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Review

The complex relationship between integrins and oncolytic herpes Simplex Virus 1 in high-grade glioma therapeutics

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High-grade gliomas (HGGs) are lethal central nervous system tumors that spread quickly through the brain, making treatment challenging. Integrins are transmembrane receptors that mediate cell-extracellular matrix (ECM) interactions, cellular adhesion, migration, growth, and survival. Their upregulation and inverse correlation in HGG malignancy make targeting integrins a viable therapeutic option. Integrins also play a role in herpes simplex virus 1 (HSV-1) entry. Oncolytic HSV-1 (oHSV) is the most clinically advanced oncolytic virotherapy, showing a superior safety and efficacy profile over standard cancer treatment of solid cancers, including HGG. With the FDA-approval of oHSV for melanoma and the recent conditional approval of oHSV for malignant glioma in Japan, usage of oHSV for HGG has become of great interest. In this review, we provide a systematic overview of the role of integrins in relation to oHSV, with a special focus on its therapeutic potential against HGG. We discuss the pros and cons of targeting integrins during oHSV therapy: while integrins play a pro-therapeutic role by acting as a gateway for oHSV entry, they also mediate the innate antiviral immune responses that hinder oHSV therapeutic efficacy. We further discuss alternative strategies to regulate the dual functionality of integrins in the context of oHSV therapy.

INTRODUCTION

Integrins are heterodimeric transmembrane receptors and cell adhesion molecules that mediate cell-cell and cell-extracellular matrix (ECM) interactions and are involved in intracellular signaling activation. Integrins are made up of two non-covalently linked subunits, α and β, which consist of an extracellular, intramembrane, and cytoplasmic domain.[1] Currently, 18 α and 8 β subunits have been identified, with the β1 integrin subgroup being the largest, and each subunit combination confers distinct ligand selectivity, binding affinity, and function. While the integrin extracellular domain binds to ECM proteins such as collagen, fibronectin, laminin, and others, the intracellular domain anchors the integrin using actin polymers in order to regulate cell adhesion to the ECM. The latter process relies on associated intracellular proteins (i.e., talin and kindlin), which serve to mediate integrin-induced inside-out signaling by promoting structural changes between the α and β subunits toward an open or active conformation and which enhances interaction with the ECM.[2] Upon binding to ECM ligands, outside-in signaling occurs downstream of integrins through the activation of kinases, such as focal adhesion kinase (FAK) and integrin-linked kinase (ILK), leading to sustained survival, proliferation, differentiation, angiogenesis, and epithelial-to-mesenchymal transition (EMT).[3] With these tumorigenic functions, it is not surprising that integrins are at the core of many solid tumors.[4]

Integrins also mediate viral entry into host cells, and this triggers the expression of a cascade of antiviral genes, particularly in response to FAK and interferon-mediated STAT1 activation.[5,6] In the context of oncolytic virus (OV) therapy against solid tumors, such as melanoma[7] and glioblastoma,[8] the activation of integrins and ensuing downstream antiviral immune response reduce therapeutic efficacy. Efforts have been made to balance the multimodal role of integrins in OV therapy in order to reduce antiviral immunity and yet maintain virus permissiveness; however, these approaches can result in off-target effects and are not always effective. In this review, we focus on the role of integrins in high-grade glioma (HGG) progression, therapeutic resistance, and engagement with oncolytic herpes simplex virus 1 (oHSV) and discuss the implications of integrin targeting in oHSV-mediated therapy for HGG.

INTEGRINS IN HGG AND THE HGG TUMOR MICROENVIRONMENT

Integrins can be found on tumor cells themselves as well as on cells within the tumor microenvironment (TME). This holds true for HGGs (Figure 1), which comprise grade III and IV brain tumors as categorized by the World Health Organization (WHO). Grade III gliomas include anaplastic astrocytomas and oligodendrogliomas, while grade IV gliomas are glioblastomas (GBM), the most commonly diagnosed primary, malignant, and aggressive brain tumor. In the case of

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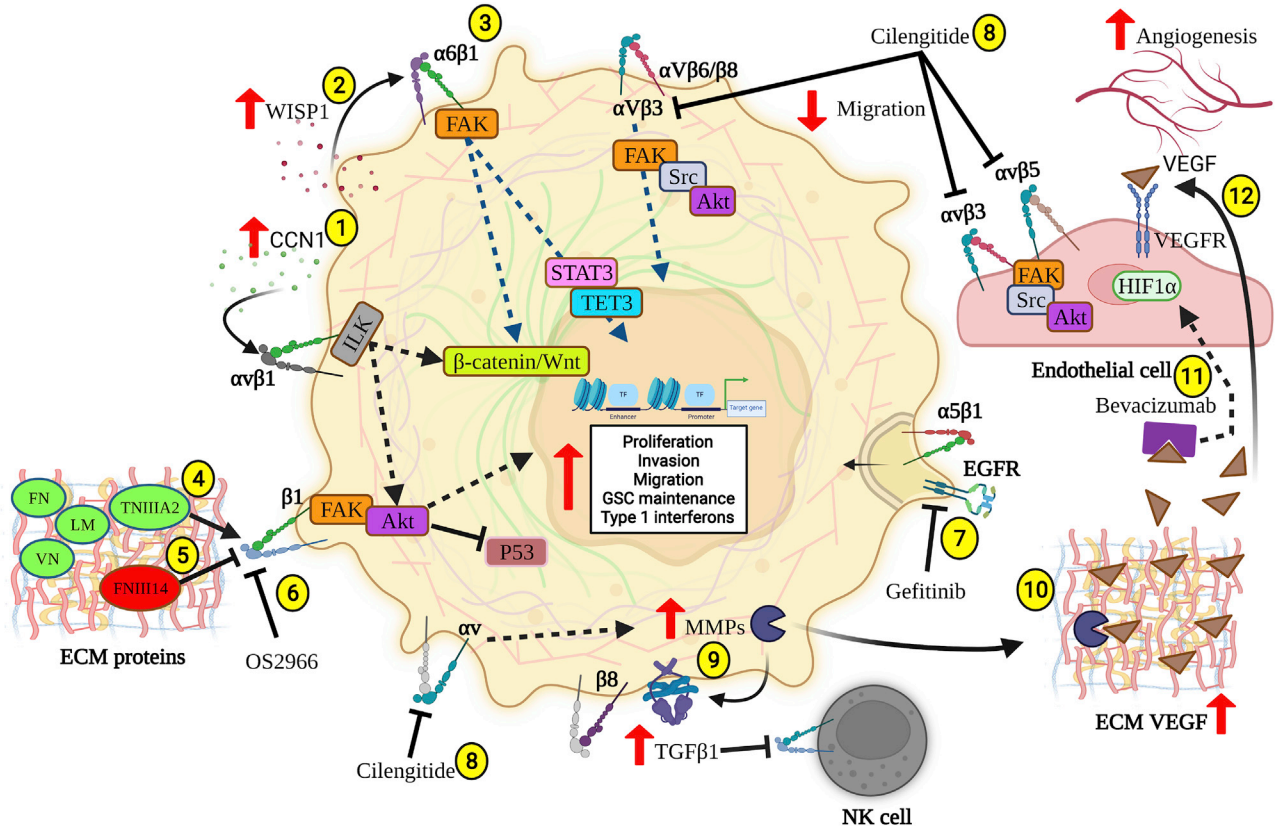

Figure 1. Schematic of the roles of integrins in high-grade gliomas

(1–3) GSCs secrete soluble factors that promote GSC maintenance and activate integrins and downstream pro-tumorigenic pathways in HGG.[9,10] (4–5) ECM proteins can activate (green) or inhibit (red) integrin-mediated activation of proliferative, invasive, and migratory programs in glioma cells.[11–13] (6–8) Monoclonal antibodies and small-molecule inhibitors that target integrins show therapeutic efficacy against endothelial-cell-mediated angiogenesis and glioma cell proliferation and can sensitize glioma cells to anti-EGFR treatment due to the formation of integrin-growth factor receptor complexes.[14,15] (9) NK cells that infiltrate GBM tumors have suppressed antitumor activity as a result of cellular reprogramming, mediated by the TGFβ-integrin αV axis, where integrin αV upregulates MMPs, which then cleave and induce the release of mature TGFβ to inhibit NK cell-mediated GSC killing.[16,17] (10–12) MMPs cleave VEGF from the ECM, which can then activate VEGFR in ECs to promote angiogenesis, but soluble VEGF can be sequestered by BVZ. CCN1, cellular communication network factor 1; WISP1, Wnt1-inducible signaling pathway protein 1; FAK, focal adhesion kinase; STAT, signal transducer and activator of transcription; TET3, Ten-eleven translocation methylcytosine dioxygenase 3; Akt, protein kinase B; FN, fibronectin; LM, laminin; VN, vitronectin; TGFB, transforming growth factor-β; MMP, matrix metalloproteinases; EGFR, endothelial growth factor receptor; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; mAb, monoclonal antibody; ECs, endothelial cells; BVZ, bevacizumab.

GBM, Malric et al., conducted a statistical analysis based on The Cancer Genome Atlas (TCGA) database to determine the relationship between integrin expression and overall survival in GBM patients. That study found that the survival rate of patients with GBM tumors negatively correlated with the expression levels of integrins β1, β3, α3, α5, and αV: with higher integrin expression there was lower overall survival.[18] The upregulation of specific integrins in GBM suggests that they have an important role in cancer pathogenesis and tumor development.

Soluble factors are usually secreted by tumor cells for self-support and survival. For instance, cysteine-rich 61 (CCN1, cellular communication network factor 1) is a matricellular factor expressed and secreted by glioma cells that has been shown to significantly upregulate integrins αV and β1, activate ILK, and induce β-catenin nuclear translocation.[9,19] This mechanism, in turn, plays a role in controlling genes implicated in cell proliferation and inhibition of apoptosis.[9] WISP1 is another member of the CCN family that has been shown to be secreted from glioma stem cells (GSCs). WISP1 plays a role in tumor cell self-maintenance and tumor-associated macrophage (TAM) maintenance via autocrine and paracrine signaling, respectively.[10] WISP1 signaling has been reported to occur through the cross talk between integrin α6β1-Akt, and Wnt/β-catenin pathways, and indeed, inhibition of the Wnt/β-catenin-WISP1-signaling pathway using carnosic acid was found to suppress GBM tumor growth.[10] The pro-tumorigenic phenotype elicited through integrin α6β1 signaling can be attributed to the laminin/integrin α6-FAK-STAT3-TET3-5hmC (ECM-intracellular) signaling axis, where TET3 mediates gene expression to promote GSC maintenance, and its knockdown enhanced the survival of mice bearing primary human GSC tumors.[20]

Similarly, the ECM proteins laminin, vitronectin, and fibronectin have been shown to confer a survival advantage to GBM cells by binding integrin αV, which then activates the FAK-paxillin-Akt-signaling pathway and suppresses p53-mediated apoptosis,[21] Whereas the α5β1 integrin interferes with p53-mediated apoptosis of HGG cells,[22] signaling through the EGF receptor (EGFR) provides an alternative survival pathway in the absence of p53,[14] exemplifying the compensatory and concerted roles of signaling pathways controlled by growth factors and integrins and shedding light on the necessity to co-target these pathways for a therapeutic advantage. As such, integrin α5β1 and EGFR have been shown to interact [23] and the expression of the fibronectin integrin receptor α5β1 has been reported to be essential for sensitizing GBM cells to gefitinib-mediated EGFR tyrosine kinase inhibition.[14] Integrins also work in concert with growth factors to propagate signals that sustain the TME. For example, integrin β8 appears to be essential for the self-renewal of GSCs, leading to tumor initiation and tumor progression, a process that results from its interaction with latent-TGFβ1 in the ECM. [16] These studies reveal the intertwined pathways between integrins and other pro-tumorigenic factors that concomitantly support HGG tumor progression and provide a rationale for a combined therapeutic strategy. Indeed, the involvement of integrins in tumorigenesis should not be studied in isolation.

Vascular endothelial growth factor (VEGF) is secreted from endothelial cells (ECs) and activates FAK, promoting EC survival, vascular permeability, and the regulation of metastasis. [24,25] Phosphorylation analyses have revealed that VEGF promotes phosphorylation of the integrin β3 cytoplasmic tail and VEGF receptor 2 (VEGFR2) by c-Src and that both are required for the modulation of EC migration and angiogenesis. [26] Indeed, targeting integrin αVβ3 using an RGD-disintegrin fusion protein derived from snake venom abolished the VEGFR2-integrin β3 interaction, preventing migration, invasion, and proliferation of ECs. [27] Moreover, histological assessment of glioma patient samples has shown an increase in the expression of integrin αVβ3 in HGG compared with lower-grade glioma patient samples; [28] therefore this integrin has been extensively investigated for its role in angiogenesis. Cilengitide is a cyclic RGD inhibitor of integrins αVβ3 and αVβ5 that has been shown to cease proliferation and promote apoptosis of glioma cells and ECs by inhibiting the phosphorylation of cell-specific signaling pathways, for example, FAK, Src, and Akt in glioma cells and FAK, Src, and VEGF-induced ERK1/2 in endothelial cells. [29] Cilengitide has also been reported to reverse bevacizumab (BVZ)-induced glioma cell invasion in a rat glioma model, and a corresponding microarray analysis showed that a single treatment of BVZ enriched for the integrin-mediated cell adhesion pathway. [30] These studies confirm the importance of the integrins αVβ3 and αVβ5 in EC migration, angiogenesis, and glioma sustenance.

In another setting, inhibition of ILK with a small-molecule inhibitor that interacts with the cytoplasmic tails of integrins β1 and β3 and inactivates the downstream Akt signaling pathway was shown to cause glioma cell cycle arrest and reduce EC invasion and VEGF secretion.[31] Mechanistically, VEGF-A binds integrin α9β1 [32] and is essential for nerve growth factor-mediated migration and tube formation of endothelial cells *in vitro,* [33] both of which are representative of angiogenesis and are implicated in glioma pathology. Accordingly, a combination study using the VEGFR inhibitor sunitinib and the EGFR inhibitor lapatinib reduced the migration of glioma cells, with each individual agent disrupting the VEGFR-integrin β3 and EGFR-integrin β1 complexes, respectively. [34] These studies indicate that growth factors, and especially those that are released by glioma-associated ECs, interact with integrins to promote the proliferation, migration, and survival of glioma cells.

Leukocytes express integrins and specifically integrin β2, primarily expressed on macrophages. When interacting with the α subunit, integrin β2 can activate three distinct functions: immune cell recruitment, immune cell interaction, and immune cell signaling. [35] Integrin β2 is also important for the pro-inflammatory responses required to recruit and assist in immune cell migration. T cells most commonly express integrins α4, αL, α5, α6, and αV and β1, β2, β7, and β3,[31] and they have been shown to play key roles in T cell signaling and differentiation. T cell differentiation occurs in the thymus, and the relative expression of integrins accompanies the T cell maturation stage: immature cells are $\alpha4\beta1^{hi}/\alpha5\beta1^{hi}$, CD4/CD8 double-positive cells are $\alpha4\beta1^{hi}/\alpha5\beta1^{lo}$, and single-positive, mature T cells are $\alpha4\beta1^{lo}/\alpha5\beta1^{int}$.[36] T cells that express integrins α4β1 and α5β1 can bind VCAM-1 and fibronectin, respectively, and mediate leukocyte-EC-ECM interactions. The expression of integrin β2 by T cells has also been shown to be critical for their homing to the lymph nodes and interacting with ECs, and this is modulated through the integrin β2 interaction with the intracellular integrin activator kindlin-3.[37,38] In addition to assisting with T cell differentiation, integrin αLβ2 on naive T cells interacts with ECs by binding ICAM-1, causing T cell arrest and the production of matrix metalloproteinases (MMPs).[39]

Matrix metalloproteinases (MMPs) within the TME are also highly involved in integrin signaling in HGGs. One example of this is the dual role played by integrin αVβ3, which promotes both GBM invasion and migration through the activation of MMP-2 and modulates glycolysis through FAK. [40,41] A second example is the role for MMP-2 in STAT3 phosphorylation and activation, which, by forming a complex with integrin α5β1, results in the regulation of cyclin D1 and c-Myc to promote cell proliferation. [42] Another example is the differential MMP3/7-mediated cleavage of osteopontin, which can reprogram microglia by promoting or inhibiting their activation through integrin αV-containing heterodimers, [43] ultimately affecting the generation of antitumor immunity. Together, these studies shed light on the critical role for integrins in the development and differentiation of immune cells and the regulation of tumor cell survival and imply an important role for integrins in HGG progression.

TARGETING INTEGRINS FOR TREATMENT OF HGG

With diverse roles in HGG biology, integrins are promising therapeutic targets. [4] To begin, integrins αVβ3 and αVβ5 were first discovered as therapeutic targets for GBM when they were seen expressed primarily on tumor-associated ECs and GBM cells but not in normal

Table 1. Targeting integrins in high-grade gliomas—approach and outcome

Integrin(s)	Approach	Outcomes	References
αVβ3/αVβ5	Cilengitide	Provided 15% PFS to recurrent GBM patients	NCT 00093964
	Cilengitide, radiotherapy, TMZ combination	Increased OS to 20.8 months in newly diagnosed GBM patients	NCT 00085254
αV	Cilengitide and TGFβ1 inhibitor combination	Restored cytotoxic activity of GBM-infiltrated NK cells reprogrammed by GSCs	Shaim et al.[17]
αVβ3	siRNA knockdown	Reduced glioma cell migration *in vitro*	Christmann et al.[45]
	siRNA knockdown and TMZ combination	Reduced NF-κB activity, increased apoptotic signaling, and triggered tumor regression *in vivo*	
αVβ6	MAb 2077Z	Inhibited HSV-1 cell entry and infection	Gianni et al.[46]
αVβ8	MAb 37E1		
β8	Crispr-Cas9 deletion	Compromised GSC tumorigenesis and invasiveness *in vitro* and *in vivo*	Guerrero et al.[16]
α5β1	SJ749	Affected proliferation, adhesion, and colony formation of astrocytoma and glioma cells; without the influence of caveolin-1, glioma cells could be sensitized to TMZ and ELL to induced apoptosis	Maglott et al.,[47] Martinkova et al.,[48] Martin et al.[49]
	K34c and ELL K34c and TMZ	Promoted apoptosis of glioma cell lines opposed to senescence by ELL or TMZ alone	Martinkova et al.[48]
α5	shRNA silencing	Reduced ELL-mediated activation of p53 and p21 mRNA expression	
α6	shRNA silencing	Compromised α6-mediated expression of TET3 and 5hmC in GSCs	Herrmann et al.[20]
	siRNA knockdown	Radiosensitized GBM cells through downregulation of ZEB1, an EMT-related transcription factor	Kowalski-Chauvel et al.[50]
α6/β1	Blocking antibodies	Decreased proliferation, tumor spheroid formation, and WISP-1-induced maintenance of GSCs and TAMs	Tao et al.[10]
β1	OS2966	Inhibited growth and invasion of BVZ-resistant GBM cells *in vitro*	Carbonell et al.[15]
	OS2966 and BVZ combination	Sensitized glioma cells to antiangiogenic treatment and reduced tumor volume *in vivo*	
	OS2966 and oHSV combination	Reduced GBM cell viability and macrophage migration *in vitro*; reduced tumor volume and enhanced animal survival *in vivo*	Lee et al.[51]

BVZ, bevacizumab; ELL, ellipticine; GBM, glioblastoma; GSC, glioma stem cells; NK, natural killer; OS, overall survival; PFS, progression-free survival; shRNA, short hairpin RNA; siRNA, small interfering RNA; TAM, tumor- associated macrophages; TMZ, temozolomide.

brain tissue. [18] Since this first discovery, there have been several clinical trials involving integrin-targeting agents for GBM and other solid tumors that are both completed and ongoing. In a phase II clinical trial for GBM patients (NCT 00093964), the integrin αVβ3- and αVβ5-targeting peptide cilengitide showed modest antitumor activity in patients treated at a high dose (2,000 mg), with 15% of patients showing increased progression-free survival (PFS) compared with patients treated at a low dose (500 mg). Later, it was combined with the standard-of-care chemotherapeutic TMZ and resulted in an overall survival (OS) advantage of 20.8 months (NCT 00085254) compared with 15.6 months with standard of care alone. [44]

The importance of combining therapeutic options with the inclusion of integrin blockade to treat HGG has been described in several studies (Table 1), but perhaps a greater emphasis should be placed on identifying methods to abrogate GSCs, given their natural tendency to evade antitumor therapies. Lathia and colleagues identified that, in addition to CD133 positivity, expression of integrin α6 can also serve as a marker for GSCs, [52] and that study showed that knockdown of integrin α6 compromised the self-renewal, proliferation, and tumor formation capacity of GSCs *in vitro*.[52] In another study, inhibition of integrin α6β1 was shown to block the ability for GSC-secreted WISP1 to sustain GSC proliferation and tumor sphere formation *in vitro*.[10] In addition to integrin α6, integrin β8 has been shown to be required for self-renewal and differentiation of GSCs *in vitro* and essential for GBM initiation, growth, and invasion *in vivo*.[16] These effects were mediated by the integrin αVβ8-TGFβ1-signaling pathway, which facilitated mitotic checkpoint progression in the GBM cells.[16] More recently, it was shown that GSCs produce TGFβ and express the integrin αV subunit, regulating TGFβ maturation through MMPs and suppressing the cytotoxic activity of NK cells.[17] Specifically, NK cells that infiltrated into patients' GBM tissue were transcriptionally altered upon interacting with GSCs, and this changed the NK cell immune-phenotype, a phenomenon that did not occur in peripheral NK cells from healthy donor patients.[17] Moreover, integrin targeting in GSCs using cilengitide inhibited the ability for secreted TGFβ1 to block NK cell activation and restored NK cell-mediated cytotoxicity and antitumor activity *in vivo*.[17]

Another area of research that has a strong integrin component is in anti-angiogenic therapy, to which HGG has exhibited resistance

and phenotypic changes.[53,54] For example, it was reported that treatment with the anti-angiogenic drug bevacizumab (Avastin; BVZ) can lead to tumor progression and infiltration to the contralateral brain hemisphere in GBM patients.[53] It has been shown, however, that combining BVZ with cilengitide can rescue the anti-angiogenic potential of BVZ after tumor cells develop therapeutic resistance.[30] Another study showed that BVZ treatment in human brain tissues led to an increase in integrin β1 and its downstream kinase FAK, resulting in the expression of hypoxia-inducible factor-1 (HIF1-α).[15] Inhibition of integrin β1 with OS2966, a humanized antibody currently in clinical trials for recurrent glioblastoma (NCT04608812), abrogated the resistance of GBM cells to BVZ treatment and induced apoptosis, reducing tumor volume in a mouse glioma model.[15] Consistent with these findings, increased integrin β1 was confirmed following BVZ treatment.[55] and this report described the mechanism whereby a BVZ-mediated reduction of VEGF and induction of hypoxia leads to activation of the c-Met-β1 axis and promotes invasive resistance in GBM.[55] Identifying approaches to decrease tumor volume and eradicate HGG by blocking integrins is thus translationally relevant.

INTEGRIN-MEDIATED CHEMO- AND RADIO-THERAPY RESISTANCE IN HGG

Accumulating data describe the importance of integrins in glioma cell survival and resistance to chemotherapy-induced cell death. The expression levels of the individual subunits of integrin α5β1 have been shown to be increased with increasing glioma grades, and it has been reported that high expression of these integrins confers a significant survival disadvantage for HGG patients.[56] In addition, increased integrin β1 expression has been associated with the prevention of anoikis, a type of cell death induced by cell-ECM detachment. For example, T98G GBM cells cultured in non-adherent conditions *in vitro* die via anoikis. [11] However, in this setting, the addition of TNIIIA2, a peptide derived from the ECM protein tenascin-C, promoted cell migration and activated integrin α5β1, which enhanced cell survival and sphere formation.[11,12] On the other hand, addition of FNIII14, a tenascin-C splicing variant, blocked TNIIIA2-induced integrin β1 activation, reduced MGMT expression, and sensitized GBM cells to TMZ, resulting in a significant reduction in tumor volume *in vivo*.[12] In line with these findings, other studies have highlighted the function of integrins in HGG resistance to TMZ through other pathways.[45,56–58]

Integrin-mediated resistance to chemotherapy and radiotherapy has also been specifically investigated for GSCs, the primary cell type known to confer therapeutic resistance in HGGs. For example, the regulation of ZEB1, an EMT transcription factor, by integrins has been implicated in both chemo- and radioresistance.[50,59] Interestingly, repurposing the antipsychotic drug penfluridol (PF) was shown to have antitumoral capacity: PF treatment of GSCs reduced the expression of integrin α6, uPAR, and Zeb1 as well as stemness markers regulated by the Akt pathway, sensitizing GSCs to TMZ.[59,60] Furthermore, the interaction between integrin αV with ECM proteins such as collagen type IV, fibronectin, and laminin has been shown to mediate GSC differentiation and promote TMZ resistance during serum stimulation.[61] Additionally, the upregulation of FERMT3 (kindlin-3) in gliomas has been shown to activate the integrin β1-Wnt-β-catenin-signaling pathway and confer TMZ resistance, an effect that can be reversed by siRNA-mediated knockdown of FERMT3.[57] Integrin β1 has also been shown to be regulated by the insulin growth factor-binding protein 2 (IGFBP-2), which activates ERK signaling and promotes cell proliferation, cell invasion, and TMZ resistance, wherease its knockdown sensitized glioma cells to TMZ.[62]

Tumor protein p53 is another player that interacts with integrins and confers TMZ resistance.[58] For example, inhibition of TMZ-induced cell death was shown to be mediated by integrin α5β1 and the p53 pathway, where disruption of the MDM2-p53 complex resulted in p53 activation and reduced integrin α5 expression, the latter of which sensitized U87 glioma cells to TMZ-induced cytotoxicity.[56] Similarly, Sani and colleagues reported on the sensitization of TMZ-resistant cells to TMZ upon integrin α5β1 inhibition and p53 activation,[63] and indeed, RNA sequencing analysis of U87 glioma cells exposed to long-term TMZ treatment revealed transcriptional changes in integrin genes, mainly the ones encoding for the integrin α5 and β1 subunits.[63] In parallel, silencing of integrins β3, β5, αV, α3, and α4 has been shown to sensitize HGG cell lines to TMZ *in vitro* by impairing double-strand break repair mechanisms, as measured by a reduction in Rad51 and an increase in γH2AX.[45] Thus, integrin signaling surpasses plasma membrane-proximal pathways and yet regulates transcriptional programs that can control therapeutic resistance.

Although integrin-mediated resistance to current GBM therapies has resulted in less-than-ideal efficacy in the clinical setting, the research surrounding this field sheds light on potential gene-targeting strategies and expression signatures that can help identify and predict responses to therapies. For example, since expression of integrin α5β1 is implicated in TMZ resistance,[56] the α5β1 integrin inhibitors SJ749 and K34c were tested and shown to reduce tumor cell proliferation and increase sensitivity of glioma cells to TMZ treatment.[47,48,64] Interestingly, SJ749 was not effective in preventing caveolin-1-mediated regulation of integrin α5β1 expression through the MAPK-signaling pathway, revealing a redundancy in the regulation of integrins.[49] In another study, whereas the use of a cyclo-RGD integrin inhibitor enhanced TMZ-mediated cytotoxicity in glioma cells *in vitro* and knockdown of integrin αVβ3 reduced glioma cell migration *in vitro*, the therapeutic combination of TMZ and αVβ3 targeting reduced NF-κB activity, increased apoptotic signaling, and triggered tumor regression *in vivo*.[45]

As mentioned above, integrins are also able to confer resistance to radiotherapy in HGG. Accordingly, ionizing radiation of human GBM biopsy specimens combined with integrin α6 knockdown increased γ-H2AX, decreased phosphorylation of the DNA damage checkpoint marker Cdc25c, and decreased ZEB1, revealing a critical role of integrin α6 in resistance to radiotherapy.[50] Similarly, since irradiation induces cellular stress by JNK, dual targeting of integrin

β1 and JNK was shown to sensitize GBM cells to radiotherapy.[65] Integrins interact with other transmembrane receptors that regulate intracellular signaling, and often this engagement regulates mechanisms of radiotherapy resistance. For instance, confocal microscopic FRET analysis showed that integrin β1 associates with EGFR and confers radioresistance in a PI3K-dependent manner *in vitro*.[23] Distinctively, it has been reported that radiation resistance is mediated by ILK rather than by FAK, and specifically, integrins αVβ3 and αVβ5 have been shown to regulate ILK- and RhoB-dependent radioresistance by controlling mitosis, and indeed, targeting these integrins, ILK, or RhoB, in combination with radiation therapy, results in glioma cell multinucleation and death.[66]

Irradiation of normal and lung carcinoma cells grown in fibronectin-coated conditions has been shown to induce integrin β1-ILK signaling and increase phosphorylation of GSK-3β (Ser9).[67] This study suggests that the integrin-ILK/PI3K-signaling pathway, related to Wnt-β catenin and increased by FERMT3,[57] may play a mechanistic role in radioresistance. Interestingly, it is known that radiation upregulates HIF1-α through ILK, and this in turn induces survivin expression. Expression of survivin can be abrogated through ILK inhibition and result in centrosome duplication and mitotic cell death upon irradiation,[68] and integrin α5β1 has been shown to negatively regulate the p53-dependent apoptotic pathway through survivin,[22] potentially associated with this resistance mechanism. In another study, integrin β8 has been proposed to be a marker for radioresistant GSCs, and its inhibition compromised the inherent radioresistant characteristics of GSCs and sensitized these cells to radiation.[69] Taken together, these studies support the major role that integrins play in regulating signaling pathways that confer resistance to chemotherapy and radiotherapy in HGG tumor cells.

oHSV THERAPY FOR THE TREATMENT OF HGGs

HGGs are difficult to treat, given the invasive nature of these tumors, which limits the success of complete surgical resection.[70] In addition, tumor cells secrete various cytokines and growth factors that encourage the infiltration of tumor-supportive immune cells. This leads to the creation of a TME that influences tumor growth and metastasis, along with resistance to conventional treatments.[71] Despite the efforts to develop effective therapies for HGG, the overall prognosis remains poor,[72] reflecting the need for novel therapeutic approaches in order to improve the survival outcomes of HGG patients. Due to the critical nature of the brain as the crux of body function, and in order to further improve HGG patients' quality of life post-treatment, the development of brain tumor-specific therapies that leave surrounding healthy tissue unaffected, is of paramount importance. Thus, there is an urgent need for a paradigm shift in the treatment of these diseases.

Oncolytic viral (OV) therapy is an approach that involves the use of either a natural strain or a genetically engineered virus that can infect and replicate specifically in cancer cells.[73] The activity of the virus is dependent on three factors: its competence to bind cell surface receptors that mediate entry, its replicative potential, and its ability to evade antiviral responses elicited by the host cell.[74] The immediate infection and oncolysis induces a strong antiviral immune response to clear the virus but at the same time generates an adaptive antitumor immune response to eradicate the tumor.[74] Further enhancing the antitumor response, the infected cell can release viral-pathogen-associated molecular patterns (PAMPs) and cytokines such as IFNγ, TNFα, and interleukin-2 (IL-12) to encourage the maturation of antigen-presenting cells (APCs), and ultimately activate cytotoxic effector T cells, as described with the wild-type HSV-1 infection.[75] These immune responses are beneficial for tumor cell killing, but they can impede viral propagation and, thus, the fine-tuning of this complex immune response to OV therapy is important for improving therapeutic efficacy.

oHSV, the most advanced OV therapy, is an attenuated HSV-1 that is frequently armed with inhibitory molecules and/or cytokines. oHSV has been re-targeted and combined with other therapies for the treatment of HGG,[8] and the modulation of cell-intrinsic barriers has been explored to leverage this therapy.[76] Talimogene laherparepvec (T-Vec) is currently FDA approved for the treatment of metastatic melanoma and was shown to provide a 26% overall response rate in metastatic melanoma patients, with measurable increases in $CD8^+$ T cells and decreases in regulatory T cells in biopsies of regressing lesions in a phase II clinical trial.[77,78] At the time of application, T-Vec showed a significant improvement in OS and suppression of tumor growth, a favorable response attributed to the generation of an antitumor immune response. DELYTACT (teserpaturev/G47Δ) is an oHSV that received conditional approval for the treatment of malignant gliomas in Japan in 2021. G47Δ, a third-generation oHSV, was generated from the G207 backbone and contains additional gene deletions with the same safety properties,[79] showing an enhanced therapeutic efficacy compared with G207.[80,81] Although there are other second-generation oHSV vectors at various stages of clinical development for the treatment of malignant gliomas (NCT00028158, NCT03657576, NCT02062827, NCT03152318) and oHSV shows promise as an effective therapeutic approach to treat cancer, the mechanisms of action of the virus need to be explored in more detail to maximize its therapeutic efficacy.

INTEGRIN TARGETING FOR oHSV-MEDIATED HGG THERAPY

Integrins play a vital role in viral entry, and most viruses have different specificities with regard to the integrin receptor that they bind for cell entry. Our group uses HSV-1 as the backbone of our oncolytic viruses, and, similar to adenovirus, the HSV-1 envelope glycoproteins have an arginine-glycine-aspartic acid (RGD) amino acid tripeptide motif that enables the interaction with RGD-binding proteins such as integrin αVβ3 on the cell surface. This interaction helps to recognize incoming virions and essentially outlines the entry pathway for the virus.[82,83] Campadelli and colleagues found that expression of integrins αVβ3, αVβ6, and αVβ8 is vital for initiating virus entry.[84] As co-receptors, these three integrins bind to the gH/gL complex located on the HSV-1 virion envelope to allow virus entry into the cell, with integrins αVβ6 and αVβ8 having 100 times higher affinity

than αVβ3.[82] As a result, blockade or depletion of either β6 or β8 subunit results in the inhibition of viral entry,[84] and both computational modeling and *in vitro* experiments have identified that dual αVβ6/αVβ8 targeting with RGD-containing cyclic pentapeptides inhibits HSV-1 infection,[85] as do neutralizing antibodies against integrins β6 and β8.[46] Together, these data emphasize the importance of the aforementioned integrins in HSV-1 viral entry. In addition to the viral glycoproteins gH/gL, the glycoprotein gD binds nectin-1 through integrin αVβ3. Nectin-1 is highly expressed in glioma cells, its expression correlates with oHSV sensitivity,[86] and its cellular localization to the lipid raft platform is regulated by integrin αVβ3, wherein gD binds nectin-1 and viral infection is facilitated.[87] Indeed, genetic modifications to the individual oHSV gH, gD, and gB glycoproteins made to express a single-chain antibody (scFv) against HER2 disrupted the integrin-mediated viral cell entry compared with the parental oHSV virus.[88]

Following integrin engagement, viral entry can occur by three different mechanisms: plasma membrane fusion (the main form of entry), integrin-mediated endocytosis, and non-integrin mediated endocytosis. Despite the benefit of engaging integrins for successful viral entry, the repercussions of this engagement in cancer cells can be detrimental. For example, the induction of signaling cascades implicated in tumorigenesis and metastasis [89] can occur from the upregulation of integrins that increase tumor cell proliferation, their interaction with adjacent receptors, the generation of a metastatic niche mediated by exosomes,[90] and the activation of intracellular signaling pathways such as FAK and Akt. Furthermore, activation of FAK can lead to adhesion, migration, and invasion of tumor cells,[91] and its downstream signaling plays a role in the TME and maintenance of EC integrity and function.[92] As addressed above, VEGF promotes vascular permeability in ECs through FAK activation, and its inhibition reduces vascular permeability.[93] In macrophages, however, integrin α5β1 activation initiates FAK-dependent changes to the morphology and functioning of macrophages,[94] making FAK signaling crucial for their motility toward affected areas upon immune activation.

With regard to the immune response, it has been shown that integrin αVβ3 is as important for virus entry as it is for initiating an innate immune response against viral infections.[95] Integrin αVβ3 promotes type I interferon (IFN) production and inflammatory cytokine secretion to recruit immune cells to the TME. This response is beneficial from a therapeutic standpoint, as it induces a robust antitumor immune response; however, it can have a negative impact in OV efficacy due to early viral clearance (Figure 2). On the other hand, integrin α6β1 promotes the activation of the Wnt-β catenin pathway,[10,57] also known to induce expression of IFN genes that suppress viral infection.[96,97] However, to combat this, HSV-1 has evolved mechanisms to inhibit β-catenin signaling and thus maximize its viral cycle inside the host cell.[98,99]

Taken together, the engagement of virus with integrins initiates a cascade of signaling pathways in both tumor cells and cells of the TME that lead to tumor growth and inflammatory responses (Figure 3). In order to achieve a balance between reduced antiviral and increased antitumoral immune responses to maintain oHSV-mediated therapeutic oncolysis and enhance tumor cell killing, the effects of viro-immunotherapy in HGG should be fully understood. Importantly, given that integrins are the protagonist in the viral entry process, they can be exploited in the context of oHSV therapy to treat cancers.

EFFECT OF INTEGRIN INHIBITION ON oHSV EFFICACY

Since integrins are key players for viral entry but also viable therapeutic targets for GBM, we will next examine the benefits and consequences of targeting integrins in the context of oHSV therapeutic efficacy. Many integrin-targeting drugs have been tested in clinical trials, and they target either specific integrins or multiple integrins.[18] Cilengitide has been tested both as a monotherapy and in combination with other agents in HGG patients. Based on what we know about integrin αVβ3 and its ability to induce an innate immune response, inhibition of this particular receptor may be a limitation for the antitumoral immunity needed to eradicate HGG tumors with oHSV. Also, integrin αVβ3 is important for viral entry; thus, combining oHSV with cilengitide may reduce the efficacy of oHSV, although this was not shown to be the case with an enhanced and armed oHSV.[100]

Another ramification of integrin blockade is related to the effect it will have on cells in the TME. We previously described the role of integrin β2 in macrophage recruitment, signaling, and migration;[35] hence, targeting this integrin may be detrimental for normal macrophage function. Specifically, although targeting integrin β2 may be beneficial for reducing virus clearance and increasing virus propagation, its blockade could reduce pro-inflammatory effects and prevent the induction of innate immunity. Integrins play a role in T cell signaling, differentiation, and maturation as well.[101] For example, the interaction of ICAM-1 with integrin αLβ2 on T cells can lead to the release of MMPs into the TME and ultimately enhance tumor growth and metastasis. Although it would be extremely beneficial to block αLβ2 to prevent these effects, αLβ2 is crucial for thymocyte differentiation. Therefore, inhibition of this integrin would prevent the induction of $CD4^+/CD8^+$ T cells and ultimately inhibit the antitumor immune response. An alternative approach would be to target MMPs, inhibitors of which have shown anti-tumorigenic efficacy in combination with OVs.[102,103] In this regard, we have previously reported on the generation of an EGFRvIII-targeted oHSV (KNE) that encodes an enzymatically active MMP-9 (KMMP9) and was found to enhance GBM tumor cell killing and viral replication *in vitro* as well as survival of GBM-tumor-bearing mice *in vivo*.[104] Considering that targeting integrin αV will upregulate EGFR as a pro-survival pathway to compensate for the p53-mediated apoptosis,[21] we can hypothesize that combining cilengitide with KNE could enhance tumor cell killing in EGFRvIII-expressing GBM cells.[105] Similarly, a novel oHSV encoding MMP-9 ($oHSV^{ULBP3\text{-}MMP9}$) showed survival benefit *in vivo* only in the presence of an anti-VEGF-neutralizing antibody,[106] and this was attributed to MMP-9 having been identified as a

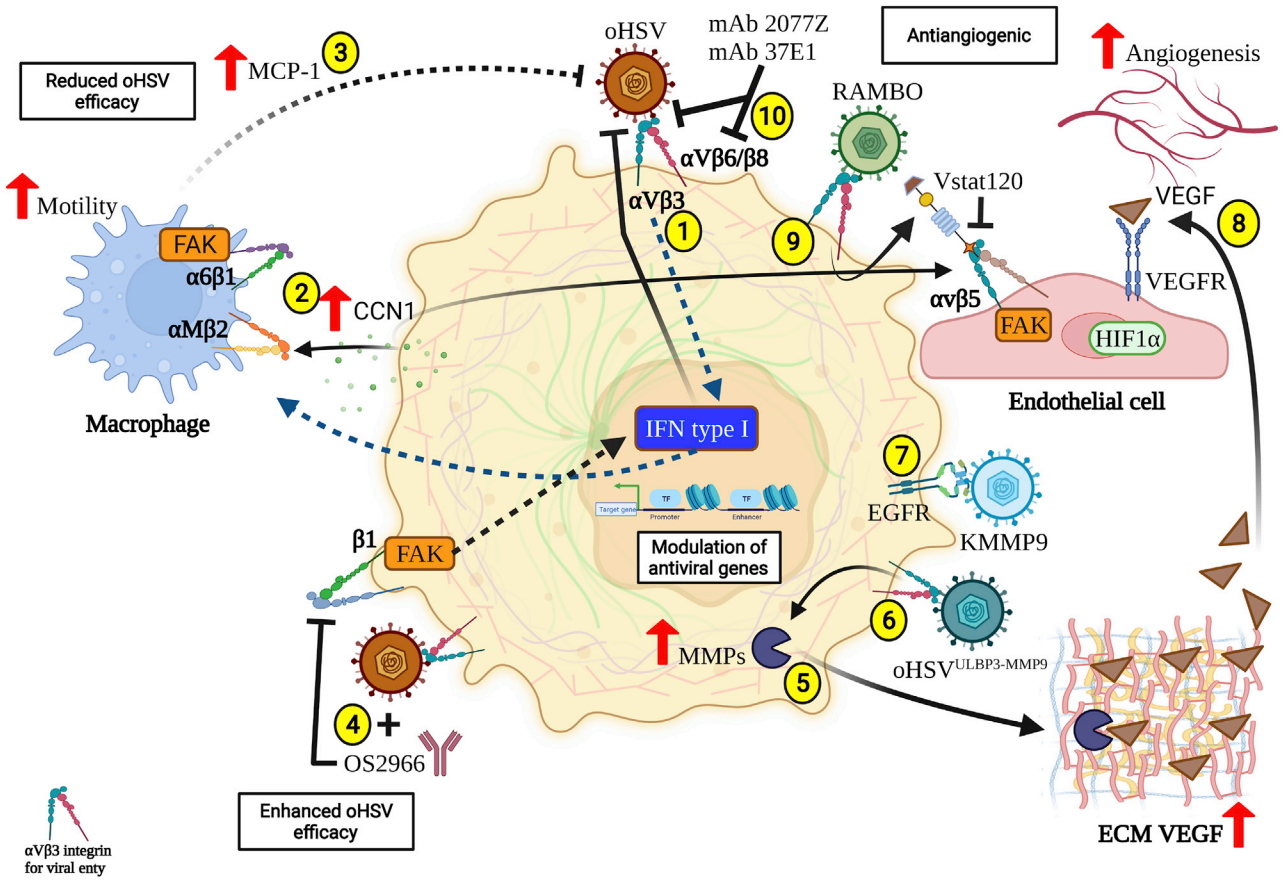

Figure 2. The roles of integrins in oHSV treatment

(1) Integrins αVβ3, αVβ6, and αVβ8 are required for oHSV virus entry and infection [46]. (2–3) Glioma cells secrete soluble factors that can mediate macrophage recruitment through integrins, further promoting activation of integrins on glioma cells and activation of the downstream antiviral signaling cascade, limiting efficacy of oHSV therapy [108,112]. (4 and 10) Blocking antibodies can prevent integrin-mediated viral entry or enhance the therapeutic efficacy of oHSV if the targeted integrins are not essential for virus entry [46,51]. (5) Integrins activate MMPs, which cleave EC-secreted VEGF and induce angiogenesis in HGG [107]. (6 and 7) Armed and re-targeted oHSV vectors inhibit integrins on endothelial cells and target EGFRs limiting the progression of HGG tumorigenesis but can also promote the negative effect of MMP-mediated cleavage of VEGF that leads to angiogenesis (8) [104,105]. (9) A Vstat-120 armed oHSV inhibits integrin αVβ5 in ECs and has anti-angiogenic properties [110]. IFN, interferon; CCN1, cellular communication network factor 1; FAK, focal adhesion kinase; MCP-1, monocyte chemoattractant protein 1; MMP, matrix metalloproteinase; EGFR, epidermal growth factor receptor; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; mAb, monoclonal antibody.

VEGF-cleaving enzyme and being responsible for releasing VEGF to the TME and promoting EC-mediated angiogenesis [106,107] (Figure 2).

Thus far, we have described a role for integrins expressed on HGG cells in promoting cancer cell survival and proliferation; however, integrins are also involved in mediating pro-tumorigenic and immune cell effects following their engagement with soluble factors that are secreted from the tumor cells as well. Our laboratory previously reported that oHSV-infected GBM cells induce secretion of CCN1 and promote the migration of monocytes and macrophages toward infected cells via its binding to the integrin αMβ2 in macrophages, thereby increasing viral clearance and limiting oHSV replication [108] (Figure 2). Indeed, blocking antibodies against CCN1, integrin αM, and integrin β2 rescued oHSV viral replication, with the potential to enhance the antitumor efficacy of oHSV.[108]

On the other hand, the brain-specific angiogenesis inhibitor 1 (BAI1) is an anti-angiogenic transmembrane protein that can bind to and block integrin αV expressed on ECs, inhibit cell proliferation, and limit the formation of new blood vessels in the brain through its cleaved extracellular domain (vasculostatin, Vstat120) that is released to the ECM.[109] With this in mind, our group generated an oHSV encoding Vstat120, rapid anti-angiogenesis mediated by oncolytic virus (RAMBO), with the idea of blocking integrin αVβ5 and enhancing the antitumor efficacy of oHSV. Since CCN1 derived from GBM cells and oHSV-infected cells could activate integrin αVβ5 on ECs, it was hypothesized that RAMBO would abrogate the CCN1-mediated limitation of oHSV efficacy (Figure 2). Indeed, the use of RAMBO significantly reduced angiogenesis *in vitro* and *in vivo* and showed enhanced antitumor efficacy in an *in vivo* survival study compared with control.[100] Importantly, combining RAMBO with cilengitide

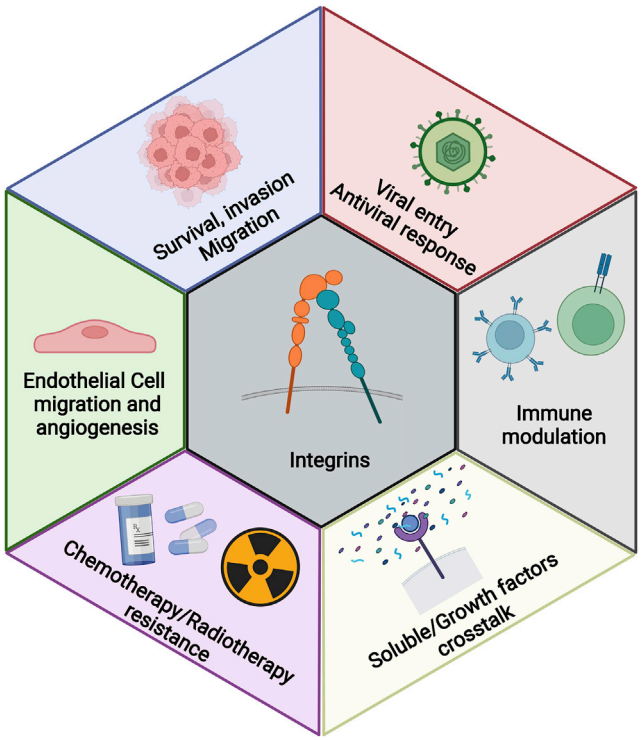

Figure 3. Diverse roles of integrins

Integrins play a role in oHSV virus entry and have been implicated in HGG tumorigenesis by regulating proliferation, maintenance, and migration of glioma cells and ECs. Integrins can promote EC-mediated angiogenesis and regulate differentiation of immune cells as well as serve as adhesion molecules toward ECs. The interaction between integrins and growth factor receptors leads to redundant pathways that can sustain tumor progression. In HGG, integrins are implicated in resistance to chemotherapy and radiotherapy. All together, therapeutic targeting of integrins can disrupt the aforementioned pathways and treat gliomas, but can also limit the use of oHSV therapy.

provided a synergistic increase in tumor cell killing *in vitro* and enhanced tumor growth inhibition and animal survival in glioma xenograft mouse models.[110] Taken together, combining two integrin-targeting mechanisms has been shown to be an effective method to enhance oHSV efficacy.

The antiviral immune response can also be modulated to maximize the oHSV therapeutic potential. For example, STAT3 antagonizes the STAT1 pathway by reducing the expression of antiviral genes and promoting the survival of GSCs,[20] both of which potentiate the therapeutic efficacy of oHSV. [111] Positively regulating STAT3 and/or negatively regulating STAT1 can result in a positive outcome for OV therapy. In addition to the aforementioned integrin αM in macrophages, integrin β1, a subunit of the α6β1 receptor found on the surface of tumor cells, has also been shown to bind CCN1 and elicit an antiviral type I IFN response.[112] This response, in turn, increases macrophage infiltration and, activation and production of antiviral factors that promote early viral clearance. Our group investigated the effect of targeting integrin β1 by using a humanized antibody (OS2966) in combination with oHSV. Combining OS2966 with oHSV resulted in an increase in viral replication along with a reduction in gene expression of antiviral proteins and macrophage migration [51] (Figure 2). Furthermore, we saw a significant reduction in tumor volume and improvement of survival when glioma-bearing mice were treated with the combination compared with the single agents. Overall, we have found a significant benefit of blocking integrin β1 in combination with oHSV therapy. Unfortunately, though, OS2966 cannot cross the blood-brain barrier (BBB); therefore, administration of this therapeutic relies on a convection-enhanced delivery device.[113] Consequently, any integrin-targeting antibody will have limited efficacy in HGG patients because of the BBB.

Finally, as of recently, the use of FDA-approved antipsychotic PF has been investigated as a repurposed cancer therapeutic. PF functions as a dopamine antagonist, blocking the dopaminergic receptor membranes.[114] As a potential cancer therapeutic, PF was reported to elicit cytotoxic effects against breast-brain metastasis and GBM, and at the transcriptional level it downregulated integrins α6 and β4.[60,115] In addition, PF has been shown to modulate the immunosuppressive TME in GBM by lowering the expression of MDSCs and increasing the expression of M1 macrophages [116] as well as regulating angiogenesis by inhibiting the VEGF-signaling pathway in ECs.[117] The specificity of PF as an integrin-targeting drug is not fully understood and therefore would be worthwhile to investigate in order to understand its implications in tumor and immune cells. Additionally, data have not yet been published showing the survival benefits of PF as a single agent *in vivo,* but the combination of PF with TMZ has shown sensitization of GSCs to the alkylating agent.[59] For this reason, it would be interesting to examine the effects of combining PF with oHSV. All together, integrin targeting has shown the potential to maximize oHSV therapy and is a promising therapeutic approach to treat HGG.

PERSPECTIVE

Integrins are key players in HGG growth and invasion as well as oHSV entry and infection. Since integrin inhibition can result in both positive and negative outcomes when combined with oHSV treatment, it is paramount to explore alternative treatment options that target tumor-supportive integrins while maintaining the functionality of viral-permissive integrins to sustain oHSV efficacy. Based on the reported studies thus far of integrin blockade combined with oHSV therapy of HGG in preclinical models, it is clear that there are more benefits than limitations with this approach. Given that αVβ3, αVβ6, and αVβ8 integrins are the protagonists for virus entry but cilengetide—which targets integrin αVβ3—has shown enhanced oHSV replication, it is evident that studies should not rely solely on their pro-viral role but rather identify integrins that can compensate for their inhibited activities. Particularly, the redundancy of integrins and resistance mechanisms play a role in host cell survival, which is crucial for virus replication. In addition, the timing of integrin blockade, whether before or after the initial oHSV infection, can dictate hindrance of oHSV entry at earlier time points, thus reducing the overall antitumor efficacy. While integrin blockade allows for the formation of an antitumor immunity, future directions should be

focused on the extent of integrin blockade in non-cancerous tissue, which remains underexplored. In summary, integrin blockade is a viable option for the enhancement of available therapies such as oHSV against HGG.

DATA AVAILABILITY

All data herein described are included in this published article.

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AUTHOR CONTRIBUTIONS

J.Y.Y. and B.K.: conceptualization and investigation. K.A.R-C., M.N., T.J.L., B.K., and J.Y.Y.: writing, review, and revision of the manuscript.

DECLARATION OF INTERESTS

The authors declare no conflicts of interest.

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