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Spotlight

Advances in co-opting anti-depressant drugs in glioma therapy

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A study by Chryplewicz et al. demonstrated the efficacy of combining tricyclic antidepressant imipramine and anti-VEGF therapy in treating genetically engineered glioma models. Dual therapy synergistically improved vascular integrity, increased autophagy, and modulated the myeloid and lymphoid compartments in glioma.

Glioblastoma (GBM) is the most aggressive primary brain tumor with median overall survival of only 12–15 months despite standard of care.[1] While the use of immune checkpoint inhibitors (ICIs) has become a major pillar of anti-cancer therapy with unprecedented successes in treating some solid tumors such as melanoma, urologic cancers, and non-small cell lung cancer, trials of ICIs in GBM have not been promising.[2] Some of the major limitations in our ability to successfully treat GBMs arise from the aggressive nature of cancer cells, dysfunctional vasculature promoted by rapid angiogenesis, immunosuppressive myeloid populations that support tumor growth, exhaustion of cytotoxic CD8 lymphocytes, and acquired resistance to therapies. Together, these conditions create a "cold" immunological environment, characterized by a paucity of intratumoral CD8 T cells and limited ability of cytotoxic T lymphocytes (CTLs) to mount an effective and sustained anti-tumor response.[3] Overcoming these challenges individually with monotherapies has not proven successful as GBMs have high inter- and intratumoral heterogeneity that promote resistance to cytotoxic, anti-angiogenic, and immunostimulatory drugs. Successfully treating GBMs will require multipronged strategies to create a self-sustaining cycle of tumor clearance, immune recruitment, immune retention, and prevention of immunosuppression and exhaustion.

Vascular dysregulation, a major feature of GBMs, is caused by rapid angiogenesis and can be ameliorated with blockade of vascular endothelial growth factor (VEGF) or its receptor. However, the effects are limited to a "normalization window" that can close with upregulation of redundant pathways,[4] and paradoxically, hypoxic changes induced by VEGF blockade can promote tumor invasiveness.[5] VEGF blockade has been studied in murine models and explored in clinical trials, either as monotherapy or as part of combination therapy, but improvement in overall survival has not been observed.[6] As a result, alternative strategies are being studied to maximize anti-tumor efficacy, including co-opting of other FDA-approved drugs with known mechanistic insights.

A major class of drugs under investigation for glioma therapy is anti-depressants. Their known safety profiles, ability to penetrate the blood-brain barrier, and the known risk of major depressive disorders in GBM patients make them good candidates to be co-opted in treating this lethal CNS tumor. Recent studies have shown that fluoxetine, a selective serotonin reuptake inhibitor, can kill glioma cells by inhibiting sphingomyelin phosphodiesterase-1 (SMPD1)-mediated sphingomyelin metabolism and preventing epidermal growth factor receptor variant III (EGFRvIII) signaling.[7] Another selective serotonin reuptake inhibitor, fluvoxamine, can interfere with focal adhesion kinase (FAK) and Akt/mammalian target of rapamycin (mTOR) pathways and disrupt actin polymerization, thereby reducing GBM migration and invasion.[8] These anti-depressants target glioma cells directly, and the enzymatic vulnerabilities behind these drugs can be mutated or downregulated in the heterogeneous background of GBM. Therefore, addition of therapeutic arms that can activate diverse immune subsets in the tumor microenvironment (TME) and recruit a broad repertoire of antigen-specific lymphocytes is urgently needed to sustain anti-tumor effects of cytotoxic drugs.

In a recent study, Chryplewicz et al. show that the addition of imipramine, a tricyclic antidepressant (TCA), to anti-VEGF therapy (B20S, an analog of bevacizumab) vastly improves anti-tumor response through increase in autophagy and normalization of vasculature and modulation of myeloid cells and lymphoid cells in GBM.[9] Despite the two drugs targeting independent mechanisms, combining them synergistically improved vascular and immunological parameters in the TME beyond that achieved with monotherapies. For example, while VEGF alone could improve vascular integrity and imipramine alone increased infiltration of CD8 T cells into the tumor, combination of both therapies vastly outperformed monotherapies in terms of vascular functionality and immune cell infiltration and survival in glioma GEMMs (genetically engineered mouse models). Recruitment of CD8 was dependent on cancer cell autophagy and secretion of chemoattractant CXCL9 and CXCL10 in the tumor, both of which were highest with dual therapy and insignificant with monotherapy. Imipramine alone was observed to promote polarization of M2-like tumor-associated macrophages (TAMs) to M1-like cells via inhibition of histamine H1 receptor (Hrh1). This reduction in myeloid-mediated immunosuppression of T cells was complemented

by anti-VEGF-induced hypoxia-inducible factor 1-alpha (HIF-1a) upregulation in CD8 T cells in hypoxic niches in the tumor, which can promote cytotoxic effector functions. Unlike monotherapies, the combination therapy also decreased the infiltration of immunosuppressive regulatory T cells (Tregs) into the tumor, indicating yet another synergistic anti-tumor effect.

Despite the changes elicited by the combination therapy, mice eventually succumbed to glioma following upregulation of programmed death-ligand 1 (PD-L1). While addition of PD-L1 blockade to anti-VEGF and imipramine further extended survival, it was not curative. Despite slowing of tumor growth, tumor persistence and chronic antigen stimulation likely allow for upregulation of alternative checkpoints and unfavorable metabolic re-wiring of intratumoral CD8 T cells. Targeting metabolic vulnerabilities in CNS tumors such as tryptophan metabolism, glucose availability, and lactate production could provide additional strategies to prevent exhaustion and promote long-lasting T cell effector and memory functions. For instance, as tumor cells outcompete CD8 T cells for glucose, lack of glycolytic intermediate phosphoenolpyruvate (PEP) in T cells dampens anti-tumor efficacy of T cells by preventing NFAT1 activation.[10] Targeted therapy to redress these metabolic stresses either directly *in vivo* or combined with an adoptive transfer approach could provide a much-needed boost to T cells to clear gliomas.

The findings from Chryplewicz et al. highlight new avenues for treatment of GBM by turning the "cold" GBM TME into an inflammatory site characterized by tumor cell death, lymphocyte infiltration, activation, and myeloid polarization, which can foster a self-sustaining cycle of tumor clearance and epitope spreading. In addition to highlighting the effects of combining VEGF blockade and TCA for treating GBM, Chryplewicz et al. also indicate the potential of histamine blockade, either through imipramine-mediated inhibition of Hrh1 or with antihistamines, as patients receiving antihistamine during or before the disease course were found to have a significant reduction in death rates from retrospective analysis of electronic medical records. Their observation that patients with low tumoral HRH1 expression have improved survival also elevates histamine signaling in myeloid cells as a targetable pathway to modulate innate immunity in myeloid-predominant GBM.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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