



# Immunometabolism, a new therapeutic development for immunotherapies of high-grade gliomas: a narrative review

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**Background and Objective:** Immunotherapy has yielded significant improvements in survival for many cancer types, but its impact on glioblastoma (GBM) has been relatively muted. There is a growing interest in understanding the role of cancer metabolism and its role in tumor growth and therapeutic response. Thus, it is equally important to consider the clinical implications of immune cell metabolism on cancer progression and implications for therapeutic development. Our objective is to present new developments in immunometabolic research that are relevant to immunotherapy development for high-grade gliomas.

**Methods:** A literature search and review was conducted, regarding original research articles studying metabolic pathways of immune cells in high-grade gliomas. Searches were conducted in PubMed and Embase databases on May 15 and June 13, 2022. English-language original research articles were selected and prioritized based on their inclusion of findings related to metabolic changes in myeloid and lymphoid cells in the glioma tumor microenvironment.

**Key Content and Findings:** There are many metabolic mechanisms by which immune cells in high-grade gliomas, like GBM, contribute to tumor growth and persistence via immunosuppression and high therapeutic resistance. There are also several ways that metabolic optimization has already been shown to improve immunotherapies already in clinical trials or in use, including dendritic cell vaccines and chimeric antigen receptor T cells.

**Conclusions:** The implications of immunometabolic research presented here should be taken into consideration in future research and immunotherapy development of high-grade gliomas for our best chances at improving patient survival.

**Keywords:** Immunometabolism; tumor microenvironment; high-grade glioma; glioblastoma (GBM)

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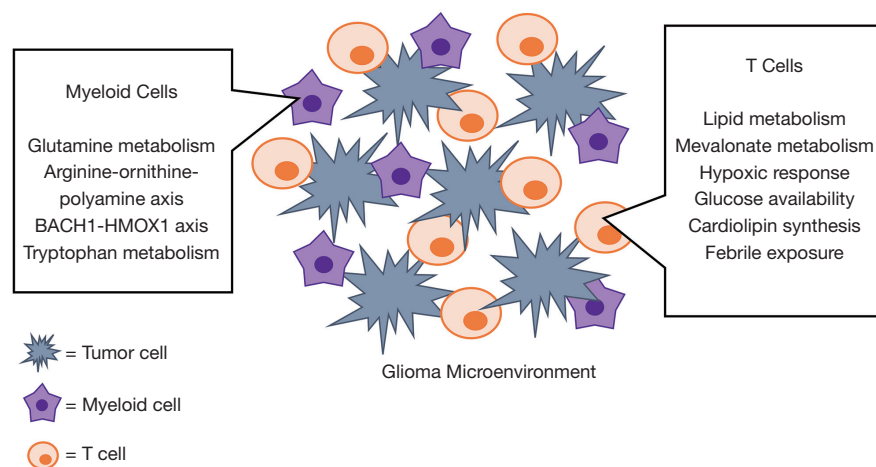
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## Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumor and high-grade glioma. While the incidence of GBM is relatively rare compared to other cancers, at 3.21 cases per 100,000 people, the prognosis of GBM is notably poor, with a one-year survival rate of 39.3% and a 5-year survival rate of only 5.5% (1,2). The

current standard of care consists of surgical resection followed by adjuvant radiation and chemotherapy. Despite these interventions, the improvement in median overall survival is limited to only a few additional months (3).

Immunotherapy is a burgeoning field that has shown potential for clinical benefit in a variety of cancer types. While the concept of leveraging the body's immune system



**Figure 1** Immune cell metabolic processes implicated in HGG growth and resistance to immunotherapy. BACH1, BTB domain and CNC homology 1; HMOX1, heme oxygenase 1; HGG, high-grade glioma.

to attack cancer has existed for decades, the field of cancer immunotherapy saw a modern resurgence with the successes of anti-PD1 and anti-CTLA4 immune checkpoint inhibitors in clinical trials for the treatment of metastatic melanoma (4-6). In the context of GBM, anti-PD1 has demonstrated less profound efficacy, as evidenced in the recent results of the CheckMate trials. The CheckMate 498 phase III trial compared the combination of nivolumab (anti-PD1) and radiotherapy with the standard-of-care combination of temozolomide and radiotherapy in newly diagnosed, unmethylated MGMT promoter GBM. The investigators did not see any improvement in median overall survival with the anti-PD1 arm (7). Additionally, the CheckMate 548 phase III trial evaluating the combination of nivolumab with standard-of-care treatment compared to placebo with standard-of-care in newly diagnosed, methylated MGMT promoter GBM did not reveal improvements in survival (8).

There remain various knowledge gaps that must be addressed in order to propel GBM immunotherapy research. One persistent challenge is the identification of unique neoantigens in GBM tumors that can dictate high target specificity for future immunotherapeutic approaches (9). Another major puzzle is disentangling the immunosuppressive milieu of cells and factors that comprise the tumor microenvironment, which has been implicated in the limited efficacy of adjuvant anti-PD1 therapy for GBM (10,11). Still other challenges exist with regards to the wide heterogeneity in genetics and epigenetics both within and between individual patients' tumors (12-14).

With the rise of advanced technologies and methods

for analyzing the metabolome, there is increasing interest in characterizing the metabolic programs of GBM cells. These metabolic mechanisms represent critical adaptive strategies that tumors employ to promote survival, growth, and proliferation (15). One of the most significant examples of how a better understanding of GBM metabolism has impacted clinical care is the discovery of isocitrate dehydrogenase (IDH) mutations in glioma (16). Mutations in IDH are hypothesized to reduce the conversion of isocitrate to alpha-ketoglutarate in the Krebs cycle and facilitate the production of D-2-hydroxyglutarate (D-2-HG), a putative oncometabolite in IDH-mutant tumorigenesis and progression (17,18). Interestingly, preclinical evidence suggests that increased intracellular 2-HG reduces the secretion of IFN- $\gamma$ -inducible chemokines like CXCL10 (19). This results in decreased CD8<sup>+</sup> T cell recruitment to the tumor microenvironment, which may abrogate the effects of immunotherapy.

Tumor cells do not exist *in vivo* in isolation, however, and immune cells are a vital component of the tumor microenvironment. Thus, it is important to consider how various metabolic pathways in immune cells change in tumor microenvironments to allow immune cells to assist in tumor growth and progression. Our purpose for this review is to present relevant research studies about the effects of metabolic changes in glioma-associated immune cells and their implications for development of immunotherapies for high-grade gliomas. We have summarized all of the metabolic pathways we discuss in this review article in *Figure 1*, with each metabolic pathway and cell type(s)

**Table 1** Metabolic targets in high grade glioma-associated immune cells

Metabolic pathway, protein, or intermediate	Type of cells targeted
Glutamine metabolism	MDSCs
Arginine-ornithine-polyamine axis	MDSCs
BACH1-HMOX1 axis	Monocytes, macrophages, and microglia
Tryptophan metabolism	MDSCs and Tregs
Mitochondrial fatty acid oxidation	Tregs
Mevalonate metabolism	$\gamma\delta$ T cells
Transient glucose restriction	CD8 T cells
Cardiolipin synthesis	CD8 T cells
Febrile temperature exposure	CD8 T cells
Sarcosine	Dendritic cells
NHE1	Microglia and myeloid cells
Cholesterol metabolism	CD8 T cells

BACH1, BTB domain and CNC homology 1; HMOX1, heme oxygenase 1; NHE1, Na<sup>+</sup>/H<sup>+</sup> exchanger 1; MDSCs, myeloid-derived suppressor cells; Tregs, T regulatory cells.

affected listed in *Table 1*. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://cco.amegroups.com/article/view/10.21037/cco-22-58/rc>).

## Methods

Searches were conducted using PubMed and Embase databases on May 15, 2022 and June 13, 2022, respectively. MeSH Major topics included macrophage, microglia, dendritic cell, myeloid cell, B cell, T cell; respiration, metabolism; glioblastoma, high-grade glioma, astrocytoma, oligodendroma, and glioma. The search results were limited to original research articles that reported in the English language, and the search selection prioritized studies of metabolic processes in immune cells in high-grade glioma or GBM *in vitro* and *in vivo* models. Research articles presenting the effects of metabolism of tumor or other cells on immune cells in the microenvironment were excluded. The search strategy is summarized in *Table 2*.

## Myeloid cell metabolism

Myeloid cells and their functions have been shown to be affected by several types of metabolic homeostasis and their surrounding environments. Lipid metabolic homeostasis, for example, is crucial for macrophage function

in general (not just within the high-grade glioma tumor microenvironment). Triacylglycerol synthesis in lipid droplet development is necessary for macrophage activation and inflammatory cytokine release in murine models (20). However, diacylglycerol Kinase  $\alpha$  (DGK $\alpha$ ) is involved in lipid metabolism and T cell checkpoint to support energy. Macrophages in DGK $\alpha$  knockout (KO) mice have increased metabolic activity and are more responsive to stimulation, and they also migrate to injury sites at greater numbers, even in the brain (21). Additionally, in the tumor microenvironment, extracellular lipid loading has been shown to enhance GBM-associated angiogenesis and macrophage recruitment, which are prognostic of poorer survival outcomes in mouse studies (22). Taken together, these studies support the notion that lipid metabolism is tightly regulated in macrophages for optimal functioning and that any dysregulation within macrophages or in the local tumor microenvironment could lead to overly active or inactive macrophages.

Microglia are also metabolically affected by the glioma tumor microenvironment, as co-culture with glioma cells is associated with microglial adaptation of lower glucose consumption, higher lactate production, and decreased ATP levels intracellularly. While microglial viability has not been shown to be affected, there was observed mitochondrial relocation that did not reverse after co-culture (23).

In this Myeloid Cell Metabolism section, we highlight

**Table 2** The search strategy summary

Items	Specification
Date of search	May 15, 2022 & June 13, 2022
Databases and other sources searched	PubMed; Embase
Search terms used	Macrophage, microglia, dendritic cell, myeloid cell, B cell, T cell; respiration, metabolism; glioblastoma, high-grade glioma, astrocytoma, oligodendroma, glioma
Timeframe	No restrictions
Inclusion and exclusion criteria	Included studies about the metabolism of tumor-associated myeloid and lymphocyte cells  Excluded studies about metabolism of tumor, cancer stem, and non-immune cells
Selection process	JY Wu and AL Ren conducted literature searches while JY Wu conducted the selection independently

several specific metabolic pathways in myeloid cells shown to affect their functions in high-grade glioma models with potential to impact immunotherapy development and patient outcomes.

### *Glutamine metabolism*

It is well known that myeloid-derived suppressor cells (MDSCs) are involved in mediating immunosuppression in high-grade gliomas, and this immunosuppression is predicated on various types of metabolic homeostasis. Glutamine metabolism has been shown to be a key modulator of MDSC function, with effects on macrophage and T cell functions as well. Inhibiting glutamine metabolism in MDSCs led to cell death (reduced number of MDSCs) and reprogrammed tumor-associated macrophages into an inflammatory phenotype, with TLR4, MHCII, CD86, CD80, and TNF $\alpha$  upregulation. Antagonism in breast cancer tumor cells and mouse models also contributes to many other immune-stimulating effects, such as increased antigen presentation mediated by macrophages to T cells, CD8 T cell cytotoxic activity, and T cell activation (24). Because T cell anergy and exhaustion are prevalent in high-grade gliomas, including GBM, it would be fruitful to investigate the role of glutamine metabolism in MDSCs in glioma models.

### *Arginine-ornithine-polyamine axis*

Aside from glutamine metabolism, the arginine-ornithine-polyamine metabolic axis is also involved in MDSC-mediated immunosuppression. Upregulation of arginase-1

and polyamines expression have been previously shown to affect myeloid-mediated immunosuppression in tumors (25).

Ornithine metabolically has three fates: the urea cycle, nitric oxide, and polyamine synthesis. In a study of the effects of arginine-ornithine-polyamine homeostasis in glioma-associated myeloid cells, downstream enzymes in the urea cycle like ornithine transcarbamylase (OTC) and carbamoyl phosphate synthetase 1 (CPS1) were downregulated in tumor-associated myeloid cells, as was inducible nitric oxide synthase (iNOS) (26). Enzymes that catabolize arginine to ornithine, including arginase-1, were shown to be upregulated in tumor-associated myeloid cells. Ornithine decarboxylase 1 (ODC1) was also upregulated, leading to upregulated polyamine synthesis. Polyamines were shown to help tumor-associated myeloid cells regulate acidic intracellular pH from the acidic high-grade glioma microenvironment, and inhibition of polyamine synthesis induced cell death in acidic pH, which was preventable with polyamine presence in the cells. Notably, depleting polyamines in these myeloid cells depleted MDSC count, decreased the myeloid:T cell ratio, enhanced CD8 $\alpha$  expression in T cells, and increased mouse survival in GBM models (26). Thus, arginase-1, ODC1 and polyamine synthesis are correlated with and may contribute to MDSC-mediated immunosuppression in the GBM tumor microenvironment. They are potential metabolic targets for immunotherapy development for high-grade gliomas.

### *The BACH1-HMOX1 metabolic axis*

BTB domain and CNC homology 1 (BACH1) is a transcription factor involved in regulating the cell cycle,

reactive oxygen species homeostasis, immunity, and stem cell self-renewal, as well as tumor metabolism, invasion, and metastasis (27,28). It also interacts downstream in an inhibitory manner with heme oxygenase-1 (HMOX1), which sequesters heme to prevent oxidative damage, regulated by both metabolic and immune homeostasis (29). Thus, suppressing BACH1 is a developing therapeutic approach for many cancers and other diseases, including osteoarthritis (29-34).

BACH1 mRNA expression was found most highly in tumor-associated macrophages and fourth-most highly in microglia out of 19 cell types/categories. BACH1 protein expression was also upregulated in GBM tissue compared to normal brain and low-grade glioma tissues. Expression was mostly closely correlated with exhaustion markers and tumor-associated macrophages chemokine release, as well as genes regulating neutrophil and eosinophil activation, T cell activation, and TNF, NF- $\kappa$ B, and IL-17 signaling pathways. Interestingly, BACH1 expression was negatively correlated with many genes involved in metabolic pathways, including the electron transport chain, oxidative phosphorylation, and cellular respiration. Additionally, it was clinically associated with worse prognosis (35).

HMOX1 expression has also been found in a subset of CD163<sup>+</sup>HMOX1<sup>+</sup> myeloid cells of the monocyte/macrophage lineage in glioma immune microenvironment. Though HMOX1 expression is inhibited by BACH1 expression, it was associated with T cell exhaustion and immune dysfunction, which also contribute to the dismal GBM prognosis (36,37). HMOX1 is upregulated in cells undergoing oxidative stress and metabolic dysregulation, helps prevent intracellular DNA damage and cell death, and activates STAT3 signaling (38). STAT3 signaling leads to IL-10 release, which also has been previously shown to be associated with an immunosuppressive microenvironment and induce T cells' transition from activation to exhaustion (39).

These findings indicate that this metabolic dysregulation within the tumor immune microenvironment contributes to immunosuppression, but exactly how BACH1 and HMOX1 expression together impact myeloid immunosuppression is still unclear. These studies on BACH1 and HMOX1 examined slightly different subsets of myeloid cells within the tumor microenvironment and examined each independently. Thus, further investigations into how the BACH1-HMOX1 metabolic axis in myeloid cells affects myeloid-induced MDSC, macrophage, and T cell-mediated immunosuppression, as well as elucidating specific mechanisms of immunosuppression, are warranted.

### *Tryptophan metabolism*

Indoleamine 2,3-dioxygenase 1 (IDO) is a tryptophan (Trp) metabolic enzyme that not only is involved in Trp degradation into kynurenine but also increases protein expression of complement factor H (CFH) isoforms: CFH and factor H like protein 1 (FHL-1) (40,41). FHL-1 expression has been shown to be associated with increased infiltration of MDSCs and T regulatory cells, both of which contribute to immunosuppression (40).

Aryl hydrocarbon receptor (AHR) is activated as a result of Trp catabolism in myeloid cells of IDH-mutant high-grade gliomas. Specifically, R-2-HG, a metabolite found in IDH-mutant gliomas, helps induce Trp degradation which activates the kynurenine pathway and AHR. This activity also induces LAT1-CD98 (a tryptophan transporter) expression, which is a key factor involved in both myeloid cell differentiation and myeloid-mediated immunosuppression in the tumor microenvironment (42). AHR and other Trp metabolism-associated genes are upregulated in GBM tumor tissue beyond myeloid cells, including in tumor cells and T cells. Higher AHR activity levels in patient tissues studied were associated with poorer patient survival. Interestingly, expression of these genes was found to be downregulated in GBM patient serum compared to controls (43).

Taken together, Tryptophan degradation via IDO, resulting in kynurenine expression and AHR activation, has been shown to induce myeloid- and T cell-mediated immunosuppression (41-43). Additionally, low levels of Trp in GBM patient serum may be a contributing factor for the low efficacy of checkpoint inhibitor immunotherapies seen in GBM patients, given the evidence presented in a previous mouse study on the effects of generalized Trp metabolite dysregulation (41,43). These are promising takeaways that will increase our understanding of why checkpoint inhibitor immunotherapies are not effective for GBM patients and what we may do to increase efficacy (44).

### **T cell metabolism**

T cells, just like myeloid cells, are metabolically affected by conditions in the tumor microenvironment. Increased glycolytic flux in tumor cells contributes to a glucose-deprived local tumor microenvironment. This contributes to decreased glycolysis, effector function, and hyporesponsiveness in tumor-infiltrating T cells, even when the tumor has high antigenicity. Furthermore, PDL1 has been



shown to enhance glycolysis in tumor cells, which may be an additional contributing factor to its tumor-promoting effects aside from its inhibition of T cells via PD1 signaling. Supporting this notion is that T cell glycolysis and effector function are rescued with checkpoint inhibitors anti-CTLA4, anti-PD1, and anti-PDL1 (45).

Additionally, one mechanism that GBM tumor cells use to suppress T cell immunity is CD73<sup>+</sup> tumor-derived extracellular vesicles (TDEVs) to confer metabolic dysregulation and inhibit aerobic glycolysis. The presence of TDEVs alone in the tumor microenvironment inhibits T cell proliferation, and when CD73<sup>+</sup>, they also alter aerobic glycolysis metabolism of T cells. CD73 KO GBM mouse models were shown to have decreased tumor size through 35 days and markedly improved survival over CD73 wildtype (WT) mice: 50% of KO mice were alive at 100 days while mice in WT and positive control arms were all dead by day 72 (46).

As with the Myeloid Cell Metabolism section, in this T Cell Metabolism section, we highlight several metabolic pathways in various types of T cells shown to affect their functions in high-grade glioma models, with potential to impact immunotherapy development and patient outcomes.

### *Lipid metabolism and hypoxia*

Tregs are immunosuppressive cells that contribute to immune dysfunction in the tumor microenvironment. Tregs normally utilize lipids for mitochondrial metabolism in the GBM tumor microenvironment, so disrupting lipid uptake or oxidation in Tregs thus suppresses their ability to suppress CD8 T cell responses (47). The GBM microenvironment is notorious for being hypoxic, and hypoxia normally induces upregulation of glycolysis in cells (48). Hypoxia inducible factor-1 alpha (HIF-1 $\alpha$ ) has been shown to inhibit Tregs' immunosuppressive abilities under hypoxic conditions, as HIF-1 $\alpha$  KO in Tregs suppress CD8 T cell function better than HIF-1 $\alpha$  WT Tregs (47). However, Tregs are able to overcome the suppressive effects of HIF-1 $\alpha$  by upregulating lipid metabolism using free fatty acids abundant in the GBM tumor microenvironment (47,49,50). This upregulation of lipid metabolism supplements glycolysis, which helps them suppress CD8 T cells even under hypoxic conditions (47,51). Miska *et al.* also reported improved survival mouse models given etomoxir (fatty acid oxidation inhibitor) treatment; thus, targeting fatty acid metabolism in high-grade gliomas could prove to be a therapeutic approach that diminishes Treg-mediated

immunosuppression in humans as well (47).

### *Mevalonate metabolism and hypoxia*

Mevalonate metabolic pathway is dysregulated in glioma cells, which can be sensed by  $\gamma\delta$ T cells to induce cytotoxic and inflammatory (cytokine and chemokine release) antitumor activity (52). More broadly, accumulation of mevalonate metabolites “alerts” a variant of  $\gamma\delta$ T cells, the V $\gamma$ 9V $\delta$ 2 T cells, and this accumulation of mevalonate pathway intermediates can be induced by nitrogen-containing bisphosphonates, drugs traditionally used to treat bone diseases including osteoporosis, osteosarcoma, bone metastasis, and multiple myeloma (53-57). Furthermore, zoledronic acid has been shown to have effects on tumor-associated immune cells in non-bone cancers, including on macrophages in breast cancer models and on  $\gamma\delta$ T cells in GBM models (52,58). Co-culture of human V $\delta$ 2 T cells with GBM cell lines induced V $\delta$ 2 T cell activation, which included cytotoxicity-induced tumor cell apoptosis and necrosis mediated by perforin release via NKG2D receptors (52). Additionally, zoledronic acid was shown to enhance the activation (via IFN- $\gamma$  signaling) and apoptotic activity of V $\delta$ 2 T cells on tumor cells (52,59,60).

While endogenous  $\gamma\delta$ T cell counts are low in both healthy and tumor brain tissues, there is currently a phase 1 clinical trial (NCT04165941) testing dose toxicity and highest possible safe dose of  $\gamma\delta$ T cells injected into the surgical resection cavity prior to closure (61). If safe dosages are determined, we can further expand investigations into metabolically-optimized  $\gamma\delta$ T cells that can differentiate into effector and memory T cells once injected into the tumor microenvironment.

Aside from the mevalonate pathway, oxygen availability affects the functionality of  $\gamma\delta$ T cells in the GBM tumor microenvironment. The degree of  $\gamma\delta$ T cell infiltration is positively correlated with GBM patient survival, but like CD8 T cells, they generally are immunosuppressed by the tumor microenvironment. Furthermore, hypoxia caused by tumor cells is associated with induced apoptosis of  $\gamma\delta$ T cells. Thus, decreasing hypoxia via metformin, by decreasing oxygen consumption rates in GL261 cells, led to smaller tumor growth and elevated  $\gamma\delta$ T (but not CD8 T) cell counts in mouse models. Additionally, the mechanism of that metformin effect (rescuing oxygen in the tumor microenvironment) was increased NKG2D receptor expression mediated by the cAMP-PKA pathway (62). Taken together with studies conducted by Cimini *et al.*,

these rescued  $\gamma\delta$ T cells could also have higher antitumor activity and could be utilized to develop more efficacious immunotherapies for high-grade gliomas (52,62).

### *Metabolic and functional optimization of CD8 T cells*

T cell exhaustion and dysregulation are common in high-grade gliomas, and the antitumor cytotoxic CD8 T cell response is often absent (44). Thus, optimizing these effector cells to withstand the conditions created by the tumor microenvironment should be addressed in T cell immunotherapy development.

CD8 T cells can be metabolically primed for enhanced functionality via transient glucose restriction followed by glucose re-exposure to enhance anabolic metabolism. Using this paradigm, molecular markers of activation, including IFN- $\gamma$ , granzyme B, and CD25, were upregulated in CD8 T cells upon glucose re-exposure as compared to cells without any conditioning (63).

Additionally, cardiolipin is an inner mitochondrial membrane lipid whose synthesis is required at threshold levels for successful memory T cell differentiation, survival, and cytokine production. Synthesis helps CD8 T cells to enhance remodeling plasticity of their mitochondria in times of stress and is associated with CD8 T cells that have “high-reserve respiratory capacity”. Thus, optimizing cardiolipin synthesis has the potential to metabolically and functionally optimize CD8 T cells’ for antitumor activity in the high-grade glioma microenvironments (64).

Lastly, effector T cells can be optimized by febrile temperatures (39 °C). In febrile conditions, mitochondrial genes in T cells were shown to be upregulated, which led to increased glucose metabolism and cytokine production (65). Interestingly, increased mitochondrial temperatures may be an endogenous process, especially in T cells, that leads to optimal protein functioning for the electron transport chain in the mitochondria of T cells, allowing them to optimally operate under febrile conditions like infection (66). Febrile exposure of CD8 T cells was also associated with increased mitochondrial mass and activity (a reversal of the normally diminished mitochondrial mass and activity in tumor-associated T cells) as well as upregulation of mitochondrial transcription genes essential for antitumor activity (65,67). While this optimization has not yet been studied in high-grade glioma *in vitro* or *in vivo* models, mice treated with febrile exposure had greater survival in myeloid leukemia models, suggesting that the effects of febrile exposure on antitumor efficacy of CD8 T cells are seen *in vivo* as well.

### **Modulating immunometabolism to enhance existing (immuno)therapies**

While we presented many avenues for further research, therapy development, and therapeutic optimization, modulating immune cell metabolism has already shown promise to improve immunotherapies in high-grade gliomas. For example, sarcosine metabolites were shown to improve the migratory ability of dendritic cells. Co-culture of sarcosine and dendritic cells enhanced CXCR2 signaling and was associated with elevations of reactive oxygen species intracellularly. Ultimately, the efficacy of human dendritic cell vaccines was improved in murine *in vivo* models (68). This metabolic and functional optimization could help us improve various dendritic cell vaccines, many of which are currently under clinical trials.

Additionally, metabolic modulation combined with chemotherapy has been shown to enhance myeloid-mediated antitumor immunity (69). A combined therapy consisting of inhibiting Na<sup>+</sup>/H<sup>+</sup> exchanger I (NHE1) with temozolomide (TMZ) enhanced the expression of oxidative phosphorylation genes in tumor-infiltrating microglia and myeloid cells; this combined treatment was associated with increased glucose uptake and mitochondrial oxidative phosphorylation, which could potentially indicate rescue of microglial and myeloid cell functions (23,69). Moreover, the efficacy of adding NHE1 blockade to TMZ and anti-PD1 combination therapy was also observed in mouse survival studies with NHE1 KO mice: median survival was improved over NHE1 conserved mice, and almost doubled from monotherapy arms (69).

Lastly, the efficacy of adoptive T cell transfers (e.g., chimeric antigen receptor T cells) has been enhanced in mouse models by ligating a liposomal formulation of avasimibe (Ava), a metabolism-modulating drug that inhibits acetyl-CoA acetyltransferase-1 and increases cholesterol concentrations in plasma membranes (70). Previous research has shown that elevating cholesterol concentrations in CD8 T cell plasma membranes enhances their cytotoxicity in part by increasing CD8 T cell proliferation, T cell receptor clustering, and efficiency of T cell activation (71). Thus, Hao *et al.* engineered a novel treatment (T-Tre/BCN-Lipo-Ava), which consisted of Ava attached or “clicked” onto T cell membranes for adoptive T cell transfer therapies. Their results were promising: three of five mice in the engineered therapeutic arm (T-Tre/BCN-Lipo-Ava) had no detectable tumor after treatment and lived through 100 days, while no other mice in other arms lived past 70 days. This survival

was significantly improved over all other arms, including non-engineered T cells, T cells given with free Ava, and T cells given with separate BCN-Lipo-Ava (70). However, this study only included five mice per arm, so further research is needed to investigate and verify the efficacy and mechanisms of action of this treatment in larger animal studies.

## Conclusions

We have presented in this narrative review a multitude of ways that metabolic mechanisms in immune cells contribute to tumor growth via immunosuppression and low therapeutic efficacy in high-grade gliomas, like GBM. Pertinent metabolic pathways in myeloid cells contributing to myeloid-mediated immunosuppression include the glutamine, arginine-ornithine-polyamine, BACH1-HMOX1, and tryptophan-kynurenine metabolic axes. Metabolic factors contributing to T cell anergy, dysregulation, and exhaustion include various lipid metabolic pathways and the mevalonate pathway. We also presented several ways in which metabolic optimization has already been shown to improve immunotherapy efficacy in mouse models, including for dendritic cell vaccines and chimeric antigen receptor T cells, as well as antitumor immunity effects of traditional therapies like temozolomide. The implications of immunometabolic research presented here should be taken into consideration in subsequent research investigations and therapy development to optimize immune function in and immunotherapeutic efficacy for high-grade gliomas, with the ultimate goal of improving patient survival.

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## References

1. Tan AC, Ashley DM, López GY, et al. Management of glioblastoma: State of the art and future directions. *CA Cancer J Clin* 2020;70:299-312.
2. Ostrom QT, Gittleman H, Xu J, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2009-2013. *Neuro Oncol* 2016;18:v1-v75.



3. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987-96.
4. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. *Cell Mol Immunol* 2020;17:807-21.
5. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455-65.
6. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23.
7. Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: An international randomized phase 3 trial. *Neuro Oncol* 2022. doi: 10.1093/neuonc/noac099.
8. Lim M, Weller M, Idbaih A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. *Neuro-Oncol* 2022.
9. Johanns TM, Bowman-Kirigin JA, Liu C, et al. Targeting Neoantigens in Glioblastoma: An Overview of Cancer Immunogenomics and Translational Implications. *Neurosurgery* 2017;64:165-76.
10. Cloughesy TF, Mochizuki AY, Orpilla JR, et al. Neoadjuvant anti-PD-1 immunotherapy promotes a survival benefit with intratumoral and systemic immune responses in recurrent glioblastoma. *Nat Med* 2019;25:477-86.
11. Filley AC, Henriquez M, Dey M. Recurrent glioma clinical trial, CheckMate-143: the game is not over yet. *Oncotarget* 2017;8:91779-94.
12. Noch EK, Ramakrishna R, Magge R. Challenges in the Treatment of Glioblastoma: Multisystem Mechanisms of Therapeutic Resistance. *World Neurosurg* 2018;116:505-17.
13. Patel AP, Tirosch I, Trombetta JJ, et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. *Science* 2014;344:1396-401.
14. Parker NR, Hudson AL, Khong P, et al. Intratumoral heterogeneity identified at the epigenetic, genetic and transcriptional level in glioblastoma. *Sci Rep* 2016;6:22477.
15. Schmidt DR, Patel R, Kirsch DG, et al. Metabolomics in cancer research and emerging applications in clinical oncology. *CA Cancer J Clin* 2021;71:333-58.
16. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med* 2009;360:765-73.
17. Turkalp Z, Karamchandani J, Das S. IDH mutation in glioma: new insights and promises for the future. *JAMA Neurol* 2014;71:1319-25.
18. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 2009;462:739-44.
19. Kohanbash G, Carrera DA, Shrivastav S, et al. Isocitrate dehydrogenase mutations suppress STAT1 and CD8+ T cell accumulation in gliomas. *J Clin Invest* 2017;127:1425-37.
20. Manigat LC, Granade ME, Taori S, et al. Loss of Diacylglycerol Kinase  $\alpha$  Enhances Macrophage Responsiveness. *Front Immunol* 2021;12:722469.
21. Offer S, Menard JA, Pérez JE, et al. Extracellular lipid loading augments hypoxic paracrine signaling and promotes glioma angiogenesis and macrophage infiltration. *J Exp Clin Cancer Res* 2019;38:241.
22. Voisin P, Bouchaud V, Merle M, et al. Microglia in close vicinity of glioma cells: correlation between phenotype and metabolic alterations. *Front Neuroenergetics* 2010;2:131.
23. Castoldi A, Monteiro LB, van Teijlingen Bakker N, et al. Triacylglycerol synthesis enhances macrophage inflammatory function. *Nat Commun* 2020;11:4107.
24. Oh MH, Sun IH, Zhao L, et al. Targeting glutamine metabolism enhances tumor-specific immunity by modulating suppressive myeloid cells. *J Clin Invest* 2020;130:3865-84.
25. Ye C, Geng Z, Dominguez D, et al. Targeting Ornithine Decarboxylase by  $\alpha$ -Difluoromethylornithine Inhibits Tumor Growth by Impairing Myeloid-Derived Suppressor Cells. *J Immunol* 2016;196:915-23.
26. Miska J, Rashidi A, Lee-Chang C, et al. Polyamines drive myeloid cell survival by buffering intracellular pH to promote immunosuppression in glioblastoma. *Sci Adv* 2021;7:eabc8929.
27. Zhang X, Guo J, Wei X, et al. Bach1: Function, Regulation, and Involvement in Disease. *Oxid Med Cell Longev* 2018;2018:1347969.
28. Wei X, Guo J, Li Q, et al. Bach1 regulates self-renewal and impedes mesendodermal differentiation of human embryonic stem cells. *Sci Adv* 2019;5:eaau7887.
29. Sun J, Hoshino H, Takaku K, et al. Hemoprotein Bach1 regulates enhancer availability of heme oxygenase-1 gene. *EMBO J* 2002;21:5216-24.
30. Kondo K, Ishigaki Y, Gao J, et al. Bach1 deficiency protects pancreatic  $\beta$ -cells from oxidative stress injury. *Am J Physiol Endocrinol Metab* 2013;305:E641-8.
31. Takada T, Miyaki S, Ishitobi H, et al. Bach1 deficiency reduces severity of osteoarthritis through upregulation of

- heme oxygenase-1. *Arthritis Res Ther* 2015;17:285.
32. Lee J, Yesilkanal AE, Wynne JP, et al. Effective breast cancer combination therapy targeting BACH1 and mitochondrial metabolism. *Nature* 2019;568:254-8.
  33. Wiel C, Le Gal K, Ibrahim MX, et al. BACH1 Stabilization by Antioxidants Stimulates Lung Cancer Metastasis. *Cell* 2019;178:330-345.e22.
  34. Ying Y, Wang Y, Huang X, et al. Oncogenic HOXB8 is driven by MYC-regulated super-enhancer and potentiates colorectal cancer invasiveness via BACH1. *Oncogene* 2020;39:1004-17.
  35. Yuan F, Cong Z, Cai X, et al. BACH1 as a potential target for immunotherapy in glioblastomas. *Int Immunopharmacol* 2022;103:108451.
  36. Ravi VM, Neidert N, Will P, et al. T-cell dysfunction in the glioblastoma microenvironment is mediated by myeloid cells releasing interleukin-10. *Nat Commun* 2022;13:925.
  37. Woroniecka K, Chongsathidkiet P, Rhodin K, et al. T-Cell Exhaustion Signatures Vary with Tumor Type and Are Severe in Glioblastoma. *Clin Cancer Res* 2018;24:4175-86.
  38. Chen HH, Chen YT, Huang YW, et al. 4-Ketopinoresinol, a novel naturally occurring ARE activator, induces the Nrf2/HO-1 axis and protects against oxidative stress-induced cell injury via activation of PI3K/AKT signaling. *Free Radic Biol Med* 2012;52:1054-66.
  39. Henrik Heiland D, Ravi VM, Behringer SP, et al. Tumor-associated reactive astrocytes aid the evolution of immunosuppressive environment in glioblastoma. *Nat Commun* 2019;10:2541.
  40. Zhai L, Bell A, Lodomersky E, et al. Tumor Cell IDO Enhances Immune Suppression and Decreases Survival Independent of Tryptophan Metabolism in Glioblastoma. *Clin Cancer Res* 2021;27:6514-28.
  41. Schramme F, Crosignani S, Frederix K, et al. Inhibition of Tryptophan-Dioxygenase Activity Increases the Antitumor Efficacy of Immune Checkpoint Inhibitors. *Cancer Immunol Res* 2020;8:32-45.
  42. Friedrich M, Sankowski R, Bunse L, et al. Tryptophan metabolism drives dynamic immunosuppressive myeloid states in IDH-mutant gliomas. *Nat Cancer* 2021;2:723-40.
  43. Panitz V, Končarević S, Sadik A, et al. Tryptophan metabolism is inversely regulated in the tumor and blood of patients with glioblastoma. *Theranostics* 2021;11:9217-33.
  44. Medikonda R, Dunn G, Rahman M, et al. A review of glioblastoma immunotherapy. *J Neurooncol* 2021;151:41-53.
  45. Chang CH, Qiu J, O'Sullivan D, et al. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell* 2015;162:1229-41.
  46. Wang M, Jia J, Cui Y, et al. CD73-positive extracellular vesicles promote glioblastoma immunosuppression by inhibiting T-cell clonal expansion. *Cell Death Dis* 2021;12:1065.
  47. Miska J, Lee-Chang C, Rashidi A, et al. HIF-1 $\alpha$  Is a Metabolic Switch between Glycolytic-Driven Migration and Oxidative Phosphorylation-Driven Immunosuppression of Tregs in Glioblastoma. *Cell Rep* 2019;27:226-237.e4.
  48. Raizer J, Parsa A. editors. *Current Understanding and Treatment of Gliomas* [Internet]. Cham: Springer International Publishing; 2015 [cited 2022 Jun 20]. (Cancer Treatment and Research; vol. 163). Available online: <http://link.springer.com/10.1007/978-3-319-12048-5>
  49. Gopal K, Grossi E, Paoletti P, et al. Lipid composition of human intracranial tumors: a biochemical study. *Acta Neurochir (Wien)* 1963;11:333-47.
  50. Martin DD, Robbins ME, Spector AA, et al. The fatty acid composition of human gliomas differs from that found in nonmalignant brain tissue. *Lipids* 1996;31:1283-8.
  51. Pacella I, Procaccini C, Focaccetti C, et al. Fatty acid metabolism complements glycolysis in the selective regulatory T cell expansion during tumor growth. *Proc Natl Acad Sci U S A* 2018;115:E6546-E6555.
  52. Cimini E, Piacentini P, Sacchi A, et al. Zoledronic acid enhances V $\delta$ 2 T-lymphocyte antitumor response to human glioma cell lines. *Int J Immunopathol Pharmacol* 2011;24:139-48.
  53. Gruenbacher G, Thurnher M. Mevalonate metabolism governs cancer immune surveillance. *Oncoimmunology* 2017;6:e1342917.
  54. Allen MR. Skeletal accumulation of bisphosphonates: implications for osteoporosis treatment. *Expert Opin Drug Metab Toxicol* 2008;4:1371-8.
  55. Green JR. Antitumor effects of bisphosphonates. *Cancer* 2003;97:840-7.
  56. Santini D, Martini F, Fratto ME, et al. In vivo effects of zoledronic acid on peripheral gammadelta T lymphocytes in early breast cancer patients. *Cancer Immunol Immunother* 2009;58:31-8.
  57. Dieli F, Vermijlen D, Fulfaro F, et al. Targeting human {gamma}delta T cells with zoledronate and interleukin-2 for immunotherapy of hormone-refractory prostate cancer. *Cancer Res* 2007;67:7450-7.
  58. Coscia M, Quaglino E, Iezzi M, et al. Zoledronic acid repolarizes tumour-associated macrophages and inhibits

- mammary carcinogenesis by targeting the mevalonate pathway. *J Cell Mol Med* 2010;14:2803-15.
59. Dunford JE, Thompson K, Coxon FP, et al. Structure-activity relationships for inhibition of farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exp Ther* 2001;296:235-42.
  60. Tanner L, Bergwik J, Single AB, et al. Zoledronic Acid Targeting of the Mevalonate Pathway Causes Reduced Cell Recruitment and Attenuates Pulmonary Fibrosis. *Front Pharmacol* 2022;13:899469.
  61. Bryant NL, Suarez-Cuervo C, Gillespie GY, et al. Characterization and immunotherapeutic potential of gammadelta T-cells in patients with glioblastoma. *Neuro Oncol* 2009;11:357-67.
  62. Park JH, Kim HJ, Kim CW, et al. Tumor hypoxia represses  $\gamma\delta$  T cell-mediated antitumor immunity against brain tumors. *Nat Immunol* 2021;22:336-46.
  63. Klein Geltink RI, Edwards-Hicks J, Apostolova P, et al. Metabolic conditioning of CD8+ effector T cells for adoptive cell therapy. *Nat Metab* 2020;2:703-16.
  64. Corrado M, Edwards-Hicks J, Villa M, et al. Dynamic Cardiolipin Synthesis Is Required for CD8+ T Cell Immunity. *Cell Metab* 2020;32:981-995.e7.
  65. O'Sullivan D, Stanczak MA, Villa M, et al. Fever supports CD8+ effector T cell responses by promoting mitochondrial translation. *Proc Natl Acad Sci U S A* 2021;118:e2023752118.
  66. Jarzab A, Kurzawa N, Hopf T, et al. Meltome atlas-thermal proteome stability across the tree of life. *Nat Methods* 2020;17:495-503.
  67. Scharping NE, Menk AV, Moreci RS, et al. The Tumor Microenvironment Represses T Cell Mitochondrial Biogenesis to Drive Intratumoral T Cell Metabolic Insufficiency and Dysfunction. *Immunity* 2016;45:374-88.
  68. Dastmalchi F, Karachi A, Yang C, et al. Sarcosine promotes trafficking of dendritic cells and improves efficacy of anti-tumor dendritic cell vaccines via CXC chemokine family signaling. *J Immunother Cancer* 2019;7:321.
  69. Hasan MN, Luo L, Ding D, et al. Blocking NHE1 stimulates glioma tumor immunity by restoring OXPHOS function of myeloid cells. *Theranostics* 2021;11:1295-309.
  70. Hao M, Hou S, Li W, et al. Combination of metabolic intervention and T cell therapy enhances solid tumor immunotherapy. *Sci Transl Med* 2020;12:eaaz6667.
  71. Yang W, Bai Y, Xiong Y, et al. Potentiating the antitumor response of CD8(+) T cells by modulating cholesterol metabolism. *Nature* 2016;531:651-5.

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