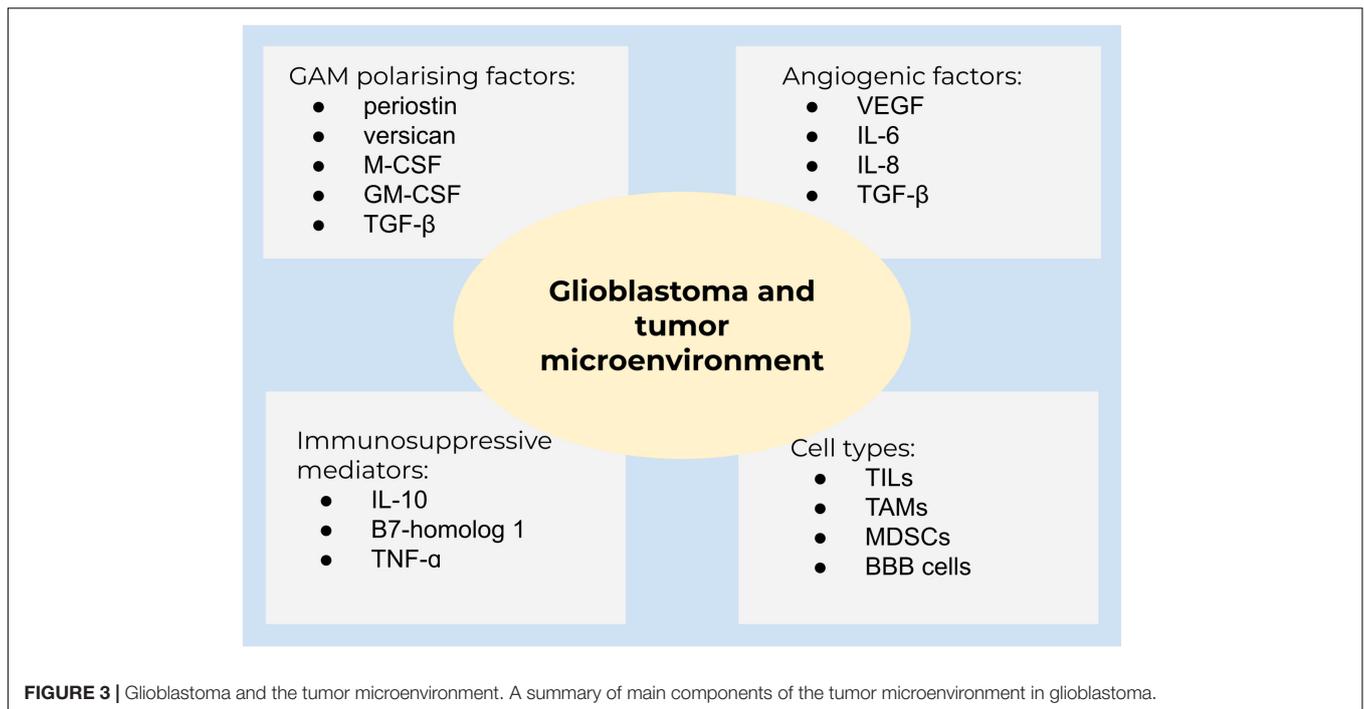
cross-talk with Tregs, and secret immunosuppressive cytokines. Mononuclear-MDSCs express, for instance, nitric oxide synthase 2 and arginase (ARG1), which inhibit T cell proliferation and further promote T cell apoptosis (Marvel and Gabrilovich, 2015; Gieryng et al., 2017).

NK cells are important for killing cancer cells (Gieryng et al., 2017). However, NK cells are found to be impaired in the glioblastoma tumor microenvironment since these cells express a limited amount of MHC I molecules, binding to inhibitory NK cell receptors, and quench NK cell activation (Wiendl et al., 2002; Gieryng et al., 2017; Burster et al., 2021). The inhibitory receptors are isoforms of the killer-cell Ig-like receptors (KIR) and Ig-like transcript/leukocyte Ig-like receptors (ILT/LIR). Moreover, TGF-β1 downregulated the expression of activating NK cell receptors, e.g., NKG2D and NKp30, thus inhibiting NK cell function (Castriconi et al., 2003). Additionally, TGF-β represses the mammalian target of the rapamycin (mTOR) pathway, which in turn reduces the proliferation and metabolic activity of NK cells (Viel et al., 2016).

Recruitment of non-neoplastic cells to the tumor microenvironment is implemented by glioblastoma. GAMs and glioblastoma cells express hepatocyte growth factor/scatter factor (HGF/SF), which binds to c-Met tyrosine kinase and promotes proliferation and invasion of glioblastoma cells (Kunkel et al., 2001). Monocyte chemotactic protein 1 (MCP-1 also named CCL2) and 3 are responsible for cell migration, for example, the binding of MCP-1 to CCR2 direct immune cells to infiltrate the tissue (Strepkos et al., 2020). This is in contrast to microglia which are attracted by a glial-derived neurotrophic factor (GDNF) expressed by neurons and glial cells (Ku et al., 2013).

Immune evasion by glioblastoma cells is achieved via immune checkpoint molecules. The programmed death-ligand 1 (PD-L1), an immune checkpoint molecule, is expressed on APCs, NK cells, parenchymal cells, and glioblastoma cells (Huang et al., 2017). After binding of PD-L1 to the PD-1 receptor, which is expressed on activated T cells, PD-L1-PD-1 receptor complex provokes T cell anergy or apoptosis (Razavi et al., 2016; Huang et al., 2017). Additional immune checkpoint molecules include cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), T cell Ig, and mucin domain 3 (TIM-3) (Razavi et al., 2016). Furthermore, the immunomodulatory mechanism in glioblastoma is achieved through indolamine 2,3-dioxygenase 1, which is a cytosolic enzyme, inhibits T effector function and supports Treg expansion and activation, hence contributing to suppressing an immune response (Adhikaree et al., 2020).

IMMUNOTHERAPY AND LIMITATION IN GLIOBLASTOMA

Immunotherapy is based on the concept that the immune system is capable of recognizing and destroying tumor cells. However, the success of immunotherapy remains challenging since tumor cells developed various pathways to avoid being detected by the immune system, leading to low therapeutic efficiency. Glioblastoma adapted a high resistance and only a few patients respond to certain immunotherapies (Jackson et al., 2019).

Antibody Drug Conjugates (ADCs)
EGFR gene amplification and mutations in the EGFR variant III (EGFRvIII) gene (Malkki, 2016; van den Bent et al., 2017) can be utilized for glioblastoma therapy by using antibody drug

conjugates (ADCs). ADCs are monoclonal antibodies linked to different cytotoxic drug components (van den Bent et al., 2017). ADCs are designed to bind to tumor-specific antigens, which are internalized through receptor-mediated endocytosis. During this process, the cytotoxic components are released from the antibody due to the low pH environment of the endocytic compartment. While the receptor is recycled back to the cell surface, the delivered cytotoxic components induce apoptosis in tumor cells. One cavity of application is the fact that ADCs might be extracellularly released because of the proteolytic labile linker or ADCs are recycled back to the cell surface without delivering the cytotoxic component, leading to a reduced drug concentration in the cell (Polson et al., 2009; Peters and Brown, 2015; Scotti et al., 2015). The recycling mechanism of ADCs is caused by the high affinity of ADCs to neonatal Fc receptors (FcRns) within early endosomes that reach the cell surface recurrently, where ADCs are released from the FcRn under physiological pH. Notably, the FcRn is predominantly expressed in the endosomes of endothelial cells (Peters and Brown, 2015).

The ADCs are often DNA alkylating agents, inhibitors of tubulin polymerization, or enediyne antibiotics which lead to DNA double-strand breaks (Scotti et al., 2015). Limitations of ADC application is indicated by the restriction of available specific tumor-associated antigens (TAA), downregulation of TAAs, and the transport of ADCs to the brain (Phillips et al., 2016; Miyauchi and Tsirka, 2018). On the other hand, previous studies acknowledged the possible uptake of ADCs in patients by disrupted blood-brain barrier (Phillips et al., 2016). Of note, distinct glioblastoma patients have a relatively low mutational burden compared to non-small cell lung cancer, minimizing the amount of potential TAAs (Miyauchi and Tsirka, 2018). Lack of blood-brain barrier penetration, tumor heterogeneity, and resistance to the cytotoxic agent impede therapy success (Gieryng et al., 2017). Although a successful uptake of ADCs through the blood-brain barrier of low-grade gliomas with little disrupted blood-brain barrier compared to high-grade gliomas could undermine complete penetration due to the size of ADCs. High-grade gliomas exhibit augmented microvascular permeability, allowing penetration of larger molecules (Roberts et al., 2000; Schneider et al., 2004). Certainly, a specific antigen for targeting glioblastoma is needed; however, tumor heterogeneity or reduced levels of antigens are one of several reasons for therapy resistance (Gan et al., 2017). An additional limitation of this approach is an acquired resistance to the cytotoxic agent of ADC, namely active efflux of the internalized drug is possible through transporters of the adenosine triphosphate-binding cassette family (Scotti et al., 2015).

Immune Checkpoint and Chemokine Inhibitors

Monoclonal antibodies, known as nivolumab, pembrolizumab, ipilimumab, and atezolizumab, are widely used in cancer treatment by interrupting checkpoint signaling pathways and leading to an immune-mediated elimination of tumor cells (Juszczak et al., 2012; Darvin et al., 2018). While the patients benefit from prolonged OS, distinct immune-related

adverse reactions exist, including pneumonitis or lymphocytic hypophysitis (an inflammation of the pituitary gland). The use of monoclonal antibodies are limited and not suitable for patients which suffer from autoimmunity because immune checkpoints in general act as barriers against autoimmune disorders (Juszczak et al., 2012). Approved immune checkpoint inhibitors are presently tested for primary and recurrent brain malignancies. The administration of nivolumab (anti-PD-1 monoclonal antibody) caused mild side effects, whereas nivolumab in combination with ipilimumab initiated severe (grade 3 and 4) adverse effects in 80% of the treated patients. Notably, 50% discontinued the medication due to intolerability. The 6-months OS rate for nivolumab was 75, 80% for the combination therapy. Currently, nivolumab in combination with bevacizumab is being tested in a phase III clinical trial (NCT02017717) (Sampson et al., 2015). Despite encouraging results in OS, only a limited number of patients benefit from monoclonal antibodies, as many tumors downregulate T cell activity or prevent T cells from infiltrating the tissue, indicating an urgent need for better predictive biomarkers (Darvin et al., 2018).

Chemokines are highly expressed in the tumor microenvironment and support tumor progression; therefore, blocking of chemokine receptors is a promising approach (Laudati et al., 2017). In a preclinical study, maraviroc, a CCR5 receptor blocker, polarized microglia toward the cytotoxic M1 phenotype by reducing the gene expression of ARG1 and IL-10, which are two M2 macrophage markers. Additionally, M1 markers are upregulated by inhibition of the mTOR pathway. The treatment with maraviroc, a small molecule CCR5 antagonist (Carter and Keating, 2007), led to a reduction of microglia migration (Laudati et al., 2017). Plerixafor, another small molecule CXCR4 antagonist, binds to the three acidic residues of the CXCR4 ligand-binding pocket (Fricker, 2008) and impairs the proliferation of glioma cells by inhibiting the invasion of CXCR4/CXCR7-expressing GSCs in vitro (Mercurio et al., 2016; Hira et al., 2017). Plerixafor, on the other hand, is not highly specific for CXCR4 as Plerixafor might bind to the receptor of CXCL12, CXCR4, and CXCR7. As a result, cardiotoxicity is one of the adverse reactions. Interestingly, a novel CXCR4 antagonist, Peptide R [Arg-Ala-(Cys-Arg-Phe-Phe-Cys), with the square brackets indicating cyclization via a disulfide bridge], reduced toxicity in mice (Portella et al., 2013; Mercurio et al., 2016).

Targeting STAT3, which is involved in maintaining an immunosuppressive environment in glioblastoma and is consistently activated in a variety of tumors, is an alternative therapeutic strategy for glioblastoma (See et al., 2012). The STAT3 inhibitor WP1066, also a small molecule, polarizes GAMs to a M1 cytotoxic phenotype and can block glioma growth in vivo (Hussain et al., 2007). A major challenge occurs with differences in the immune system between humans and animals; therefore, further clinical studies are needed to determine the benefits for patients (Horuk, 2009). Furthermore, long-term application of chemokine receptor inhibitors, e.g., CXCR4, is needed since considerable disadvantageous adverse reactions could occur in healthy tissue (Wang et al., 2016). Functional inhibition of CXCR4 can also cause stem cell mobilization,

causing leukocytosis, thrombocytopenia, or spleen rupture when administered in a long-term manner (Wang et al., 2016; Kwon et al., 2019).

Chimeric Antigen Receptor (CAR) T Cell Therapy

The function of CD8$^+$ T cells is largely inhibited by the tumor and the surrounding tumor microenvironment. A promising approach is the use of CD8$^+$ T cells to eliminate tumor cells by a so-called chimeric antigen receptor (CAR) T cell therapy. T cells are taken from a patient and transduced with a lentiviral vector to express a modified T cell receptor specifically recognizing TAAs. CAR-T cells are a complex of an Ig molecule and the T cell receptor. After *ex vivo* cell culture and stimulation, CAR-T cells are transferred back to the patient in order to eliminate tumor cells (Salinas et al., 2020). The advantage of CAR-T cells is that they are not dependent on MHC, as MHC expression is often downregulated in glioblastoma to hinder T cell activation (Fousek and Ahmed, 2015; Miyauchi and Tsirka, 2018). In a phase I study, recurrent glioblastoma and refractory glioblastoma were treated with CAR-T cells that have a high affinity to TAA interleukin-13 receptor α 2 (IL-13Rα2), which is overexpressed in recurrent glioblastoma. CAR-T cells were introduced into the tumor resection cavity, followed by infusions into the ventricular system of the brain. After administration the disease remission was sustained for 7.5 months with augmented levels of cytokines in one patient. It was suggested that recurrence occurs by decreased expression of IL-13R α2 (Brown et al., 2016; Dunn-Pirio and Vlahovic, 2017). One of the most severe complications in CAR-T cell treatment is cytokine release syndrome since inflammatory cytokines and chemokines are released, leading to nausea, headaches, tachycardia, hypotension, rashes, shortness of breath, and even multiorgan failure. Reversing the cytokine release syndrome with corticosteroids and anti-cytokine therapy is possible (Dunn-Pirio and Vlahovic, 2017). An alternative approach is the use of engineered CAR-NK cells to attack glioblastoma cells. However, CAR-NK cells demonstrated a minimal and unreliable response after application of NK cell lines. Primary NK cells from umbilical cord blood (UCB) could overcome this cavity and stimulation with IL-2 and IL-15 or UCB-derived NK cells expressing the TGF-β- dominant-negative receptor II, consuming TGF-β of the tumor microenvironment of glioblastoma is of interest (Burster et al., 2021).

Vaccination to Induce Immune Responses Against Glioblastoma

A different study followed the idea of tumor vaccination to induce immune responses against specific antigens, peptides, DNA or mRNA-based (with or without vector) components. Vaccination could be used to target highly immunogenic TAAs or tumor-specific antigens to trigger a specific immune response. In this regard, glioblastoma care is challenging since tumor mutational load (burden) is rather low compared to other cancer types and glioblastoma patients have high variations of mutations. The tumor mutational burden correlates with the abundance of neoantigens, which can be potential biomarkers for immunotherapy (Hodges et al., 2017; Wang L. et al., 2020).

Rindopepimut—a peptide vaccine—targets EGFRvIII, which was administrated in combination with TMZ, displayed an improvement in early clinical trials, but did not reach the criteria for therapeutic efficacy in phase III (NCT01480479) (Malkki, 2016). The reappearance of the wildtype EGFR in recurrent glioblastoma precludes further treatment with Rindopepimut targeting EGFRvIII (Schuster et al., 2015). This mechanism is one immune evasion strategy by glioblastoma, which could be overcome by the use of vaccines directing homogenously expressed markers to tackle tumor cells, such as transformed IDH, targeting a broader range of TAAs (Phuphanich et al., 2013). For instance, a vaccine (IMA 950) directed 11 different human peptides (brevican; chondroitin sulfate proteoglycan 4; fatty acid binding protein 7; hepatitis B virus core antigen; insulin-like growth factor 2 messenger RNA-binding protein 3; neuronal cell adhesion molecule; protein tyrosine phosphatase, receptor-type, Z polypeptide 1; tenascin C; baculoviral inhibitor of apoptosis protein repeat-containing 5; Met proto-oncogene; neuroligin 4 X-linked). Of these, the first nine were previously identified on MHC I (human leukocyte antigen A*02, HLA-A*02), the other two are MHC II peptides derived from primary glioblastoma (Halford et al., 2014; Rampling et al., 2016). IMA 950 combined with poly-ICLC, a vaccine adjuvant enhancing innate and adaptive immune responses, revealed both CD4$^+$ T cell and CD8$^+$ T cell activation; with a median OS of 19 months (NCT01920191) (Migliorini et al., 2019). Peptide vaccines are specific for the respective tumor cells; however, peptide vaccines may only work for a small group of patients and might lead to immune evasion (Schneble et al., 2016). Targeting homogenously expressed targets or multi-peptide vaccines could interfere with immune evasion of tumor cells. Moreover, vaccination for glioblastoma management fail to sufficiently stimulate the immune system to achieve a clinical benefit, further approaches, e.g., combinational therapy, should be considered (Schneble et al., 2016; Lim et al., 2018).

In general, DC-based vaccines are generated by exposing DCs isolated from patients to the respective antigens and thereby educate DCs to maintain an adaptive immune response (Phuphanich et al., 2013). More precisely, DC-based vaccine ICT-07 targets six glioblastoma markers. Three of the six glioblastoma markers are human epidermal growth factor receptor 2 (HER2/neu), tyrosine-related protein 2, and absent in melanoma 2 which are also overexpressed in cancer stem-like cells (Phuphanich et al., 2013; Wen et al., 2019). Therefore, ICT-07 is thought to improve PFS and reduce the number of GSCs. Newly diagnosed glioblastoma patients had an increased OS and significantly extended PFS by 2.2 months in phase II. The vaccine was well tolerated with only a mild negative impact (due to insufficient financial resources, the phase III study is currently suspended, NCT02546102) (Phuphanich et al., 2013; Wen et al., 2019). Furthermore, a DC-based vaccine (DCVax®-L), where DCs are pulsed with tumor cell lysate and injected into the patient, is used for medication of newly diagnosed glioblastoma (NCT00045968). Phase I/II clinical trials determined the safety of the vaccine (Liau et al., 2018). 33% of patients with glioblastoma

had a median OS of 48 months, 27% even achieved a median OS of 72 months in the long-term survival analysis, encouraging the use of DCVax®-L for glioblastoma therapy in the future (Dunn-Pirio and Vlahovic, 2017). Nevertheless, developing vaccines for individual neoantigens of patients is expensive and time-consuming because preparation of vaccines from the tumor samples take between 3–5 months (Peng et al., 2019). An additional limitation is the generation of sufficient DCs, as DCs comprise only < 1% of peripheral blood mononuclear cells. To overcome this obstacle, DCs were generated from monocytes *ex vivo*. However, it is questionable whether these monocyte-derived DCs compared to primary DCs from peripheral blood are efficient in an anti-tumor immune response (Huber et al., 2018). Furthermore, phagocytosis of tumor cells by APCs was enhanced by blocking the anti-phagocytosis molecule CD47 in combination with TMZ, inducing an effective anti-tumor immune response (von Roemeling et al., 2020). However, the use of whole tumor lysate to pulse DCs could cause autoimmune encephalitis since tumor lysate contains healthy brain tissue and induces an immune response toward the normal brain (Polyzoidis and Ashkan, 2014).

Moreover, a highly promising approach for cancer immunotherapy, denotes mRNA vaccine, which express tumor-specific antigens or TAA in APCs, has become into focus to treat glioblastoma. mRNA does not pose the risk of an infectious or an integrating agent, the potential of mRNA vaccines is the effectiveness, safety in administration, and low cost of manufacturing (Pardi et al., 2018; Weng et al., 2020). A phase I study utilizing DCs, loaded with TAA mRNA targeting cytomegalovirus pp65 protein that is expressed in > 90% of glioblastoma cases, demonstrated an OS of 35 months. As a consequence, co-delivery of mRNA vaccines together with immunotherapeutics can increase the host anti-tumor immune response (Batich et al., 2020; Miao et al., 2021). Notwithstanding the expected advantages, several factors limit the use of mRNA in therapy, including immunosuppressive effects of the tumor, half-life period of mRNA, and delivery complications *in vivo* (Vik-Mo et al., 2013; Weng et al., 2020). To overcome such issues, the chemical nucleotide modifications, capping analogs, and alternative delivery are currently being investigated and hold a great promise with current successful use of lipid nanoparticles to deliver mRNA vaccines (Weng et al., 2020; Rui and Green, 2021) or the use of viral vectors (Weng et al., 2020) and is therefore anticipated to increase the attention in glioblastoma immunotherapy.

Heat Shock Protein (HSP) Vaccines

The exposure of environmental stress to cells leads to the production of HSPs. While HSPs act as chaperones, stabilizing protein conformation, and preventing protein aggregation, HSPs might also force misfolded proteins for degradation. Interestingly, a correlation between cancer and high levels of HSPs was determined, possibly by the excess of misfolded proteins found within the tumor (Ampie et al., 2015). On the one hand, gliomas overexpress HSP70 and HSP90 to prevent stress-induced apoptosis; on the other hand, HSPs have the ability to bind TAAs to elicit an immune response, making

HSPs an interesting protein for immunotherapy (Ampie et al., 2015). The binding of HSPs to antigens can encounter the cell surface receptor CD91 of APCs in order to stimulate endocytosis and cross-present antigens to CD8$^+$ T cells (Ampie et al., 2015). Although the application of an autologous HSP96-based vaccine (gp96-associated cellular peptides non-covalently bound to HSP96, HSPPC-96) in patients with recurrent glioblastoma are promising, this strategy is limited since the peptide pool is generated from the patient's tumor and the amount of vaccine depends on the tumor size (Crane et al., 2013). Anti-inflammatory cytokines, such as IL-10 and TGF-β, segregated by the tumor microenvironment may also interfere with gp-96 vaccines and limits current clinical trials (Ampie et al., 2015; Li et al., 2020). Additionally, surgical resection is not always possible, the biopsy needs to be taken from glioblastoma patients to generate the vaccine, indicating the possibility of tumor progression (Bloch et al., 2014).

ONCOLYTIC VIRUSES IN IMMUNOTHERAPY

Myeloid cells are often activated by an oncolytic viral infection, which promotes an inflamed microenvironment by infiltration of T cells into the tumor. Therefore, oncolytic virotherapy is thought to be useful for overcoming the immunosuppressive environment in glioblastoma (Mogensen, 2009; Lim et al., 2018). Current oncolytic viral treatment applies replication-competent viruses rather than replication-incompetent viruses, explicitly adeno- and retroviruses, herpes simplex viruses, or measles- and polioviruses. Replication-competent viruses have the advantage of overcoming low transduction efficiency and vector loss. These viruses are genetically engineered to selectively infect and lyse cancer cells but the surrounding brain parenchyma is spared (Dunn-Pirio and Vlahovic, 2017; Foreman et al., 2017; Lim et al., 2018).

Oncolytic poliovirus originates from the oral poliovirus Sabin type I, which was genetically modified to replace its internal ribosome entry site with a human rhinovirus type 2 to eliminate neurovirulence. Oncolytic poliovirus infects cells expressing the poliovirus receptor (CD155), an oncofetal cell adhesion molecule, which is also expressed in glioblastoma, and subsequently in an immunogenic clearance of cancer cells (Desjardins et al., 2016; Mehta et al., 2017). Contrastingly, side effects of the viral treatment include cerebral edema as a result of a local inflammatory response and also known as pseudoprogression. Pseudoprogression is common in solid cancers after immunotherapy. In the case of brain malignancies, differentiation is difficult between pseudoprogression and tumor progression based on the neuroimages (Payer, 2011).

The replication-incompetent adenovirus is a tumoricidal gene vector. Aglatimagene besadenovec (AdV-tk) provokes the expression of the HSV-TK gene, which allows the conversion of prodrug ganciclovir or valacyclovir into a toxic nucleotide analog. This nucleotide analog kills replicating tumor cells by damaging the DNA and is also known as gene-mediated cytotoxic immunotherapy (Lim et al., 2018; Miyauchi and Tsirka, 2018).

Two phase II clinical trials (BrTK02 and HGG-01) administered the virus intratumorally (BrTK02) or by intra-arterial cerebral infusion (HGG-01). Common detrimental effects were mostly fatigue, fever, and headaches (NCT00589875 for BrTK02 and NCT00870181 for HGG-01) (Chiocca et al., 2011; Ji et al., 2016; Wheeler et al., 2016). Nevertheless, non-replicating adenoviruses indicate limited distribution and low transduction efficiency of the vector (Ji et al., 2016). Furthermore, only a small amount of the injected adenovirus reaches the tumor due to elimination of the virus through the liver or by inactivation via binding to blood cells, complement, or to neutralizing antibodies, limiting further the successful application (Gao et al., 2014). The immune response represents an important factor for the efficiency of the drug. On the one hand, immune response limits the efficacy of oncolytic viruses, on the other hand, an anti-tumor immune response is crucial to fight against tumor cells.

COMBINATION THERAPIES ARE MORE EFFECTIVE IN TREATMENT OF GLIOBLASTOMA

Despite the expected potential of immunotherapy to treat glioblastoma, many monotherapy trials failed to reach sufficient efficiency. Besides the use of standard care of radiation/chemotherapy, combination therapies provide further enhancement in disease management (Dunn-Pirio and Vlahovic, 2017).

Adaptive resistance of tumor cells is an important factor contributing to the failure of monotherapy. Based on the nature of self-tolerance of the immune system, cancer cells can upregulate various immune checkpoint pathways to disturb the immune response (Medikonda et al., 2021). Notwithstanding that the use of monoclonal antibodies against these pathways might prevent inhibition of the immune response, phase II/III clinical studies targeting a single immune checkpoint pathway failed to be beneficial for glioblastoma patients (Majc et al., 2021; Medikonda et al., 2021). It is possible that immune checkpoint monotherapy forces PD-1-blockade resistance and upregulation of alternative immune checkpoint molecules, for instance, TIM-3 in a lung adenocarcinoma model (Koyama et al., 2016) may occur. While concurrent administration of anti-PD-1 and anti-TIM-3 antibodies improved preclinical glioblastoma, therapies with both antibodies and stereotactic radiosurgery resulted in 100% OS (Kim et al., 2017) and anti-PD-1 led to an enhanced vaccination-induced immune response (Antonios et al., 2016). Optimal timing of administration is important and concomitant treatment marks an optimal disease management (Lesterhuis et al., 2013). Other benefits of combining immune checkpoint inhibitors with standard care therapies or control of immune checkpoints, increase $CD8^+$ T cell activity and decrease the infiltration of Treg cells (Huang et al., 2017). Bevacizumab in combination with common care (radio- and chemotherapy) remain below the expectation for immunotherapy since preclinical studies defined that high doses of TMZ lower the anti-PD-1 related immune response. Furthermore, the impact of che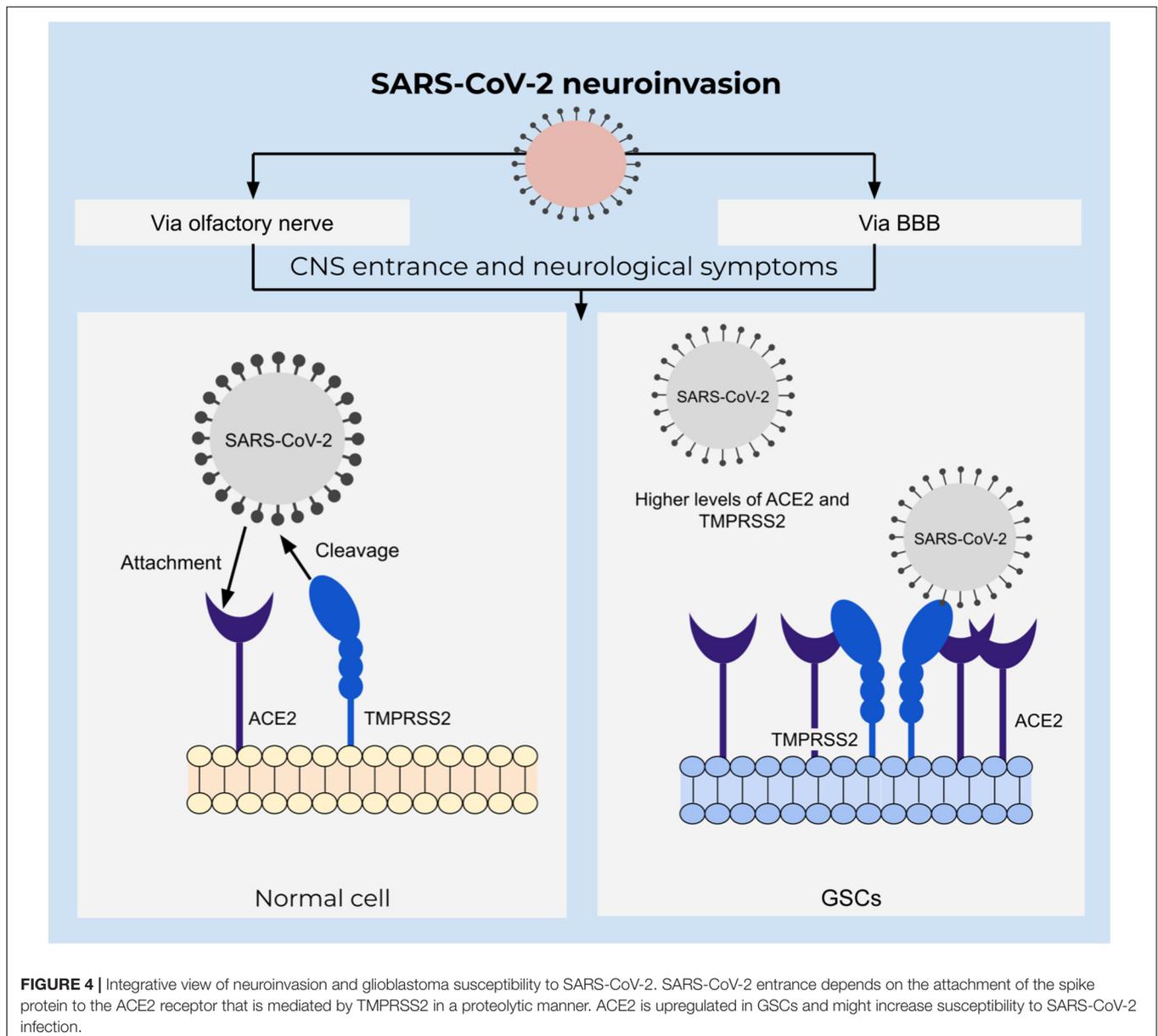motherapy to immunity is critical, for instance, it was not feasible to induce an antitumor response in mice treated with systemic chemotherapy when enabling a tumor re-challenge (Mathios et al., 2016; Lim et al., 2018).

Similarly, a combinatorial approach of different immunotherapies, including vaccines, immune checkpoint inhibitors, and effector lymphocytes, was verified for efficacy in glioblastoma treatment (Weenink et al., 2020). A recent study of CAR-T cell therapy combined with immune checkpoint blockade exhibited an enhanced tumor suppression effect compared to a single CAR-T construct in murine and canine models (Yin et al., 2018). Currently, clinical trials assessing the safety of CAR-T cells in combination with monoclonal antibodies (pembrolizumab, ipilimumab, and nivolumab; NCT03726515 and NCT04003649) are on the way. A different clinical trial, comprising neoantigen vaccination, indicated a systemic immune response and expression of multiple inhibitory checkpoints by infiltrating vaccine specific T cells, which was limited to individuals not receiving dexamethasone, suggesting a potential for combination of neoantigen vaccines with immune checkpoint inhibitors (Keskin et al., 2019). Nevertheless, severe side effects caused by the combination of nivolumab and ipilimumab (anti-CTLA-4) requires careful consideration of the possibility of disadvantageous reactions by combining different immunotherapies (Sampson et al., 2015).

FURTHER COMPLICATIONS IN GLIOBLASTOMA

The 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak has brought its own significant obstacles to the care of patients suffering from glioblastoma. The pandemic disturbed the healthcare system leading to high hospital resource loads, risk of lack of treatment, and exposure to viral infection. Systemic immunosuppressive effects of standard anticancer medication, such as surgery and combined radio- and chemotherapy is a particular concern for glioblastoma patients. These patients are at a higher risk of infection and consequent complications (Amoo et al., 2020; Bernhardt et al., 2020; Noticewala et al., 2020).

SARS-CoV-2 belongs to a family of coronaviruses that are known as respiratory system pathogens, using their spike protein to bind cell surface receptors. In the case of SARS-CoV-2, this is mainly angiotensin-converting enzyme 2 (ACE2), which is a metallocarboxypeptidase present on surfaces of respiratory tract epithelial cells (Letko et al., 2020). Viral entrance is mediated by the serine protease transmembrane protease serine subtype 2 (TMPRSS2) that hydrolyze and prime the spike protein or alternatively via cathepsin B and cathepsin L in early endosomes (Wu et al., 2020). High abundance of ACE2 and TMPRSS2 in respiratory epithelial tissues explain the pathogenesis; however, expression of ACE2 is not limited to respiratory tract tissues, but is also found on brain cells (**Figure 4**). Moreover, an increasing number of obtained data on SARS-CoV-2 pathology indicate the presence of various neurological symptoms, such as fatigue, headaches, as well as smell- and taste impairments among more than a third of all the infected individuals (Mao et al., 2020). Cases

FIGURE 4 | Integrative view of neuroinvasion and glioblastoma susceptibility to SARS-CoV-2. SARS-CoV-2 entrance depends on the attachment of the spike protein to the ACE2 receptor that is mediated by TMPRSS in a proteolytic manner. ACE2 is upregulated in GSCs and might increase susceptibility to SARS-CoV-2 infection.

of acute cerebrovascular disease with impaired consciousness suggests neural invasion of the virus (Conde Cardona et al., 2020; Mao et al., 2020). Several studies have identified the presence of the viral RNA in the central nervous system (Puelles et al., 2020; Meinhardt et al., 2021) as well as brain damage evidenced by neuroimaging studies (Coolen et al., 2020).

Accompanied by an increased vascular permeability caused by active chemokine secretion upon the viral infection, CNS becomes particularly susceptible to viral invasion (McGavern and Kang, 2011; Letko et al., 2020). An alternative route of CNS invasion was identified via the olfactory bulb and peripheral neurons, which was outlined to be the dominant pathway of entrance by the virus in transgenic mice (Wu et al., 2020; Song et al., 2021). Neurotropism and neural invasion of SARS-CoV-2 are defined by single cell transcriptome sequencing

analysis of glioblastoma tissue (Wu et al., 2020). Moreover, an analysis of both U-87 and U-373 glioblastoma cell lines defined a susceptibility to infection and resistance to apoptosis. Additionally, these cells express ACE2, TMPRSS2, cathepsin B as well as cathepsin L which is important for entrance of SARS-CoV-2 to the target cell (Bielarz et al., 2021). An abundance of ACE2 receptors in glioblastoma tissue suggests glioblastoma patients to be at a particularly high risk of acquiring infection (Wu et al., 2020).

Preliminary findings from experimental studies on cancer patients prompt an involvement of tumor markers as additional sites for SARS-CoV-2 entry. One of the promising candidates is CD147 (also termed basigin) that was found to be overexpressed in glioblastoma tissue and positively correlated with the viral invasion. CD147 is involved in the assessment of T cells

engineered to express CAR specific for CD147 (CD147-CART) treatment in an anticancer therapy under the phase I trial in patients with recurrent glioblastoma (NCT04045847) (Landras et al., 2019; Wang K. et al., 2020; Xia and Dubrovska, 2020). Despite the findings that CD147 is used for the entrance of SARS-CoV-2 to the target cell, these data are currently challenged (Shilts et al., 2021). While innovative insights have to be considered during the pandemic, tumor heterogeneity and immunosuppressive state are important in the development of more potent therapeutic applications for glioblastoma patients.

CONCLUSION

In recent years, the debate of using immunotherapy in glioblastoma care has continuously been raised. The application of ADCs, peptides or mRNA vaccines, CAR-T cells and CAR-NK T cells, checkpoint and chemokine inhibitors, or oncolytic viruses are hopeful treatment constituents. Notwithstanding these encouraging strategies, only a few patients respond to immunotherapy, indicating the improvement of therapies or co-delivery of multiple immunotherapeutics to be successful in the management of glioblastoma. The complications can be attributed to immonoresistance mechanisms and the complex heterogenous nature of the tumor. Understanding the pathophysiological features of glioblastoma provides an emergence of different immunotherapy strategies, including the focus on a combination of medications and personalized approaches to sensitize glioblastoma to immunotherapies and improve the treatment outcome.

AUTHOR CONTRIBUTIONS

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