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Targeting Immune Activation and Suppression Genes in Glioma: Implications for Immunotherapy

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Abstract

Gliomas, a type of brain tumor originating in glial cells, present great challenges in treatment due to their heterogeneous nature and resistance to immunotherapy. This computational bioinformatic study aimed to identify immune-related gene expression trends that may provide future immunotherapeutic strategies. Using publicly available datasets from the GlioVis database and the Adult TCGA_GBMLGG dataset, expression patterns of 22 immune suppression and 10 immune activation genes were examined by grade to uncover genes associated with tumor progression. Statistical analysis highlighted five immune suppression genes—Fibrinogen-like protein 2 (FGL2), Programmed cell death protein 1 (PDCD1), Programmed death-ligand 2 (PDCD1LG2), B7-H3 (CD276), Lymphocyte-activation gene 3 (LAG3))—and two immune activation genes (Tumor necrosis factor (TNF), Killer Cell Lectin Like Receptor K1 (KLRK1)) as showing notable changes in expression. When integrated with current literature, these findings suggest that immunotherapeutic targets such as PDCD1 and LAG3 inhibitors may enhance immune activation and help overcome glioma resistance. This study underscores the potential of combining immune checkpoint inhibition with immune activation strategies to improve outcomes for glioma patients and advance the development of more effective treatments.

Keywords: Glioma Immunotherapy, Immune Activation Genes, Immune Suppression Genes, Brain Tumor Immunology, PDCD1 and LAG3 Inhibitors, Tumor Microenvironment in Glioma, Gene Expression in Glioma Therapy

1. Introduction

Gliomas, tumors originating in glial cells of the brain or spinal cord, are among the most aggressive and treatment-resistant cancers. Approximately six glioma cases are diagnosed per 100,000 people annually in the United States (Mesfin et al., 2024). These tumors arise from abnormal proliferation of glial cells (Greek: glia, “glue”) and are classified by cell type and malignancy grade—a system first introduced by Bailey and Cushing (Nomiya et al., 2007; Stoyanov & Dzhenkov, 2018). High-grade gliomas (HGG) (III-IV), such as glioblastoma (GBM) are known for their infiltrative nature and poor prognosis, while pilocytic astrocytomas tend to grow more slowly (Mesfin et al., 2024).

Current standards of care include maximal surgical resection followed by radiotherapy and temozolomide chemotherapy, which has extended the median survival time (MST) from 12.1 to 14.1 months (Stupp et al., 2009; Sanai et al., 2011; Bush et al., 2017). However, the prognosis of HGG remains poor, with overall survival ranging from 13-26 months depending on grade (Lacroix et al., 2001; Prasat Neurological Institute, 2024). The fact that glioma cells closely resemble healthy glial cells presents a notable challenge, complicating immune detection (Mayo Clinic, 2024; Stupp et al., 2009; McGirt et al., 2009).

In other cancers such as melanoma and lung cancer, immunotherapies such as adoptive cell transfer (ACT), immune checkpoint inhibitors (ICIs), cancer vaccines, cytokine therapies, and oncolytic viruses have demonstrated considerable success (Knight et al., 2023; Massarelli et al., 2014). Furthermore, monoclonal antibodies targeting

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PDCD1 and its ligand (PDL-1) have shown success in reactivating cytotoxic T cells in many solid tumors (Holt et al., 2011). These strategies rely on the immune system's ability to recognize and eliminate tumor cells. Furthermore, according to *Immunotherapy to Treat Cancer,* tumor-infiltration lymphocytes (TILs) have been associated with improved outcomes, and new technologies like single-cell RNA sequencing and CyTOF have advanced our understanding of immune cell heterogeneity within tumors (Zhang and Zhang, 2020). However, gliomas remain largely unresponsive to these approaches, highlighting a critical research gap: the lack of well-defined molecular targets that can reliably activate immune responses in glioma.

This study addresses the gap by performing computational bioinformatic analysis of 22 immune suppression and 10 immune activation genes across glioma grades using the GlioVis TCGA_GBMLGG dataset.

By examining differential expression patterns of these immune-related genes, this study highlights potential therapeutic avenues for immunomodulation in glioma.

2. Materials and Methods

As shown in Table 1, a panel of 22 immune suppressive and 10 immune activation genes was curated based on their previous roles in tumor immunology, particularly within gliomas and related solid tumors. Selection of these genes was guided by published literature identifying them as key regulators of immune activation, suppression, or interaction with the tumor microenvironment. These genes were analyzed using the GlioVis online platform, focusing on the Adult TCGA_GBMLGG dataset and primary tumor type samples.

Table 1. List of Genes Analyzed Across Glioma Samples

Immune Suppression Marker List	Immune Activation Marker List
TGFB1	TNF
IDO1	TNFSF10
IL4	IFNG
IL10	GZMA
SPP1	PRF1
FGL2	FASLG
LGALS3	NKG7
PDCD1	KLRK1
CD274	TMEM173
PDCD1LG2	IRF3
CD276	
CTLA4	
KLRC1	
KLRK1	
ENTPD1	
NT5E	
ADORA2A	
HAVCR2	
LAG3	
TIGIT	
VSIR	
LAIR1	

Note. Genes were chosen based on prior literature identifying their roles in tumor immunology, particularly within gliomas. The list provided was analyzed using data from the TCGA_GBMLGG dataset to investigate gene expression patterns across glioma grades.

Table 2. Breakdown of Immune Suppressive Gene Grades (II, III, IV) and 25% percentiles with median mRNA expression levels

Grade 2	Grade 3	Grade 4
Q1 (25th percentile):	Q1 (25th percentile):	Q1 (25th percentile):
IDO1 (-1) IL4 (-1) CTLA4 (1.76) KLRC1 (0.55) PDCD1 (1.10)	TGFB1 (0.58) IDO1 (0.58) IL4 (-1) CTLA4 (1.92) KLRC1 (0.65)	IL4 (-1) TGFB1 (0.58) IDO1 (0.58) KLRC1 (0.65)
Q2 (50th percentile):	Q2 (50th percentile):	Q2 (50th percentile):
IL10 (2.02) LGALS3 (8.29) CD274 (3.26) PDCD1LG2 (4.19) KLRK1 (6.59) ADORA2A (6.58) TIGIT (2.28)	IL10 (2.25) FGL2 (8.15) PDCD1 (1.83) CD274 (3.71) PDCD1LG2 (4.90) ADORA2A (6.68) KLRK1 (6.42) TIGIT (2.44)	IL10 (2.25) CTLA4 (2.69) PDCD1 (1.83) CD274 (3.71) PDCD1LG2 (4.90) KLRK1 (6.42) TIGIT (2.44)
Q3 (75th percentile):	Q3 (75th percentile):	Q3 (75th percentile):
TGFB1 (9.56) SPP1 (12.48) FGL2 (7.43) CD276 (9.76) ENTPD1 (10.26) NT5E (9.72) HAVCR2 (8.54) LAG3 (3.71)	LGALS3 (8.54) ENTPD1 (10.28) NT5E (9.68) HAVCR2 (8.96) LAG3 (3.84) LAIR1 (8.12)	SPP1 (12.98) FGL2 (8.15) LGALS3 (8.54) CD276 (10.09) ENTPD1 (10.28) NT5E (9.68) HAVCR2 (8.96) LAG3 (3.84)
Q4 (100th percentile):	Q4 (100th percentile):	Q4 (100th percentile):
VSIR (10.78) LAIR1 (8.12)	SPP1 (12.98) CD276 (10.09) VSIR (10.82)	VSIR (10.82) ADORA2A (6.68) LAIR1 (8.12)

Note. Median mRNA expression levels were grouped by glioma grades II, III, and IV, then further divided into quartiles (25th, 50th, 75th, and 100th percentiles). Expression data was extracted from the Adult TCGA_GBMLGG dataset using the GlioVis database. From there, trends in gene expression were observed and compared across grades to identify patterns associated with tumor progression.

Expression data were extracted and stratified by glioma grade using GlioVis visualization and analysis tools, enabling the creation of set median mRNA expression values for each grade (II, III, IV). As shown in Table 2 and 3, each grade was then divided into four percentile groups (25th, 50th, 75th, 100th), allowing for comparative categorization based on expression distribution.

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Pairwise two-tailed t-tests were performed on median expression values using Microsoft Excel to determine whether gene expression varied significantly across grades. A significance threshold value of $p < 0.05$ was used. No multiple-testing correction was applied, as the analysis was exploratory in nature. Box plots were generated using Python libraries including Matplotlib and Seaborn based on GlioVis-extracted data.

Data validation was performed through manual cross-checking of median mRNA values between GlioVis visual outputs and statistical summaries. Genes with redundant entries or inconsistent expression values were excluded to maintain internal consistency and data accuracy.

Table 3. Breakdown of Immune Activation genes grades (II, III, IV) and 25% percentiles with median mRNA expression levels

Grade 2	Grade 3	Grade 4
Q1 (25th percentile):	Q1 (25th percentile):	Q1 (25th percentile):
IFNG (-1.0) GZMA (1.34) FASLG (-0.18)	IFNG (-1.0) GZMA (2.41) FASLG (0.15)	TNF (4.23) IFNG (-1.0) FASLG (1.18)
Q2 (50th percentile):	Q2 (50th percentile):	Q2 (50th percentile):
PRF1 (3.77) NKG7 (2.93)	PRF1 (4.24) NKG7 (3.63)	GZMA (4.4) KLRK1 (4.5)
Q3 (75th percentile):	Q3 (75th percentile):	Q3 (75th percentile):
TNF (4.65) KLRK1 (6.59)	TNF (4.71) KLRK1 (6.42)	PRF1 (6.18) NKG7 (5.02)
Q4 (100th percentile):	Q4 (100th percentile):	Q4 (100th percentile):
TNFSF10 (6.92) TMEM173 (7.36) IRF3 (9.05)	TNFSF10 (7.13) TMEM173 (7.78) IRF3 (9.2)	TNFSF10 (8.09) TMEM173 (8.44) IRF3 (9.64)

Note. Median mRNA expression levels were grouped by glioma grade II, III, IV and divided into percentile quartiles (25th, 50th, 75th, 100th). Expression data was extracted from the Adult TCGA_GBMLGG dataset using the GlioVis portal. Genes were then selected based on prior literature identifying their immunological roles in glioma progression. Lastly, descriptive trends were analyzed to observe potential associations with tumor grade, though no statistical tests were applied due to the exploratory nature of this study.

3. Results

Using extracted data from Table 2 and the calculated pairwise t-test p-values based on mRNA expression medians, 7 genes were collected: 5 immune suppression genes, and 2 immune activation genes. Genes showing statistically significant variation in mRNA expression across grades ($p < 0.05$) were prioritized for final selection. For example, PDCD1 ($p = 8.0 \times 10^{-6}$ between grades II and III; $p = 2.9 \times 10^{-23}$ between grades II and IV; $p = 8.4 \times 10^{-10}$ between grades III and IV) showed significant increases in expression with tumor grade. Similarly, **CD276** also demonstrated highly significant variation ($p = 8.7 \times 10^{-13}$ between grades II and III; $p = 7.6 \times 10^{-89}$ between grades II and IV; $p = 1.3 \times 10^{-55}$ between grades III and IV), reinforcing its relevance in tumor progression.

Final Immune Suppression Marker List: FGL2, PDCD1, PDCD1LG2, CD276, LAG3

Final Immune Activation Marker List: TNF, KLRK1

All selected genes demonstrated expression trends that were statistically significant or showed consistent changes across glioma grades, demonstrating their potential relevance in tumor progression. For example, PDCD1 expression increased from grade II (1.10) to grade IV (1.83). Likewise, CD276 rose from 9.776 in grade II to 10.09 in grade IV. TNF also increased across grades, with mRNA values of 4.65 (grade II), 4.71 (grade III), and 4.23 (grade IV).

Some immunosuppressive molecules, however, had little to no mRNA expression variation with grade and were excluded from final selection. These include IL-4 (II -1, III -1, IV -1), CTLA-4 (II 1.76, III 1.92, IV 2.69), KLRC1 (II 0.55, III 0.65, IV 0.65), ENTPD1 (II 10.26, III 10.28, IV 10.28), NT5E (II 9.72, III 9.68, IV 9.68), ADORA2A (II 6.58, III 6.68, IV 6.68), and TIGIT (II 2.28, III 2.44, IV 2.44).

Table 2 shows the median mRNA expression levels for immune suppression genes across grades II through IV. Some genes—including PDCD1, PDCD1LG2, and CD276—showed increasing expression across quartiles, supporting their selection. However, genes like IL-4 and NT5E had relatively constant mRNA levels, leading to their exclusion from the final list.

Table 3 provides a percentile breakdown of immune activation genes across each grade. Genes such as TNF, KLRK1, and IRF3 showed increases in mRNA expression across grades, especially in the upper quartiles. These changes support their inclusion in the final activation gene list, reflecting possible shifts in immune response during glioma progression over time. The percentile stratification further reveals how these genes behave on average and across expression distributions, providing a more detailed understanding of their potential activation and tumor progress.

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4. Discussion

This study examined previously published data and literature to evaluate the roles of the selected genes and their involvement in cancer. Furthermore, it examined whether these genes have been previously targeted and included in clinical trials.

Fibrinogen-like protein 2 (FGL2) is a prothrombinase contributing to fibrin deposition and thrombosis (Figure 1). It is expressed by endothelial cells, macrophages, and T cells, influencing inflammation and immune response modulation. In cancer (more specifically, in gliomas), FGL2, part of the thrombospondin family, has been found to play a critical role in regulating the activity of immune and tumor cells in GBMs, and plays a role in the GBM tumor microenvironment (ecosystem surrounding tumor), promoting malignant tumor progression. So, elucidating the role of this gene can help improve immunotherapy efficacy (Ma et al., 2022). A clinical trial observed FGL2's role in regulating immunosuppression, which may contribute to the malignant transformation of gliomas from low to high-grade by inhibiting T cell proliferation (Essam, 2019).

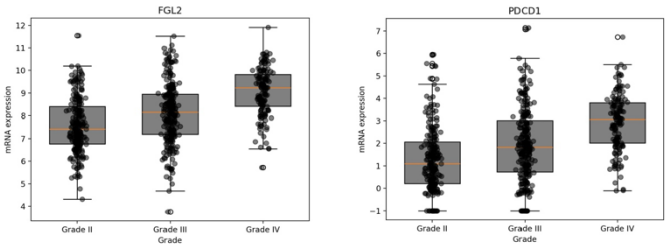

Figure 1. Box and whisker plot of FGL2 and PDCD1 mRNA expression based on glioma grade
Note. Lines represent the 25% median and 75 percentiles; whiskers represent the 1.5*(IQR).

Programmed cell death protein 1 (PD-1 or PDCD1) is an inhibitory receptor on T cells that, when engaged by its ligands (PD-L1 or PDCD1LG2), leads to the suppression of T-cell activity (Figure 1). PDCD1 plays a critical role in the regulation of immune responses and tolerance. As for its role in cancer, PDCD1 methylation provides an independent prognostic biomarker for the overall survival of patients diagnosed with lower-grade glioma. Additionally, it has also been found that its methylation is correlated with the infiltration of immune cells in lower-grade gliomas as well, leading to the possibility that the inhibition of the PDCD1/PD-L1 and CTLA-4 immune checkpoints is a promising therapeutic approach for the treatment of primary brain tumors (Röver et al., 2018).Additionally, according to a clinical trial, ERK1/2 phosphorylation can predict survival following PDCD1 immunotherapy in two independent recurrent glioblastoma (rGBM) patient cohorts (Arrieta et al., 2021). An interventional study in phase 1 evaluated PDCD1 knockout engineered T cells in treating metastatic non-small cell lung cancer, one of the major types of lung cancer (Lu, 2021).

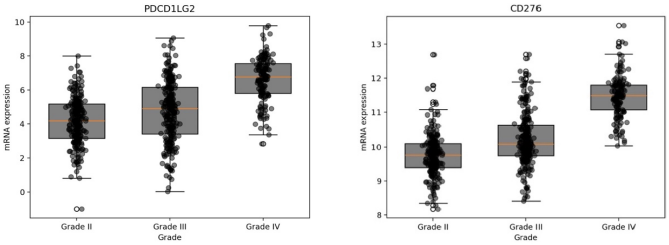

Figure 2. Box and whisker plot of PDCD1LG2 and CD276 mRNA expression based on glioma grade
Note. Lines represent the 25% median and 75 percentiles; whiskers represent the 1.5*(IQR).

Programmed death ligand 2 (PD-L2 or PDCD1LG2) is another ligand for PDCD1 and is expressed on macrophages, dendritic cells, and certain cancer cells (Figure 2). PDCD1LG2 was found to be correlated with immune infiltration and some anti-tumor immune functions. It functions similarly to PD-L1 by inhibiting T-cell activation. PDCD1LG2 is a prognostic biomarker for low-grade glioma (considered II and III from one study), providing insight into potential individualized glioma therapeutic strategies, and guiding effective immunotherapy (Xie et al., 2022). PDCD1LG2 has also been known to (along with PDCD1) hamper immune responses in tumors, including Chronic lymphocytic leukemia (CLL). A clinical trial has investigated the effects of vaccination of PD-L1 and PDCD1LG2 evokes responses that can overcome leukemic cells CLL (Pedersen, 2022).

B7-H3 (CD276) is a member of the B7 family of immune regulatory ligands and can inhibit the function of T cells (Figure 2). It is expressed on antigen-presenting cells and some tumor cells, playing a role in immune modulation.

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Additionally, based on systematic analysis, there is a possibility that CD276 may serve as a biomarker for cancer (Dai et al., 2023). Expressed on tumor-associated macrophages, CD276 plays a role in diminishing immune response against tumors (Cheng et al., 2024). There have been several clinical trials conducted using CAR- T cell therapy. An ongoing clinical study found that CD276 is highly expressed in glioblastoma on a subset of patients studied and looked to use CAR-T cells made from isolated patient peripheral blood mononuclear cells to attack glioblastoma cells containing CD276 (Second Affiliated Hospital, 2022).

Lymphocyte-activation gene 3 (LAG3), a novel immune checkpoint inhibitor and monoclonal antibody, negatively regulates T cell expansion and function (Figure 3). LAG3 is expressed on activated T cells, NK cells, B cells, and plasmacytoid dendritic cells, and demonstrates binding affinity to MHC class II molecules present on antigen-presenting cells. In a preclinical murine model, it has been shown that LAG3 inhibition with a blocking antibody is efficacious against GBM, and, with a combination of immune checkpoint inhibitors, can induce complete glioblastoma tumor eradication (Harris-Bookman et al., 2018). A clinical study aimed to determine the maximum dosage of anti-LAG3 which could potentially, alone or in combination with nivolumab—an anti-cancer medication, kill more tumor cells (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, 2023).

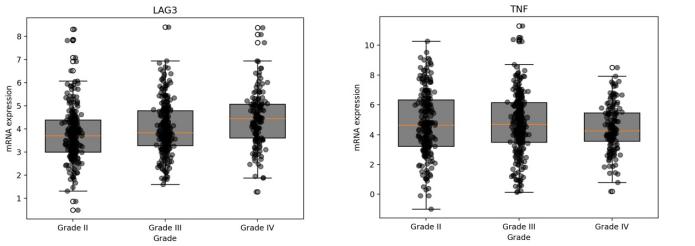

Figure 3. Box and whisker plot of LAG3 and TNF mRNA expression based on glioma grade.
Note. Lines represent the 25% median and 75 percentiles; whiskers represent the 1.5*(IQR).

Tumor necrosis factor (TNF) is a pro-inflammatory cytokine that is a member of the TNFSF family (Figure 3). It has a regulatory effect on immune cells and is involved in the acute inflammatory reaction, achieved by the infiltration of plasma and leukocytes into injured tissue. TNF acts as a mediator of the death receptor pathway of apoptosis (DeFilippo & Beck, 2018; Green, 2022). A clinical study attempted to study gene expression and early epigenetic changes in myeloid cells using Tough RNA-seq, and ATAC-seq. Immunological characteristics of the tumor will be evaluated through cytokine level analysis, including the use of TNF to elucidate potential treatment alternatives (Martinez, 2024).

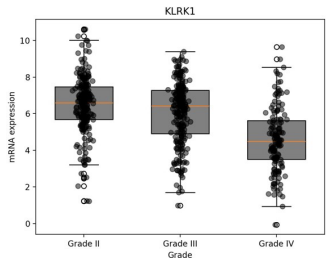

Figure 4. Box and whisker plot of KLRK1 mRNA expression based on glioma grade
Note. Lines represent the 25% median and 75 percentiles; whiskers represent the 1.5*(IQR).

Killer Cell Lectin Like Receptor K1 (KLRK1) are lymphocytes that mediate the lysis of tumor and virus- infected cells without previous infection (innate immune response), playing an additional role in humoral and cell- mediated immunity (Figure 4) (National Center for Biotechnology Information, 2025). Studies have shown that high KLRK1 expression has indicated a higher overall chance for survival among patients with lung cancer and may be a prognostic biomarker for lung adenocarcinoma cancer (Zhang et al., 2022). One preclinical study evaluated the NK cell-based immunotherapies targeting neuro-malignancies and tracking the delivery of infused NK cells through molecular neuroimaging to demonstrate cellular events (Fares et al., 2023).

When considered together, the selected immune suppression and activation genes highlight the complex and opposing forces that shape glioma immune regulation. Suppressive genes like PDCD1, LAG3, and CD276 contribute to immune evasion by inhibiting T cell activity, while activation genes like TNF and KLRK1 may represent the body's attempt to elicit an anti-tumor response. These pathways do not act in isolation, however; suppressive signals such as PDCD1 may counteract inflammatory pathways from genes like TNF, reflecting a dynamic yet immune-evasive tumor microenvironment. As gliomas progress, this imbalance appears to favor immune suppression, potentially explaining the limited efficacy of immunotherapies in HGGs (Hegde & Chen, 2020). Understanding how these immune pathways interact may guide the development of combination immunotherapies that target both checkpoint inhibition and immune activation to restore effective anti-tumor immunity.

While this study identifies key immune genes with expression changes across glioma grades, several limitations

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should be acknowledged. First, the analysis relied exclusively on transcriptomic data from the publicly available TCGA_GBMLGG dataset and did not include experimental validation. Although the dataset is well- established, further studies involving in vitro or in vivo experiments will be necessary to confirm the functional relevance of identified genes. Second, statistical comparisons were executed on median mRNA expression levels, and larger or independent datasets may be required to evaluate these trends. Third, the study did not include non- glioma or healthy tissue as a control group. The inclusion of such reference data could have provided a clearer contrast when interpreting relative expression shifts and strengthened the identification of tumor-specific alterations. Future analyses may benefit from including normal brain tissue controls to contextualize gene expression changes and enhance specificity. Additionally, future work should consider integrating healthy tissue comparisons and functional studies to enhance the robustness and contextual understanding of gene behavior in glioma progression.

5. Conclusion

The immunosuppressive gene FGL2 demonstrated the least effective role in eliminating tumor-induced cells. Given the limited research on FGL2 inhibition against glioma cells, further investigation is needed to fully understand its therapeutic potential. While FGL2 plays a role in modulating immune responses and inflammation, its effects appear to be less directly linked to tumor-specific immune activation. This could potentially reduce its efficacy in glioma treatment.

In contrast, a combined approach using PDCD1 and LAG3 inhibitors may offer more promising results. These targets have shown the ability to work synergistically, enhancing immune activation while reducing the risk of tumor resistance. Studies have shown that multi-gene strategies often prove more effective than single-gene therapies, potentially producing more sustained and stronger outcomes regarding tumor resistance.

Moreover, methylation of PDCD1 has provided a promising therapeutic approach for the treatment of brain tumors. Additionally, LAG3 has been found to induce glioma tumor eradication, increasing the survival rate of glioma patients. Thus, the blockage of PDCD1 and LAG3 may lead to tumor elimination and improved MST through the removal of inhibitory signals on T cells, leading to a stronger immune response against glioma cells. With this approach, the outcome for GBM patients, or patients with high-grade tumors, could take a radical turn in the field of cancer, and the medical field.

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