Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU26462

Decoding PD-1 Resistance: From Microenvironment to Combination Therapies in Glioblastoma

Wenqin Ding

East China Normal University, Shanghai, China
venciding@outlook.com

Abstract. Glioblastoma (GBM) is one of the most aggressive malignant brain tumors. The Stupp protocol is associated with a short median survival and high recurrence rate, referring to limited effective therapeutic alternatives. Various immunotherapies are therefore under active investigation. However, to date, their clinical application has been hindered by an unfavorable risk-benefit profile, with drug resistance posing a major barrier to therapeutic success. This review focuses on an immune checkpoint PD-1/PD-L1 inhibitors, which have shown limited efficacy as monotherapy. Key mechanisms of resistance include the immunosuppressive tumor microenvironment, aberrant genetic and epigenetic regulation, and impaired T-cell function and infiltration. To address these challenges, combination strategies targeting these resistance mechanisms have been developed, including combination of dual or triple drug regimens, targeting multiple pathways to reverse the immunosuppressive tumor microenvironment or correct underlying genetic abnormalities, along with the optimization of drug delivery routes to fundamentally enhance the drug efficacy. These approaches offer a promising theoretical framework for enhancing the therapeutic efficacy of immune checkpoint inhibitors in GBM.

Keywords: Glioblastoma, immunotherapy, PD-1 inhibitor, resistance, Combination therapy

1. Introduction

Glioblastoma multiforme (GBM) is the most aggressive and prevalent primary neoplasm of the central nervous system in adults, accounting for globally 15% of all primary brain [1] and CNS tumors and 48.6% of malignant CNS tumors [2]. The reported annual incidence rates range from 3.19 to 4.5 cases per 100,000 people [2]. The Stupp protocol confers a median overall survival (OS) of 14.6 months, along with a 2-year survival rate of 27% [3]. Nevertheless, the 5-year survival rate remains below 10% and recurrence is nearly inevitable [3].

Immunotherapy represents a transformative approach in glioblastoma treatment by leveraging the patient's immune system to target tumor cells through diverse modalities, including immune checkpoint inhibitors (e.g., anti-PD-1), chimeric antigen receptor T-cell (CAR-T) therapy, tumor vaccines, and oncolytic viruses [3]. However, clinical efficacy of immunotherapy remains limited. Most immunotherapies are in early-phase (I/II) trials, with few advancing to phase III, and none have yet supplanted the Stupp regimen as standard care [3-4].

DOI: 10.54254/2753-8818/2025.AU26462

This review primarily focuses on PD-1/PD-L1 inhibitors as one of the extensvie immune checkpoint inhibitors. The resistance mechanisms of PD-1 inhibitors will be explored from the immunosuppressive microenvironment, gene mutations and epigenetic regulation as well as T cell dysfuction and insufficient immune infiltration. Overcoming these hurdles are critical for advancing GBM treatment. The reported countermeasures are either in the early stages of clinical studies or still in preclinical investigations, potentially offering a theoretical foundation for the more effective application of PD-1 inhibitors in clinical treatment. Be advised that papers in a technically unsuitable form will be returned for retyping. After returned the manuscript must be appropriately modified.

2. Clinical responses in PD-1/PD-L1 inhibitor therapy

Glioblastoma evade immune surveillance by upregulating programmed death-ligand 1 (PD-L1), which binds to PD-1 receptors on T cells, triggering phosphorylation. Phosphorylated PD-1 recruits Src homology 2 domain, and thus dephosphorylates key signaling molecules downstream of the T cell receptor (TCR). Sustained PD-1/PD-L1 signaling induces T cell exhaustion, characterized by co-expression of multiple inhibitory receptors, which further impairs antitumor immunity, thereby fostering an immunosuppressive tumor microenvironment [5-6]. PD-1 inhibitors competitively bind PD-1 or PD-L1, blocking inhibitory signaling and restoring T-cell activation and proliferative capacity. PD-1 inhibitors reverse T-cell dysfunction by disrupting PD-1/PD-L1 signaling in regulatory T cells (Tregs), thereby attenuating their immunosuppressive activity and enhancing $CD8^+$ T-cell function [6].

PD-1 inhibitors utilized in glioblastoma therapy primarily include Nivolumab, Pembrolizumab, and Durvalumab. Nivolumab was evaluated in the Phase III CheckMate 143 trial for recurrent GBM, demonstrating a median OS of 9.8 months, with no significant difference compared to bevacizumab control (10.0 months) [7]. Pembrolizumab monotherapy in PD-L1-positive rGBM patients (KEYNOTE-028 trial) achieved a disease control rate (DCR) of 29% but a median progression-free survival (PFS) of only 2.8 months, and an Overall Response (ORR) of 8% [8]. Durvalumab monotherapy showed a median OS of 28.9 weeks (~7.2 months) and median PFS of 13.9 weeks across multiple trials [9].

However, compared with the 6-9 months achieved by traditional therapies (e.g., bevacizumab), single-agent PD-1 blockade represents an absolute survival benefit of only 1-3 months [8], exhibiting limited improvement. Meanwhile, clinical evidence from the KEYNOTE-028 trial (NCT02054806) demonstrates a 6-month progression-free survival rate of 37.7% with pembrolizumab monotherapy in recurrent PD-L1-positive GBM, indicating a high recurrence rate [8]. Current clinical data indicate that further research is essential to elucidate the resistance mechanisms of anti-PD-1 therapy and develop corresponding strategies.

3. Mechanisms of resistance to PD-1/PD-L1 inhibitors

3.1. Immunosuppressive tumor microenvironment

The immunosuppressive tumor microenvironment (TME) in glioblastoma is primarily characterized by the infiltration of immunosuppressive cell populations such as myeloid-derived suppressor cells (MDSCs) and M2-polarized tumor-associated macrophages (TAMs). This immunosuppressive TME inhibits T-cell activation and proliferation, and promotes immune evasion through dysregulated PD-

DOI: 10.54254/2753-8818/2025.AU26462

L1 expression. Elevated PD-L1 levels suppresses T-cell function, whereas diminished expression eliminates molecular targets for PD-1 inhibitors, thereby limiting the therapeutic efficacy [10-11].

GBM-derived extracellular vesicles (EVs) critically sustains immunosuppressive microenvironments in glioblastoma [12]. EVs transport immunosuppressive molecules, including PD-L1 and IDO1, to drive monocyte differentiation into MDSCs and non-classical monocytes (NCMs). Differentiated MDSCs and NCMs promote Treg expansion while concurrently inhibiting CD8+ T cell activity. This process establishes an alternative immunosuppressive axis independent of PD-1/PD-L1 signaling, directly influencing the therapeutic requirements for achieving effective PD-1 blockade.

The TGF-β signaling pathway contributes to therapy resistance by remodeling the metabolic microenvironment [13]. Activated TGF-β induces a shift toward aerobic glycolysis in tumor cells and enhance glucose uptake.This metabolic reprogramming supports rapid tumor proliferation and leads to lactate accumulation, which acidifies the TME, further impairing effector T-cell function and promoting M2 macrophage polarization. This cascade ultimately attenuates T-cell-mediated anti-tumor activity, undermining PD-1 inhibitor efficacy.

3.2. First section

PTEN loss-of-function or mutations drive resistance to PD-1 inhibitors. PTEN deficiency upregulates immunosuppressive cytokines such as TGF-β and IL-10, thereby contributing to form a TME that suppresses T-cell effector functions [11]. PTEN mutations impair autophagy-dependent processes, resulting in attenuated T-cell-mediated tumor cytotoxicity. Clinical evidence from the CheckMate 143 trial substantiates this mechanistic relationship, demonstrating significantly elevated PTEN mutation frequencies in non-responders to PD-1 blockade. Oncogenic BRAF mutations exemplify constitutive activation of the MAPK signaling pathway, promotes tumor immune evasion and confers resistance to PD-1 inhibitors [11]. Aberrant activation of MAPK signaling upregulates PD-L1, inducing exhaustion of tumor-infiltrating T lymphocytes. Clinical analyses reveal that MAPK pathway alterations are significantly enriched in responders to anti-PD-1 therapy, suggesting their potential utility as predictive biomarkers. Combinatorial inhibition of MAPK and PD-1 signaling pathways represents a promising strategy to overcome therapeutic resistance.

Mismatch repair deficiency (MMRD) and mutations in DNA polymerase genes elevate tumor mutational burden(TMB), supposing to enhance immunotherapy responses. However, high heterogeneity of GBM dilutes neoantigen-directed immune responses by dispersing targetable epitopes, thereby diminishing focused T-cell cytotoxicity against tumor cells [6]. Concurrently, MMRD upregulates IDO1 expression, thereby suppressing suppress T-cell proliferation and amplifing therapeutic resistance [11]. TMZ therapy also induces acquired MMRD that generates hypermutated tumor clones with absent lymphocyte infiltration, rendering them refractory to PD-1 blockade [6].

EGFR amplification contributes to immunotherapy resistance [6]. Tumors exhibiting EGFR-driven PD-L1 overexpression demonstrate reduced T-cell infiltration and consequently exhibit primary resistance to PD-1 blockade. Furthermore, PD-L1 expression displays temporal heterogeneity during therapeutic interventions including radiotherapy and chemotherapy so that pretreatment biopsy specimens are thus unreliable for accurate patient stratification.

DOI: 10.54254/2753-8818/2025.AU26462

3.3. T-cell dysfunction and insufficient infiltration

T cell dysfunction and molecular barriers collectively impede PD-1 inhibitors from effectively activating antitumor immune responses in glioblastoma. In GBM patients, tumor-infiltrating lymphocytes (TILs) and peripheral blood lymphocytes exhibit significant upregulation of immune checkpoint molecules(e.g., PD-1, CTLA-4, TIM-3). This results in a T cell exhaustion state phenotypically resembling virus-induced dysfunction, which directly compromises the capacity of PD-1 inhibitors to reactivate T cells [6].

The thymus-derived natural Tregs (nTregs) constitute the predominant Treg subset in gliomas, suppressing effector T cells through contact-dependent, cytokine-independent mechanisms. Immunosuppression is mediated by nTregs through constitutive PD-L1 expression, yet PD-1 inhibitors fail to effectively eliminate this population [6]. Furthermore, PD-1 inhibitors trigger compensatory upregulation of immune checkpoints such as TIM-3 driving T cell exhaustion on effector T cells [14] which further triggers adaptive resistance and thus diminishes therapeutic efficacy [15].

GBM is classified as an "immune desert" tumor due to minimal effector T cell infiltration and insufficient antitumor immunity. Low MHC class I expression further restricts antigen recognition [6]. Pronounced intratumoral heterogeneity diversifies immunosuppressive mechanisms across tumor regions, rendering single-target PD-1/PD-L1 inhibition inadequate. Regional BBB integrity varies significantly within GBM. Vascular abnormalities or inflammatory factors (e.g., VEGF) cause localized BBB "leakage" [14], while other regions remain intact. This heterogeneity restricts uniform drug distribution, limiting intratumoral PD-1 inhibitor concentrations and overall efficacy [6,14].

4. Reversing resistance to PD-1/PD-L1 inhibitors

4.1. Reversing the immunosuppressive TME

Dual targeting of CSF-1R and PD-1 represents a viable strategy for reversing TME immunosuppression and inhibiting tumor growth. Resistance to PD-1 inhibitor monotherapy is primarily mediated by tumor-associated macrophages (TAMs), impeding CD8+ T-cell functionality by suppressing activation markers such as CD154. CSF-1R inhibitor BLZ945 selectively depletes M2-TAMs, evidenced by reduced CD163 expression, and decreased TGF-β1/IL-10 secretion. The combination of BLZ945 with PD-1 inhibitors overcomes resistance by significantly enhancing CD154+CD8+ T-cell infiltration, promoting pro-inflammatory TNF-α release, and inducing tumor apoptosis [16]. Similar combinatorial benefits are observed in colorectal cancer models, validating the mechanism across cancer types [17].

The resistance application strategy that simultaneously targets TGF-β and PD-L1 has supported by the phase I expansion cohort trial (NCT02517398) in recurrent glioblastoma patients. Bintrafusp alfa (M7824) overcomes resistance to PD-1 inhibitors through its bifunctional mechanism simultaneously targeting TGF-β and PD-L1 [18]. TGF-β is overexpressed in the immunosuppressive TME and drives immune evasion by promoting Treg activation, suppressing effector T-cell function. Bintrafusp alfa combats this resistance through its dual-pronged strategy. The extracellular domain of TGF-βRII functions as a TGF-β "trap", neutralizing TGF-β signaling, thereby reversing the inhibition of immune cells exerted by TGF-β and restoring T-cell-mediated antitumor activity. Simultaneously, the human IgG1 antibody in Bintrafusp alfa blocks PD-L1 binding to PD-1, alleviating T-cell exhaustion and enhancing immune responses.

DOI: 10.54254/2753-8818/2025.AU26462

Combined blockade using a CXCR4 antagonist (e.g., AMD3100) and a PD-1 inhibitor significantly enhanced the efficacy of PD-1 monotherapy reported in a preclinical research [19]. CXCR4 antagonist reprograms the immunosuppressive "cold" TME into an immunologically active "hot" state by inhibiting the CXCL12/CXCR4 signaling and thus increasing the infiltration and proportion of CD8+ T lymphocytes. This dual mechanism reduced immunosuppressive cell populations and simultaneously blocked the compensatory PD-L1 upregulation, resulting in a potentiated antitumor immune response. A parallel study in hepatocellular carcinoma demonstrated similar resistance mechanisms [20].

4.2. Targeting genomic and epigenetic aberrations

A preclinical study in a GL26 syngeneic glioblastoma mouse model reported that PARP-targeted alpha-particle therapy ([^{211}At]MM4) overcomes resistance to PD-1 inhibition by remodeling the immunosuppressive TME and enhancing immunogenicity [21]. Mechanistically, high-linear energy transfer alpha-particles from [^{211}At]MM4 induced direct DNA double-strand breaks(DSBs) in tumor cells, leading to the release of damage-associated molecular patterns (DAMPs). DAMPs promoted phagocytic activity of macrophages and enhanced T-cell infiltration, thereby reversing TME immunosuppression. Furthermore, DSBs promoted the release of tumor antigens. Subsequent activation of the innate immune response, in combination with PD-1 blockade, mitigated PD-L1-induced T-cell exhaustion and synergistically enhanced both antigen presentation and T-cell activation. All mice (100%) in the combination group remained disease-free, demonstrating effective reversal of PD-1 inhibitor resistance through systemic immune activation.

Triple therapy combining anti-CD47 antibody, TMZ, and PD-1 blockade effectively overcomes acquired resistance to anti-PD-1 therapy by dual-targeting innate and adaptive immunity [22]. Combining TMZ solely with PD-1 blockade proved insufficient due to inadequate innate immune activation. Tumor cells continued to evade phagocytosis via the CD47-SIRPα "don't eat me" signal, and subsequent T-cell cross-priming remained deficient. The addition of CD47 blockade directly inhibited this immune evasion signal, synergizing with TMZ to significantly amplify the pro-phagocytic effect of antigen-presenting cells. This sequential approach resulted in long-term remission in 55% of GL261 glioma models. Furthermore, the combination therapy increased serum levels of IL-2 and TNFα, indicative of a systemic antitumor response.

Epigenetic silencing of AP-2α represents a key mechanism underlying resistance to anti-PD-1 immunotherapy. The AP-2α promoter is hypermethylated and silenced by the EZH2/H3K27me3/DNMT1 complex in 99% of GBM cases, leading to its low expression. This downregulation of AP-2α results in the upregulation of PD-L1, facilitating tumor immune evasion through the PD-1/PD-L1 pathway, which contributes to poor response to immune checkpoint inhibitors. The DNA methyltransferase inhibitor (Decitabine) reactivates AP-2α, restoring its tumor-suppressive function [23]. Combining Decitabine with anti-PD-1 antibodies significantly reduced tumor volume and delayed progression. The combination therapy also markedly increased CD8+ T cell infiltration, enhanced proliferation, and elevated effector molecule expression, overcoming T cell exhaustion in the tumor microenvironment.

4.3. Restoring T cell function and optimizing delivery

The combined blockade of PD-1 and TIM-3 receptors overcomes PD-1 inhibitor resistance by cooperatively reversing T cell exhaustion and modulating immunosuppressive Tregs. In murine glioblastoma models, PD-1^{+}TIM-3^{+} TILs exhibit severe functional impairment characterized by

DOI: 10.54254/2753-8818/2025.AU26462

reduced IFNγ/ TNFα production and diminished proliferative capacity [24]. While anti-PD-1 monotherapy yielded an overall survival of 27.8%, combination with anti-TIM-3 therapy significantly increased OS to 57.9%, demonstrating critical reversal of PD-1 pathway resistance. Immune profiling demonstrated that the triple therapy, consisting of anti-PD-1, anti-TIM-3, and stereotactic radiosurgery (SRS), further promotes durable immunity by optimizing T cell functional quality.

The combination of MSC_IL-12 and anti-PD-1 blockade effectively overcomes resistance mechanisms to PD-1 inhibitors in glioblastoma by reshaping the immunosuppressive TME [25]. MSC_IL-12 delivers sustained IL-12 directly to the tumor site via its pathotropism, secreting functional IL-12 for over 30 days and augmenting $CD4^+$ T cell and NK cell infiltration. Single-cell RNA-seq analysis confirmed that the combined therapy significantly decreased exhausted T cells and M2-polarized microglia while increasing activated microglia, collectively reversing the immune-resistant milieu. This synergy resulted in a complete tumor remission rate of 50.0% in the combination group, substantially higher than anti-PD-1 alone (25.0%), demonstrating enhanced efficacy against resistance. The intratumoral delivery of MSC_IL-12 bypassed the blood-brain barrier, ensuring high local cytokine concentrations and minimizing systemic toxicity.

The blood-brain barrier (BBB), uniquely restrictive in GBM, constitutes a core mechanism limiting PD-1 inhibitor delivery and contributing to therapeutic resistance. Focused ultrasound (FUS) combined with microbubbles transiently opens the BBB, significantly enhancing the permeability of large-molecule antibodies like PD-1 inhibitors into brain tissue [26]. This physical disruption overcomes the BBB's natural blockade to immune checkpoint inhibitors, addressing the critical limitation of inadequate drug delivery to tumor sites observed with monotherapy. Experimentally, the combination group demonstrated significantly reduced tumor volume and prolonged survival in rat models, offering a novel strategy for GBM immunotherapy.

5. Conclusion

Immunosuppressive tumor microenvironment serves as the core mechanism driving resistance to PD-1 inhibitors. Myeloid-derived suppressor cells, M2-type tumor-associated macrophages, and inhibitory cytokines (e.g., IL-10 and TGF-β) establish a collaborative network that attenuates the immune response. Reversal of TME-mediated immunosuppression constitutes a primary strategy to overcome this resistance. Dual blockade targeting CSF-1R, TGF-β, and CXCR4 has been shown to create a more favorable microenvironment for PD-1 inhibitors. Extracellular vesicles (EVs) assume a pivotal role in shaping the TME. It has been reported that heparin impedes the interaction between EVs and target cells, partially reinstating T cell proliferation and inhibiting immunosuppressive reprogramming. The combination of heparin and PD-1 inhibitors might represent a potential approach to overcome the TME suppression.

Genomic instability and epigenetic dysregulation, including PTEN loss, MAPK pathway activation, MMRD, and EGFR amplification, collectively contribute to the immune escape mechanism of glioblastoma, leading to sustained resistance to PD-1 inhibitors. Targetting genomic and epigenetic abnormalities remains a primary research focus in combating immunotherapy resistance. PARP targeted therapy promotes the release of tumor antigens, sensitizing tumors to PD-1 inhibitors. Triple combination therapy of anti-CD47 antibodies, temozolomide and PD-1 inhibitors co-activates innate and adaptive immunity to overcome TMZ-associated acquired resistance. DNA methylation inhibitors facilitate epigenetic reprogramming, enhancing the efficacy of PD-1 inhibitors. In head and neck squamous cell carcinoma (HNSCC), PI3K inhibition (e.g., Buparlisib) downregulates PD-L1 expression by suppressing the PI3K/Akt/mTOR pathway, potentially

DOI: 10.54254/2753-8818/2025.AU26462

reversing immune resistance in PTEN-deficient tumors. Dual targeting of PI3K and PD-1 could exhibit a comparable effect in GBM.

T cell dysfunction and glioblastoma-specific physical barriers collectively drive inadequate T cell infiltration. PD-1 inhibitors are unable to effectively and durably initiate the immune response. Restoring T cell functionality and enhancing drug delivery are prevalent research strategies for reversing PD-1 resistance. The combined treatment of PD-1 inhibitors with TIM-3 inhibitors counter T cell exhaustion and reinstate T cell function. Combination of CBP/β-catenin antagonists and CAR-T cells has been used to facilitate more efficient dendritic cell antigen presentation and enhance T cell responses. This combined treatment may also augment the efficacy of PD-1 inhibitors. Engineered mesenchymal stem cells expressing IL-12 (MSC_IL12) or ultrasonic technology can surmount the physical barrier constraints of the blood-brain barrier and enhance CNS drug delivery. Facilitating the penetration of drugs and immune cells into the brain offers potential solutions for sustained immune activation.

References

[1] Tang, J., Karbhari, N., & Campian, J. L. (2025). Therapeutic Targets in Glioblastoma: Molecular Pathways, Emerging Strategies, and Future Directions. Cells, 14(7), 494.

[2] Grochans, S., Cybulska, A. M., Simińska, D., Korbecki, J., Kojder, K., Chlubek, D., & Baranowska-Bosiacka, I. (2022). Epidemiology of Glioblastoma Multiforme–Literature Review. Cancers, 14(10), 2412.

[3] Obrador, E., Moreno-Murciano, P., Oriol-Caballo, M., López-Blanch, R., Pineda, B., Gutiérrez-Arroyo, J. L., Loras, A., Gonzalez-Bonet, L. G., Martinez-Cadenas, C., Estrela, J. M., & Marqués-Torrejón, M. Á. (2024). Glioblastoma Therapy: Past, Present and Future. International Journal of Molecular Sciences, 25(5), 2529.

[4] Agosti, E., Zeppieri, M., De Maria, L., Tedeschi, C., Fontanella, M. M., Panciani, P. P., & Ius, T. (2023). Glioblastoma Immunotherapy: A Systematic Review of the Present Strategies and Prospects for Advancements. International Journal of Molecular Sciences, 24(20), 15037.

[5] Singh, S., Dey, D., Barik, D., Mohapatra, I., Kim, S., Sharma, M., Prasad, S., Wang, P., Singh, A., & Singh, G. (2025). Glioblastoma at the crossroads: current understanding and future therapeutic horizons. Signal transduction and targeted therapy, 10(1), 213.

[6] Khasraw, M., Reardon, D. A., Weller, M., & Sampson, J. H. (2020). PD-1 Inhibitors: Do they have a Future in the Treatment of Glioblastoma?. Clinical cancer research : an official journal of the American Association for Cancer Research, 26(20), 5287–5296.

[7] Reardon DA, Omuro A, Brandes AA, Rieger J, Wick A, Sepulveda J, Phuphanich S, de Souza P, Ahluwalia MS, Lim M, Vlahovic G, Sampson J. OS10.3 randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. Neuro Oncol. 2017; 19: iii21

[8] Reardon, D. A., Kim, T. M., Frenel, J. S., Simonelli, M., Lopez, J., Subramaniam, D. S., Siu, L. L., Wang, H., Krishnan, S., Stein, K., & Massard, C. (2021). Treatment with pembrolizumab in programmed death ligand 1-positive recurrent glioblastoma: Results from the multicohort phase 1 KEYNOTE-028 trial. Cancer, 127(10), 1620–1629.

[9] Yang, T., Kong, Z., & Ma, W. (2020). PD-1/PD-L1 immune checkpoint inhibitors in glioblastoma: clinical studies, challenges and potential. Human Vaccines & Immunotherapeutics, 17(2), 546–553.

[10] Zhao, Y., Song, Y., Li, W., Wu, J., Zhao, Z., Qu, T., Xiao, H., Wang, M., Zhu, M., Zheng, P., Wan, H., Song, Q., Zheng, H., & Wang, S. (2025). Clofazimine enhances anti-PD-1 immunotherapy in glioblastoma by inhibiting Wnt6 signaling and modulating the tumor immune microenvironment. Cancer immunology, immunotherapy : CII, 74(4), 137.

[11] Wu, J., & Wang, N. (2024). Current progress of anti-PD-1/PDL1 immunotherapy for glioblastoma (Review). Molecular medicine reports, 30(6), 221. https: //doi.org/10.3892/mmr.2024.13344

[12] Jung, M. Y., Aibaidula, A., Brown, D. A., Himes, B. T., Cumba Garcia, L. M., & Parney, I. F. (2022). Superinduction of immunosuppressive glioblastoma extracellular vesicles by IFN-γ through PD-L1 and IDO1. Neuro-oncology advances, 4(1), vdac017.

[13] Gong, L., Ji, L., Xu, D., Wang, J., & Zou, J. (2021). TGF-β links glycolysis and immunosuppression in glioblastoma. Histology and histopathology, 36(11), 1111–1124. https: //doi.org/10.14670/HH-18-366

DOI: 10.54254/2753-8818/2025.AU26462

[14] Fu, M., Xue, B., Miao, X., & Gao, Z. (2025). Overcoming immunotherapy resistance in glioblastoma: challenges and emerging strategies. Frontiers in pharmacology, 16, 1584688.
[15] Wang, E. J., Chen, J. S., Jain, S., Morshed, R. A., Haddad, A. F., Gill, S., Beniwal, A. S., & Aghi, M. K. (2021). Immunotherapy Resistance in Glioblastoma. Frontiers in genetics, 12, 750675.
[16] Cui, X., Ma, C., Vasudevaraja, V., Serrano, J., Tong, J., Peng, Y., Delorenzo, M., Shen, G., Frenster, J., Morales, R. T., Qian, W., Tsirigos, A., Chi, A. S., Jain, R., Kurz, S. C., Sulman, E. P., Placantonakis, D. G., Snuderl, M., & Chen, W. (2020). Dissecting the immunosuppressive tumor microenvironments in Glioblastoma-on-a-Chip for optimized PD-1 immunotherapy. eLife, 9, e52253.
[17] Shimizu, D., Yuge, R., Kitadai, Y., Ariyoshi, M., Miyamoto, R., Hiyama, Y., Takigawa, H., Urabe, Y., & Oka, S. (2024). Pexidartinib and Immune Checkpoint Inhibitors Combine to Activate Tumor Immunity in a Murine Colorectal Cancer Model by Depleting M2 Macrophages Differentiated by Cancer-Associated Fibroblasts. International journal of molecular sciences, 25(13), 7001.
[18] Khasraw, M., Weller, M., Lorente, D., Kolibaba, K., Lee, C. K., Gedye, C., I de La Fuente, M., Vicente, D., Reardon, D. A., Gan, H. K., Scott, A. M., Dussault, I., Helwig, C., Ojalvo, L. S., Gourmelon, C., & Groves, M. (2021). Bintrafusp alfa (M7824), a bifunctional fusion protein targeting TGF-β and PD-L1: results from a phase I expansion cohort in patients with recurrent glioblastoma. Neuro-oncology advances, 3(1), vdab058.
[19] Wei, R., Li, J., Lin, W., Pang, X., Yang, H., Lai, S., Wei, X., Jiang, X., Yuan, Y., & Yang, R. (2024). Nanoparticle-mediated blockade of CXCL12/CXCR4 signaling enhances glioblastoma immunotherapy: Monitoring early responses with MRI radiomics. Acta biomaterialia, 177, 414–430. https: //doi.org/10.1016/j.actbio.2024.02.007
[20] Morita, S., Lei, P. J., Shigeta, K., Ando, T., Kobayashi, T., Kikuchi, H., Matsui, A., Huang, P., Pittet, M. J., & Duda, D. G. (2025). Combination CXCR4 and PD-1 Blockade Enhances Intratumoral Dendritic Cell Activation and Immune Responses Against Hepatocellular Carcinoma. Cancer immunology research, 13(2), 162–170.
[21] Dabagian, H., Taghvaee, T., Martorano, P., Martinez, D., Samanta, M., Watkins, C. M., Chai, R., Mansfield, A., Graham, T. J., Maris, J. M., Pryma, D. A., Mach, R. H., & Makvandi, M. (2021). PARP Targeted Alpha-Particle Therapy Enhances Response to PD-1 Immune-Checkpoint Blockade in a Syngeneic Mouse Model of Glioblastoma. ACS pharmacology & translational science, 4(1), 344–351.
[22] von Roemeling, C. A., Wang, Y., Qie, Y., Yuan, H., Zhao, H., Liu, X., Yang, Z., Yang, M., Deng, W., Bruno, K. A., Chan, C. K., Lee, A. S., Rosenfeld, S. S., Yun, K., Johnson, A. J., Mitchell, D. A., Jiang, W., & Kim, B. Y. S. (2020). Therapeutic modulation of phagocytosis in glioblastoma can activate both innate and adaptive antitumour immunity. Nature communications, 11(1), 1508.
[23] Long, S., Huang, G., Ouyang, M., Xiao, K., Zhou, H., Hou, A., Li, Z., Zhong, Z., Zhong, D., Wang, Q., Xiang, S., & Ding, X. (2023). Epigenetically modified AP-2α by DNA methyltransferase facilitates glioma immune evasion by upregulating PD-L1 expression.
[24] Kim, J. E., Patel, M. A., Mangraviti, A., Kim, E. S., Theodros, D., Velarde, E., Liu, A., Sankey, E. W., Tam, A., Xu, H., Mathios, D., Jackson, C. M., Harris-Bookman, S., Garzon-Muvdi, T., Sheu, M., Martin, A. M., Tyler, B. M., Tran, P. T., Ye, X., Olivi, A., … Lim, M. (2017). Combination Therapy with Anti-PD-1, Anti-TIM-3, and Focal Radiation Results in Regression of Murine Gliomas. Clinical cancer research : an official journal of the American Association for Cancer Research, 23(1), 124–136.
[25] Park, J., Park, S. A., Kim, Y. S., Kim, D., Shin, S., Lee, S. H., Jeun, S. S., Chung, Y. J., & Ahn, S. (2024). Intratumoral IL-12 delivery via mesenchymal stem cells combined with PD-1 blockade leads to long-term antitumor immunity in a mouse glioblastoma model. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 173, 115790.
[26] Shan, H., Zheng, G., Bao, S., Yang, H., Shrestha, U. D., Li, G., Duan, X., Du, X., Ke, T., & Liao, C. (2024). Tumor perfusion enhancement by focus ultrasound-induced blood-brain barrier opening to potentiate anti-PD-1 immunotherapy of glioma. Translational oncology, 49, 102115.