

ORIGINAL RESEARCH ARTICLE

Prognostic significance of *HTR6* expression and its association with immune infiltration in low-grade glioma

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Abstract

Introduction: Low-grade glioma (LGG), defined herein as WHO grade II and III diffuse gliomas including astrocytomas and oligodendrogliomas, is a clinically and molecularly heterogeneous group of primary brain tumors with variable outcomes, highlighting the need for reliable prognostic biomarkers and immune-related therapeutic targets.

Objective: The purpose of this research was to determine the prognostic significance of *HTR6* in LGG and its connection to immune cell infiltration.

Methods: Multiple bioinformatics analyses were performed to characterize *HTR6* expression in normal and tumor tissues and to examine its associations with clinicopathological characteristics, prognosis, and immune infiltration status.

Results: In LGG, *HTR6* expression was inversely correlated with *SPI1*, a candidate upstream transcription factor predicted to regulate *HTR6*. Low *HTR6* expression was closely linked to shorter overall survival and progression-free survival. Kaplan–Meier survival analysis, along with univariate and multivariate Cox regression analyses, suggested that *HTR6* expression is associated with prognosis in LGG. Functional enrichment and immune infiltration analyses demonstrated that *HTR6* was involved in immune-related pathways and correlated with tumor immune infiltration patterns, which was further confirmed by immune checkpoint gene correlation analysis.

Conclusion: Lower *HTR6* expression was associated with poorer survival outcomes and distinct immune-infiltration patterns in LGG. However, this study is limited by its retrospective bioinformatics-only design without experimental validation, and by the use of a traditional glioma classification system that does not fully incorporate the WHO 2021 molecular criteria (e.g., isocitrate dehydrogenase status and 1p/19q

codeletion). Therefore, the conclusions should be considered preliminary and warrant further verification.

Keywords: *HTR6*; Low-grade glioma; Immune infiltration; Prognostic biomarker

1. Introduction

Gliomas are common primary central nervous system (CNS) tumors and account for the majority of intracranial neoplasms.^{1,2} Clinically, diffuse gliomas have been broadly categorized into two main subtypes: low-grade glioma (LGG) and high-grade glioma (HGG).³ LGG is defined as WHO grade II and III diffuse gliomas, including astrocytomas and oligodendrogliomas. LGG exhibits substantial biological heterogeneity. Although multiple treatment options are available for LGG, treatment outcomes remain unsatisfactory in some patients.⁴ Certain patients with LGG have a poor prognosis and are at risk of progression to the deadly glioblastoma multiforme (GBM). For example, WHO grade II isocitrate dehydrogenase (IDH)-mutant astrocytomas may undergo malignant progression to astrocytoma, IDH-mutant, CNS WHO grade 4. Therefore, identifying novel prognostic biomarkers and therapeutic targets for LGG is important.

HTR6 encodes the 5-hydroxytryptamine receptor 6, a serotonin receptor expressed predominantly in the CNS, gastrointestinal tract, and platelets.⁵⁻⁷ *HTR6* regulates neuronal migration and *differentiation* during the development of the nervous system.⁸ Previous studies suggest that *HTR6* is essential for regulating dopaminergic function.⁹ Recent research has demonstrated a link between *HTR6* and a number of disorders of the nervous system, including major depressive disorder,¹⁰ sporadic Alzheimer's disease,¹¹ vestibular migraine,¹² and haloperidol-induced Parkinsonism.¹³ The significance of *HTR6* in carcinogenesis has also been demonstrated.^{14,15} *SPI1* regulates downstream genes such as *HTR6*. *SPI1* expression has recently been reported to be elevated in gliomas.¹⁶ Therefore, the potential roles of *HTR6* and *SPI1* in LGG warrant further investigation.

In the present study, we first assessed *HTR6* mRNA expression across selected normal human tissues and tumors and then examined the associations between *HTR6* mRNA expression and clinical characteristics. The prognostic significance of *HTR6* in LGG was evaluated by examining the association between lower *HTR6* expression and adverse patient outcomes. Functional enrichment analysis of *HTR6*-correlated genes, together with analyses of the associations of *HTR6* with immune-related genes

and immune cell infiltration, suggested that *HTR6* may be associated with the immune microenvironment. The association was further explored by analyzing the correlations of *HTR6* expression with immune checkpoint genes, immunostimulators, major histocompatibility complex (MHC) molecules, chemokine receptors, and chemokines. Finally, by assessing the expression of transcription factors (TFs) predicted to regulate *HTR6*, we investigated potential transcriptional mechanisms associated with *HTR6* downregulation and found that *HTR6* expression was inversely correlated with that of its upstream TF, *SPI1*.

2. Materials and methods

2.1. Gene Expression Profiling Interactive Analysis

The Cancer Genome Atlas (TCGA) data and the Genotype-Tissue Expression (GTEx) normal-tissue data were analyzed using Gene Expression Profiling Interactive Analysis (GEPIA2; <http://gepia2.cancer-pku.cn/>, accessed September 10, 2021), a web-based platform for gene expression profiling and interactive analysis. The sample classification was mainly based on an earlier classification system. Some cases lacked complete molecular classification information, such as IDH status and 1p/19q codeletion, and therefore could not be reclassified according to the 2021 WHO classification criteria in the original analysis. In this study, we examined *SPI1* and *HTR6* mRNA expression across normal human tissues and tumors and further quantified *HTR6* expression in LGG ($n = 518$) versus normal tissues ($n = 207$) using RNA sequencing data.

2.2. UALCAN

UALCAN (<https://ualcan.path.uab.edu/>, version 1.0) is a comprehensive online platform for cancer data analysis and mining that provides access to TCGA data. Using UALCAN, we assessed *HTR6* expression in LGG and its associations with various clinicopathological features, including race, sex, age, tumor grade, histological subtype, and *TP53* mutation status.

2.3. Kaplan–Meier Plotter

We utilized the Kaplan–Meier Plotter (<http://kmplot.com/analysis/>, accessed September 10, 2021) to assess the prognostic significance of *HTR6* in LGG. Patients with

LGG were divided into high- and low-expression groups based on *HTR6* expression levels, and the hazard ratios for overall survival (OS) and progression-free survival (PFS) were estimated with 95% confidence intervals and log-rank *p*-values.

2.4. Tumor immune infiltration analysis

ACLBI (<https://www.aclbi.com/static/index.html#/>, accessed September 10, 2021) is a web-based platform for analyzing TCGA data. The association between *HTR6* expression and immune infiltration levels was analyzed using ACLBI with six quantification algorithms: TIMER, EPIC, CIBERSORT, QUANTISEQ, MCPOUNTER, and XCell. EPIC, CIBERSORT, and QUANTISEQ primarily infer the absolute abundance of different cell subsets through deconvolution algorithms, whereas TIMER, MCPOUNTER, and XCell mainly compare the relative abundance of various cell types using marker gene-based approaches.

2.5. LinkedOmics

LinkedOmics (<https://www.linkedomics.org/#/>, accessed September 10, 2021), a publicly accessible online resource that integrates multi-omics data from TCGA and the Clinical Proteomic Tumor Analysis Consortium,¹⁷ was used to identify genes coexpressed with *HTR6*.

2.6. Human Transcription Factor Targets

Human Transcription Factor Targets (hTFtarget; <https://guolab.wchscu.cn/hTFtarget/#/>, accessed September 10, 2021) is an extensive repository that integrates data on human TFs and their target genes. hTFtarget was used to analyze potential upstream TFs regulating *HTR6* in brain tissue.

2.7. Statistical analysis

The Wilcoxon test was used to assess the significance of differential expression. Survival analysis was performed using the log-rank test. Univariate and multivariate Cox regression analyses were used to assess the effects of individual and multiple factors on the outcome, respectively. Correlation of *HTR6* expression with *SPI1* and *NRF1* expression was assessed using Spearman rank correlation analysis. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Decreased *HTR6* expression in low-grade glioma

Using GTEx data accessed through GEPIA, *HTR6* mRNA expression was examined across normal human tissues.

Elevated *HTR6* expression was observed in several organs, including the brain, pituitary gland, and testis, with particularly high expression in the brain (Figure 1A). TCGA analysis showed that *HTR6* mRNA expression was significantly lower in GBM, LGG, and kidney chromophobe (KICH), but significantly higher in kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), uterine corpus endometrial carcinoma (UCEC), breast invasive carcinoma (BRCA), and colon adenocarcinoma (COAD) (Figure 1B). Decreased *HTR6* expression in LGG was further confirmed by comparing its expression between LGG and normal tissues using GEPIA (Figure 1C).

3.2. Association of *HTR6* mRNA expression with clinical features

HTR6 expression was assessed according to several clinical parameters, including patient race, sex, age, tumor grade, histological subtype, and *TP53* mutation status, using the UALCAN online analysis tool. *HTR6* expression differed between Caucasian and Asian patients (Figure 2A). As shown in Figure 2B, *HTR6* expression was higher in female than in male patients ($p = 0.0174$). Regarding age or tumor grade, no statistically significant differences in *HTR6* expression were observed among the groups (Figure 2C and 2D). *HTR6* expression differed among patients with different histological subtypes: patients with oligodendroglioma showed the highest expression, those with oligoastrocytoma showed intermediate expression, and those with astrocytoma showed the lowest expression (Figure 2E). Patients with *TP53*-mutant LGG showed lower *HTR6* expression than those with *TP53* wild-type LGG (Figure 2F).

3.3. Association of low *HTR6* expression with poor prognosis in low-grade glioma

We examined the prognostic role of *HTR6* in LGG using the Kaplan–Meier Plotter. As shown in Figure 3A and 3B, low *HTR6* expression in patients with LGG was associated with worse OS and PFS. Univariate Cox regression analysis indicated significant associations of LGG prognosis with *HTR6* expression, age, tumor grade, and radiation therapy (Figure 3C). Multivariate Cox regression analysis identified age, tumor grade, and *HTR6* expression as significantly associated with LGG prognosis (Figure 3D). The nomogram assigned greater prognostic risk to lower *HTR6* expression and higher tumor grade (Figure 3E); calibration of the model is shown in Figure 3F. These findings suggest that *HTR6* expression, together with clinicopathological factors, may be useful for prognostic assessment in LGG.

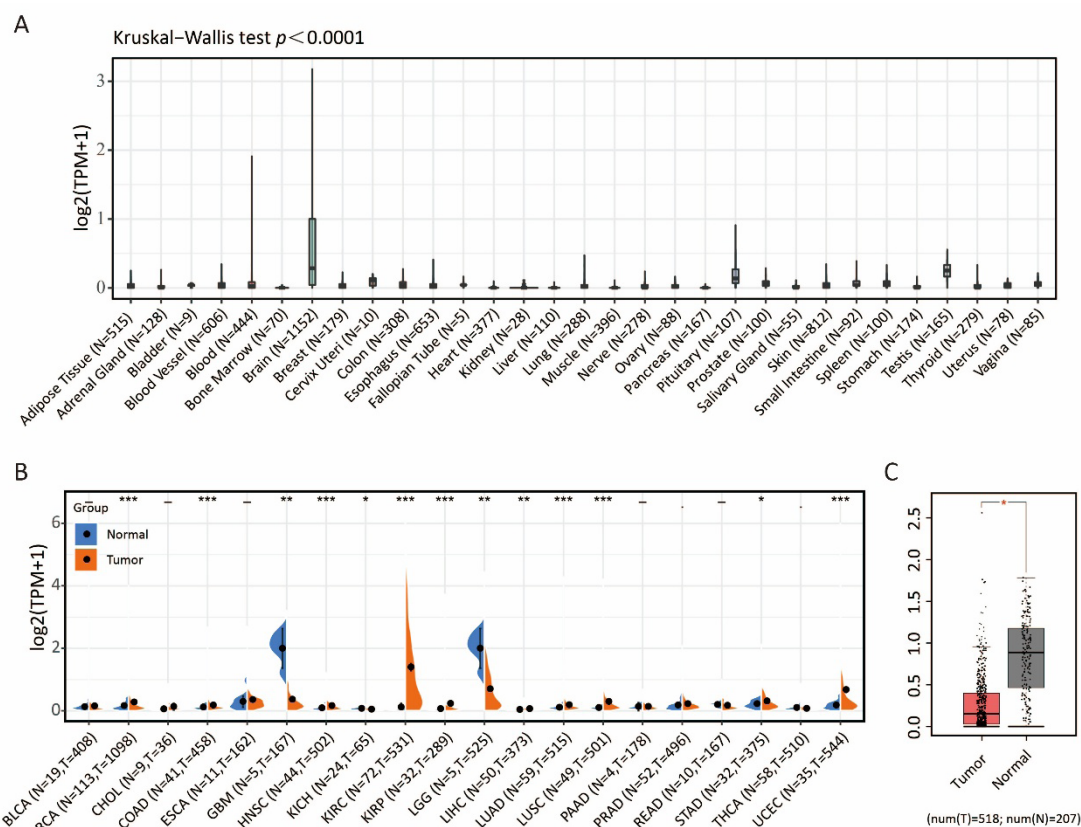


Figure 1. Reduced *HTR6* expression in low-grade glioma. *HTR6* expression in normal tissues was analyzed using data from (A) GTEx. (B) Pan-cancer *HTR6* expression in TCGA tumor and corresponding normal samples analyzed using GEPIA; (C) *HTR6* expression in LGG versus normal brain tissue using GEPIA.

Abbreviations: N: Normal tissues; T: Tumor tissues.

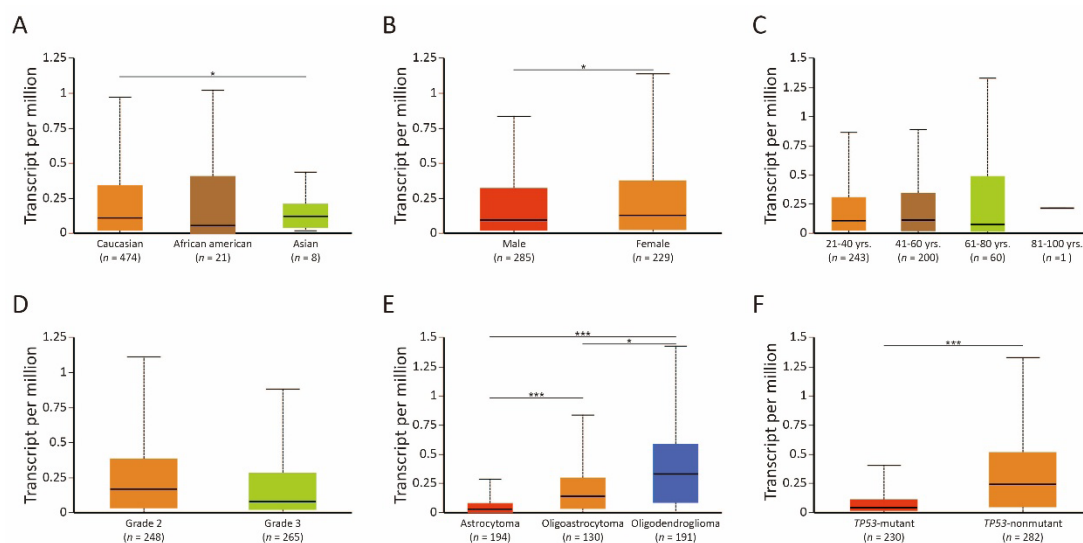


Figure 2. UALCAN box plots showing *HTR6* expression stratified by clinical parameters. (A) Race, (B) sex, (C) age, (D) tumor grade, (E) histological subtype, and (F) *TP53* mutation status.

Notes: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

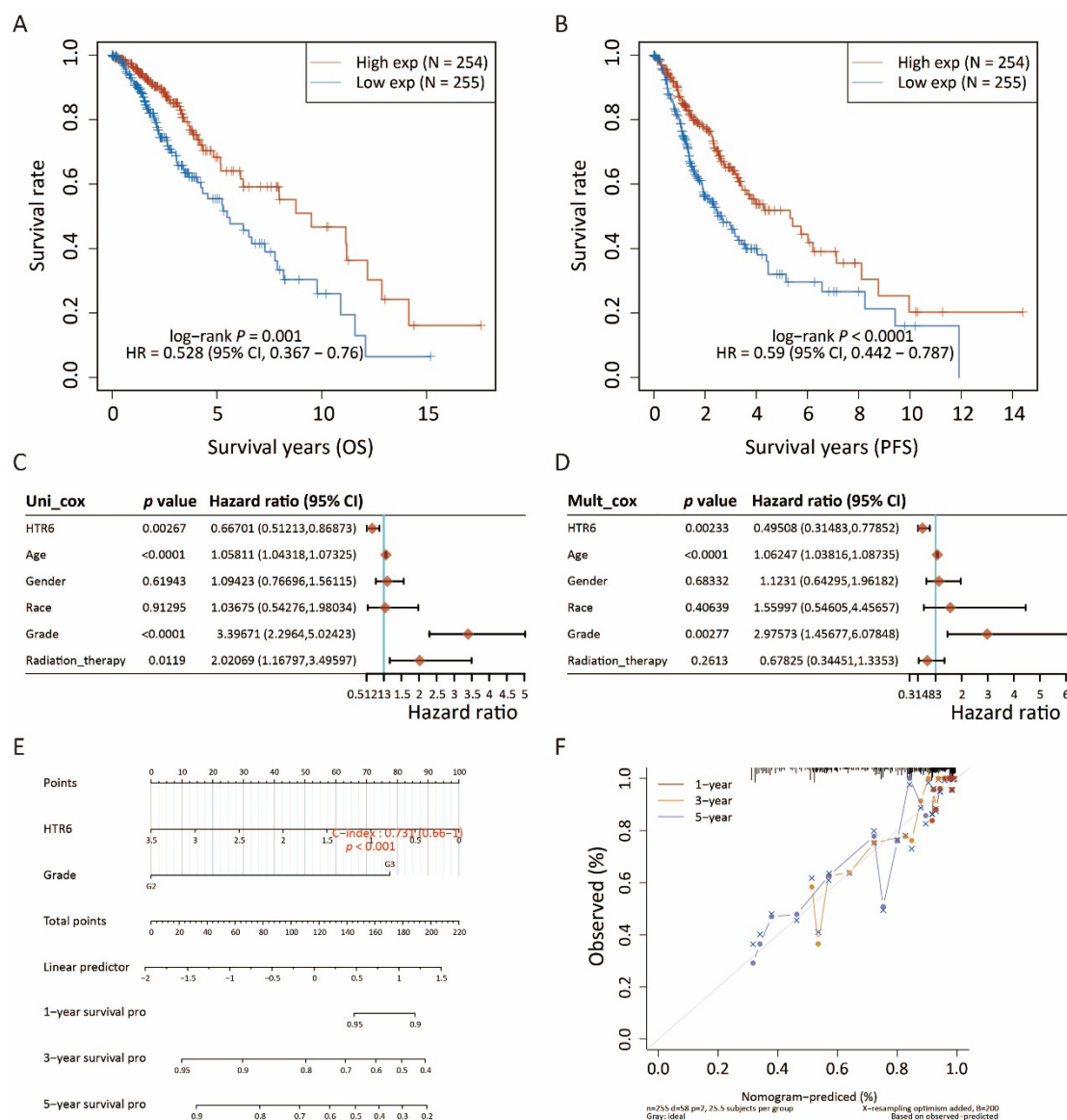


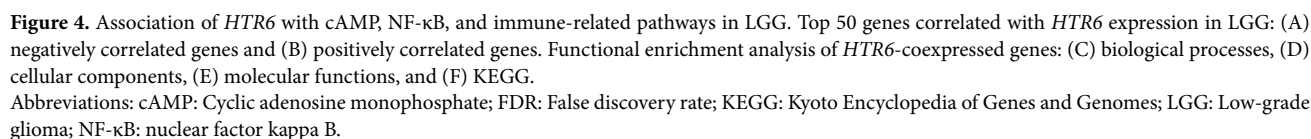
Figure 3. Associations of *HTR6* expression with prognosis in LGG. Kaplan–Meier survival curves for (A) OS and (B) PFS. (C) Univariate Cox regression analysis of prognostic factors in LGG. (D) Multivariate Cox regression analysis of prognostic factors in LGG. (E) Nomogram incorporating *HTR6* expression and tumor grade. (F) Calibration plot for 1-, 3-, and 5-year survival.

Abbreviations: CI: Confidence interval; LGG: low-grade glioma; OS: Overall survival; PFS: Progression-free survival.

3.4. Association of *HTR6* with cAMP, NF- κ B, and other immune-related pathways in low-grade glioma

Our findings indicated an association between decreased *HTR6* expression and LGG prognosis, prompting further investigation of *HTR6*-correlated genes and pathways using the LinkedOmics database. Figure 4A and 4B show the top 50 genes negatively and positively correlated with *HTR6* expression in LGG, respectively.

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were subsequently conducted using these related genes. Figure 4C shows significant enrichment of coexpressed genes in biological processes: neuroactive ligand-receptor interaction, cyclic adenosine monophosphate (cAMP) signaling pathway, synaptic vesicle circulation, calcium signaling pathway, leukocyte transendothelial migration, nuclear factor kappa B (NF- κ B) signaling pathway, and antigen processing and presentation. In the cellular component analysis,



the coexpressed genes were significantly enriched in the GABAergic synapse, immunological synapse, and MHC protein complex (Figure 4D). In terms of molecular function, the coexpressed genes were associated with neurotransmitter receptor activity, G protein-coupled amine receptor activity, MHC protein binding, and immunoglobulin binding (Figure 4E). KEGG analysis further revealed that coexpressed genes were primarily associated with neurotransmitter transport, recognition, calcium ion regulation of exocytosis, cytokine metabolism, regulation of innate immune response, and response to type I interferon (Figure 4F). These findings indicated that *HTR6*-correlated genes were associated with both nervous system functions and immune-related processes and pathways, suggesting a potential association of *HTR6* with neurological and immune functions.

3.5. Association of *HTR6* mRNA expression with immune infiltration

The involvement of *HTR6*-related genes in immune-related pathways prompted us to further examine the association between *HTR6* expression and tumor immune infiltration. CIBERSORT and Xcell revealed positive correlations between *HTR6* expression and plasma cell abundance (Figure 5A and 5F). Positive correlations between *HTR6* expression and natural killer (NK) cell abundance were observed using MCPOUNTER (Figure 5D) and QUANTISEQ (Figure 5E). Myeloid dendritic cell abundance (Figure 5C and 5D) and activated myeloid dendritic cell abundance (Figure 5A and 5F) were negatively correlated with *HTR6* expression. According to most algorithms, macrophage abundance also exhibited a negative correlation with *HTR6* expression (Figure 5B, 5C, 5D and 5F). These results suggested that *HTR6* expression was associated with immune infiltration patterns in LGG. A positive association between *HTR6* expression and CD8⁺ T-cell abundance was observed using EPIC (Figure 5B), whereas negative associations were observed using MCPOUNTER (Figure 5D) and QUANTISEQ (Figure 5E). The apparently contradictory patterns observed for certain immune cell types (e.g., CD8⁺ T cells) could be attributed to differences in the assumptions and technical frameworks underlying immune infiltration estimation algorithms. For instance, QUANTISEQ¹⁸ and MCPOUNTER¹⁹ may assign different weights to gene expression data when inferring CD8⁺ T-cell abundance, whereas EPIC²⁰ and TIMER²¹ may be more influenced by reference expression matrices. Thus, the opposing trends observed for CD8⁺ T cells may reflect differences in model assumptions and reference gene sets rather than biological inconsistency. Furthermore, such discrepancies may be partly attributable to differences in the sensitivity

of each algorithm to low gene-expression levels. To further validate these computational findings, future studies should incorporate experimental approaches such as immunohistochemistry or flow cytometry to directly assess the relationship between *HTR6* expression and CD8⁺ T-cell infiltration.

3.6. Associations of *HTR6* expression with immune-related genes in low-grade glioma

To determine whether *HTR6* expression was associated with immune-related genes, we examined its correlations with immune checkpoint genes, immunostimulators, MHC molecules, chemokine receptors, and chemokines. *HTR6* expression was negatively correlated with the immune checkpoint genes *CD274*, *CTLA4*, *HAVCR2*, *LAG3*, *PDCD1*, and *PDCD1LG2* (Figure 6A). Figure 6B shows that *HTR6* expression was positively correlated with *NT5E*, *PVR*, *TNFRSF18*, *HHLA2*, *KLRC1*, and *KLRK1* and negatively correlated with several immune-related genes (e.g., *CD27*, *CXCR4*, *ICOS*, *IL6*, and several *TNFRSF* family members). *HTR6* expression showed negative correlations with multiple MHC molecules (Figure 6C). With respect to chemokine receptors, *HTR6* expression was positively correlated with *CCR9* and negatively correlated with a broad range of other chemokine receptors (Figure 6D). Regarding chemokines, *HTR6* expression was positively correlated with *CCL1*, *CCL28*, *CX3CL1*, and several members of the CXCL family, whereas negative correlations were observed with other CXCL family members, a subset of CCL chemokines, and the XCL family members *XCL1* and *XCL2* (Figure 6E). These findings further supported an association between *HTR6* expression and immune-related gene expression in LGG.

3.7. Negative correlation between *SPI1* and *HTR6* expression in low-grade glioma

To explore potential mechanisms underlying decreased *HTR6* expression in LGG, the hTFtarget database was used to identify TFs predicted to regulate *HTR6* in brain tissue (Table S1), yielding six candidate TFs. Using the LinkedOmics platform, 5,529 genes coexpressed with *HTR6* were identified ($p < 0.05$, |correlation coefficient| ≥ 0.3) (Table S2). Intersection analysis of the candidate *HTR6*-regulating TFs and *HTR6*-coexpressed genes identified two TFs (Figure 7A). Correlations between the expression of these two TFs and *HTR6* expression were subsequently examined using TCGA data, revealing that only *SPI1* expression was negatively correlated with *HTR6* expression ($p = 1.4 \times 10^{-37}$, $r = -0.53$) (Figure 7B and 7C). Higher *SPI1* expression in LGG than in normal tissues was further confirmed using GEPIA (Figure 7D). These results indicated a negative correlation between *SPI1* and *HTR6*

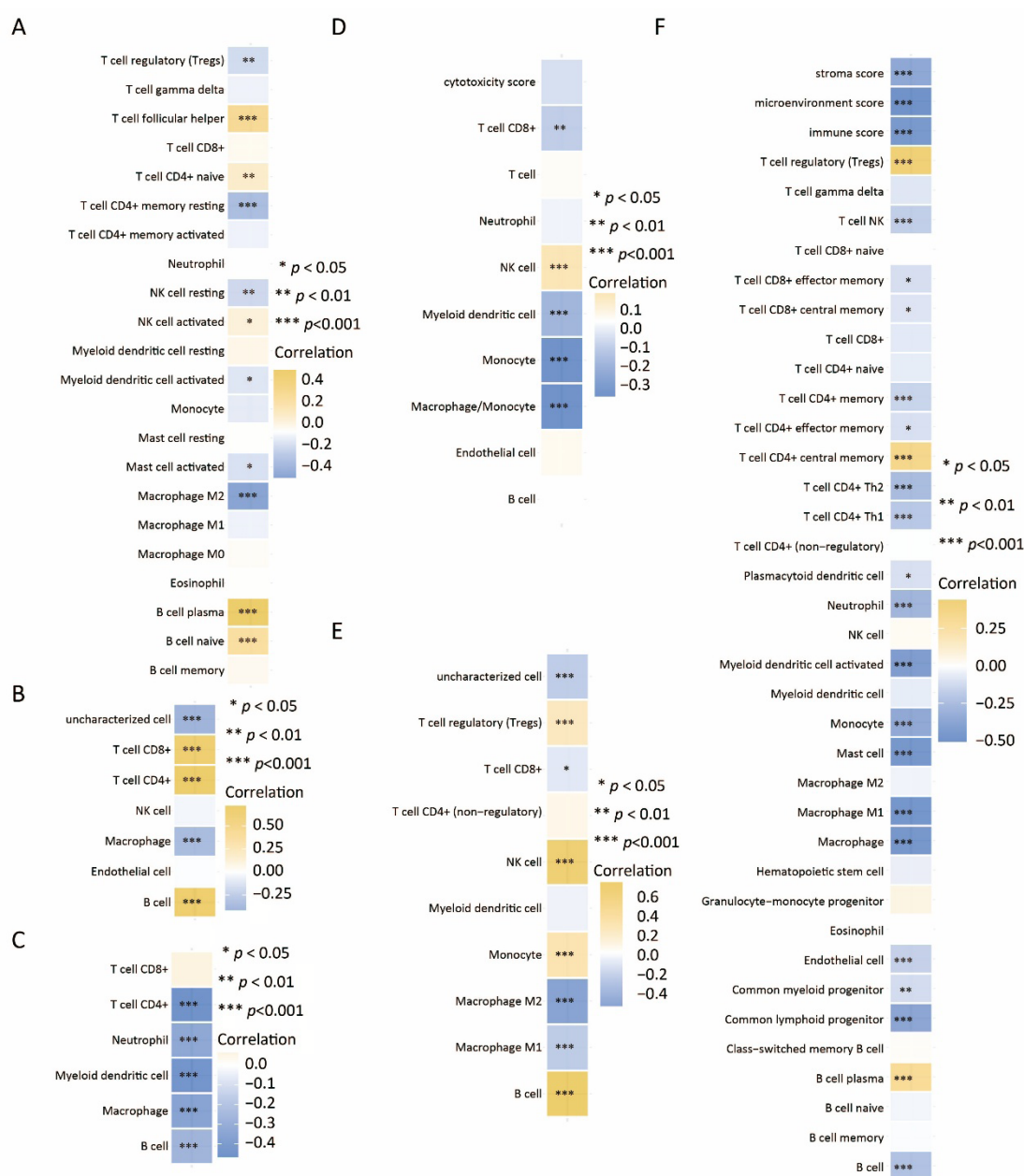


Figure 5. Association of *HTR6* expression with immune infiltration in low-grade glioma. (A) CIBERSORT, (B) EPIC, (C) TIMER, (D) MCPOUNTER, (E) QUANTISEQ, (F) Xcell.

expression in LGG.

4. Discussion

Gliomas are highly malignant primary tumors of the CNS. Despite major therapeutic advances in oncology, therapeutic options remain limited for a subset of patients with LGG, and some patients continue to have poor outcomes.^{22,23} Thus, it is crucial to identify new therapeutic

targets and prognostic molecular markers.

Using GTEx and TCGA databases, we analyzed *HTR6* mRNA expression across normal tissues and tumors and found high expression in the brain and pituitary gland but significantly reduced expression in GBM and LGG compared with normal tissues. Subsequently, associations between *HTR6* expression and various clinicopathological features, including race, sex, age, tumor grade, histological

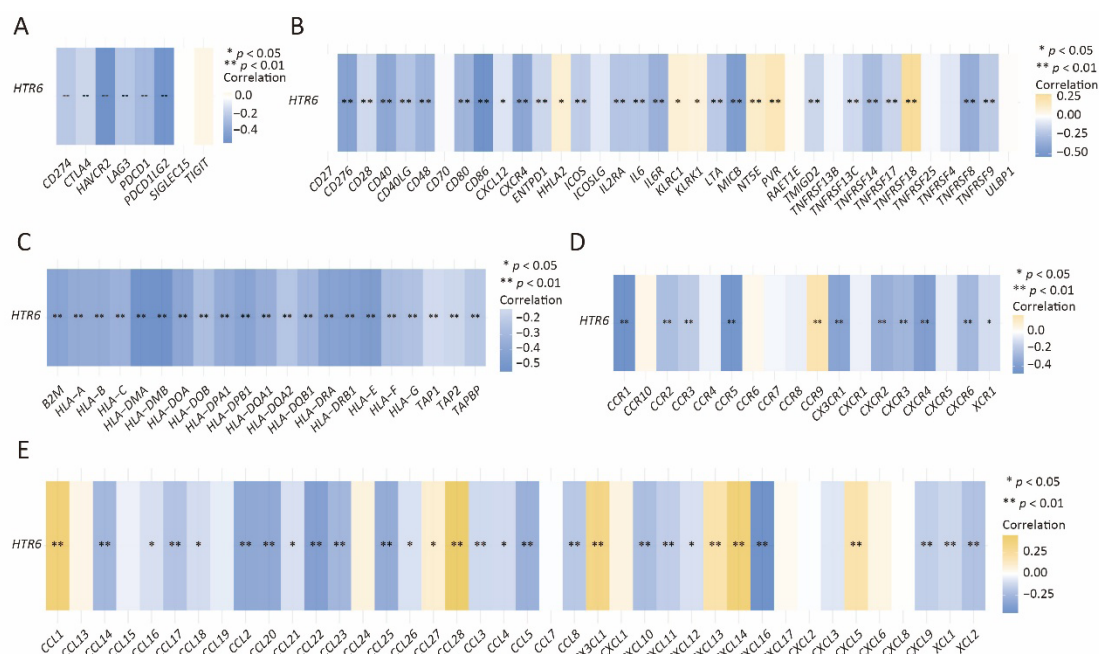


Figure 6. Correlations between *HTR6* expression and immune-related gene categories. (A) Immune checkpoints, (B) immunostimulators, (C) major histocompatibility complex molecules, (D) chemokine receptors, and (E) chemokines.

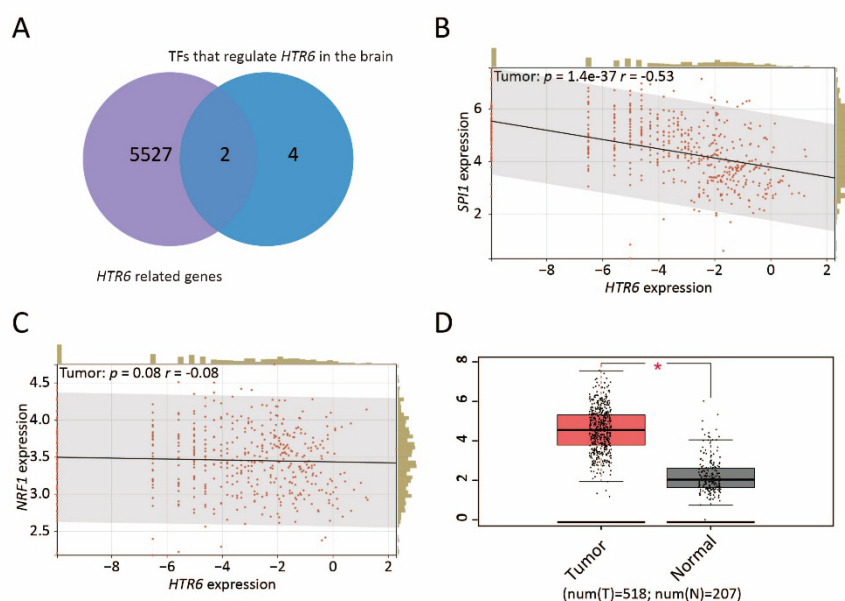


Figure 7. Negative correlation between *SPI1* and *HTR6* expression in low-grade glioma. (A) Overlap between candidate transcription factors predicted to regulate *HTR6* in brain tissue and *HTR6*-coexpressed genes. Correlation of *HTR6* expression with (B) *SPI1* and (C) *NRF1* expression. (D) *SPI1* expression in low-grade glioma versus normal brain tissue using GEPIA.

subtype, and *TP53* mutation status, were examined. Low *HTR6* expression was associated with unfavorable OS and PFS in LGG patients, as shown by Kaplan–Meier analyses.

Univariate and multivariate Cox regression analyses further identified *HTR6* expression as an independent prognostic factor that may improve prognostic assessment

when considered together with other clinicopathological factors. *HTR6* expression was also closely associated with immune infiltration patterns in LGG, as shown by immune infiltration and immune-related gene analyses. Upstream TF analysis further suggested an inverse relationship between *SPI1* and *HTR6* expression. Collectively, these findings suggest an association of *HTR6* with LGG prognosis and the immune microenvironment, although the underlying molecular mechanisms require additional experimental investigation.

Tumor progression is modulated by crosstalk among tumor cells, stromal cells, and immune cells within the tumor microenvironment.²⁴⁻²⁸ *HTR6* expression was positively correlated with plasma cell and NK cell abundance but negatively correlated with myeloid dendritic cell, activated dendritic cell, and macrophage abundance. Higher macrophage infiltration has been associated with poorer survival in patients with glioma, and M2-polarized macrophages have been implicated in glioma progression.²⁹ Macrophages are important regulators of tumor immunity and immunotherapy, and anti-inflammatory M2 macrophages can promote tumor growth and invasion.^{30,31} Notch-activated macrophages suppress T-cell proliferation and cytotoxic function, thereby facilitating tumor progression through immune evasion.³² Macrophage and CD8⁺ T-cell infiltration have also been associated with prognosis in LGG.³³ Because of differences in gene-expression signatures, normalization strategies, and analytical resolution among algorithms,³⁴ the inferred abundance of certain immune cells (such as B cells, regulatory T cells, and CD8⁺ T cells) was not entirely consistent. These discrepancies may be attributable to several factors:³⁵ (i) differential weighting of cell type-specific gene signatures among algorithms; (ii) different strategies for handling background noise in expression data; and (iii) the inherent complexity of immune interactions in the tumor microenvironment, which may be difficult to fully capture using a single algorithm. Nonetheless, multi-algorithm analysis remains a valuable approach for examining the complex immune microenvironment because it provides complementary perspectives.³⁴ Notably, some associations between *HTR6* expression and immune cell abundance were observed across multiple algorithms, supporting a potential association between *HTR6* expression and the tumor immune microenvironment. Future studies should employ experimental methods such as flow cytometry or single-cell RNA sequencing to determine whether *HTR6* is functionally involved in tumor immune escape or immunosuppression through specific immune cell populations.

Immunotherapy has emerged as an effective cancer

treatment strategy by modulating antitumor immune responses.^{36,37} Immune checkpoint inhibitors are among the most extensively studied immunotherapies. Immune checkpoints maintain appropriate immune responses and protect normal tissues from immune-mediated damage.^{38,39} Interestingly, our analysis revealed significant associations between *HTR6* expression and several categories of immune-related genes, such as immune checkpoint genes, immunostimulators, MHC molecules, chemokine receptors, and chemokines.

An effective anticancer immune response depends on antigen recognition by T cells together with appropriate co-stimulatory signaling provided by antigen-presenting cells.^{40,41} Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), a key coinhibitory receptor, delivers inhibitory signals to T cells, thereby limiting their activation,⁴² and contributes to peripheral tolerance by limiting T-cell activation and proliferation.⁴³⁻⁴⁵ The interaction between CD86 and CTLA-4 plays a critical role in immune responses against malignancies.⁴⁶ Studies have shown that *CD86* expression correlates strongly with immune infiltration by macrophages, neutrophils, and dendritic cells,^{47,48} is associated with poor prognosis in several tumors, including LGG,⁴⁹⁻⁵¹ and increases with higher LGG grade.⁵¹ Therefore, we postulate that decreased *HTR6* expression may be associated with an immunosuppressive microenvironment in LGG, as reflected by its correlations with immune-related molecules such as *CD86*. However, these observations were derived from computational analyses and should be interpreted cautiously.

HTR6 expression was negatively correlated with macrophage abundance (Figure 5), and macrophages have been implicated in tumor progression.⁵² NK cells are an important component of tumor immune surveillance. Upon activation, NK cells secrete cytotoxic granules containing perforin and granzymes, which directly lyse tumor cells.⁵³ NK cells enhance immune surveillance against tumors and viruses by exerting cytotoxic effects on susceptible cells and secreting proinflammatory cytokines.^{54,55} Human leukocyte antigen G (HLA-G), a non-classical human leukocyte antigen class I molecule, has immunosuppressive functions mediated through receptor signaling⁵⁶ and is present in the tumor microenvironment but absent in adjacent normal tissues. Previous studies have indicated that elevated HLA-G expression is associated with advanced tumor stages and poorer prognosis.⁵⁷ Modulation of chemokine signaling by HLA-G has also been associated with changes in NK cell recruitment to the tumor microenvironment. M2 macrophages may reduce NK cell cytotoxicity by enhancing HLA-G expression.⁵⁸ In the present study, *HTR6* expression was negatively correlated with *HLA-G*

expression (Figure 6C). The inverse correlation may also explain that in LGG patients, *HLA-G* expression increases as *HTR6* expression decreases, resulting in a poor prognosis through interference with corresponding chemokine signaling. Given the observed associations between *HTR6* expression and multiple immune-related signatures, *HTR6* may represent a potential biomarker of the LGG immune microenvironment. These findings offer a theoretical foundation for future studies examining the relationship between *HTR6*-associated pathways, glioma immune status, and therapeutic response.

The results of the present study showed that *HTR6* was coexpressed with genes enriched in multiple immune-related signaling pathways, including the NF- κ B and cAMP pathways. Both pathways are well-established regulators of tumor immunity and gliomagenesis. NF- κ B is a key TF involved in inflammatory responses and immune cell activation.⁵⁹ Aberrant NF- κ B activation is frequently observed in gliomas and has been associated with tumor progression and therapeutic resistance.⁶⁰ The observed association between *HTR6* and NF- κ B pathway-related genes may suggest that reduced *HTR6* expression contributes to dysregulated immune responses in LGG. Specifically, diminished *HTR6* levels may impair normal NF- κ B-mediated inflammatory signaling, thereby promoting an immunosuppressive microenvironment conducive to tumor growth. The cAMP signaling pathway plays integral roles in cellular communication, immune regulation, and neurotransmitter signaling.⁶¹ In gliomas, this pathway is involved in tumor cell proliferation, invasion, and immune evasion.⁶² The 5-HT₆ receptor, encoded by *HTR6*, is a G protein-coupled receptor and may influence cAMP signaling through the modulation of second-messenger systems. Our findings suggest that dysregulation of *HTR6* could disrupt cAMP-mediated immune pathways, thereby affecting tumor-immune interactions. For instance, impaired cAMP signaling may reduce the recruitment and activation of regulatory T cells, which are known to suppress antitumor immune responses in gliomas. Nevertheless, whether *HTR6* directly modulates NF- κ B and cAMP pathways in gliomas remains to be experimentally tested.

In recent years, immunotherapy has emerged as one of the promising treatments for a variety of cancers, including gliomas. The primary strategies focus on restoring or enhancing the antitumor immune responses suppressed in the tumor microenvironment. Immune checkpoint inhibitors targeting programmed cell death protein 1, programmed death-ligand 1, and CTLA-4 have revolutionized cancer therapy in several malignancies, such as melanoma and lung cancer. However, their clinical efficacy in gliomas

has been less pronounced due to the immunosuppressive nature of the glioma microenvironment and the unique challenges posed by the CNS, such as limited T cell infiltration and the blood-brain barrier.⁶³ Our study reveals strong correlations between *HTR6* and molecules involved in immune evasion. Future studies could explore whether *HTR6* modulation enhances the responsiveness to immune checkpoint inhibitors in LGG. Numerous glioma-specific antigens, such as epidermal growth factor receptor variant III (EGFRvIII), have been targeted in glioma vaccine development.⁶⁴ These vaccines aim to elicit a robust and tumor-specific immune response. Given the potential of *HTR6* in modulating immune-related pathways, it is worth investigating whether combinatorial approaches involving tumor vaccines and *HTR6* modulation could improve vaccine efficacy. Adoptive cell therapy (ACT), particularly chimeric antigen receptor (CAR) T-cell therapy, is being actively investigated for glioma.⁶⁵ CAR T cells targeting glioma-specific markers such as interleukin-13 receptor alpha 2, human epidermal growth factor receptor 2, and EGFRvIII have shown promise in pre-clinical and early-phase clinical trials. However, immunosuppressive signals in the glioma microenvironment often dampen the effectiveness of CAR T cells.⁶⁵ Our findings on the relationship between *HTR6* and critical immune pathways could lead to insights into engineering CAR T cells or other ACT approaches that overcome these barriers. Cytokines, such as interferon-alpha and interleukin-2, have been investigated as potential glioma treatments due to their capacity to stimulate immune cell activity.⁶⁶ The enrichment of type I interferon-response processes among *HTR6*-associated genes, as observed in our study, suggests that *HTR6* might negatively regulate the immune response. Targeting *HTR6* and cytokine pathways simultaneously could open new avenues for glioma immunotherapy.

5. Limitations

This study has several limitations. The first limitation of this study is the use of an outdated glioma classification system, which distinguishes tumors only as LGG or HGG without incorporating the 2021 WHO classification criteria. The updated framework emphasizes the integration of molecular markers, including IDH mutation status and 1p/19q codeletion, which are critical for delineating biologically distinct tumor subtypes associated with divergent prognoses and therapeutic responses.⁶⁷ The absence of this molecular classification introduces heterogeneity into our patient cohorts and may have confounded the observed results. For instance, IDH-mutant LGG is generally associated with a more favorable prognosis than IDH-wild-type LGG, and the lack of such stratification in our analysis limits the biological interpretability of the

prognostic role of *HTR6*. Future studies should stratify glioma cases based on these molecular markers to enable a more nuanced understanding of the biological significance of *HTR6* in specific glioma subtypes. Another limitation of this study is its exclusive reliance on retrospective bioinformatic analyses, conducted without experimental validation or the inclusion of independent external cohorts. Although such bioinformatic approaches offer preliminary insights, they lack the methodological rigor provided by functional assays or cohort-based validation, both of which are essential for establishing the biological relevance of the findings. To substantiate the observed associations among *HTR6* expression, immune infiltration, and prognosis in LGG, future studies should incorporate in vitro experiments, animal models, or independent clinical datasets. In the absence of such validation, the conclusions drawn herein should be considered preliminary and hypothesis-generating, rather than definitive.

6. Conclusion

Our findings demonstrate the clinical relevance of *HTR6* as a prognostic factor in LGG, its role in modulating the immune microenvironment, and the upstream TF that regulates its expression. This study indicates that *HTR6* serves as a molecular marker for LGG progression and prognosis, offering a potential strategy for its immunotherapy.

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Conflict of interest

The authors declare no conflict of interest.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding authors upon reasonable request.

Further disclosure

During the preparation of this manuscript, the authors used AI tools, specifically OpenAI's GPT-4 for literature retrieval, language polishing, and verification of reference formatting compliance. The authors reviewed and edited the output as necessary and take full responsibility for the content of this publication.

References

1. Ostrom QT, Price M, Ryan K, *et al.* CBTRUS Statistical Report: Pediatric Brain Tumor Foundation Childhood and Adolescent Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014–2018. *Neuro Oncol.* 2022;24(Suppl 3):iii1–iii38.
doi: 10.1093/neuonc/noac161
2. Gusyatiner O, Hegi ME. Glioma epigenetics: From subclassification to novel treatment options. *Semin Cancer Biol.* 2018;51:50–58.
doi: 10.1016/j.semcancer.2017.11.010
3. Zhang B, Xu C, Liu J, *et al.* Nidogen-1 expression is associated with overall survival and temozolomide sensitivity in low-grade glioma patients. *Aging.* 2021;13(6):9085–9107.
doi: 10.18632/aging.202789
4. Tan Y, Zhang S, Xiao Q, *et al.* Prognostic significance of ARL9 and its methylation in low-grade glioma. *Genomics.* 2020;112(6):4808–4816.
doi: 10.1016/j.ygeno.2020.08.035

5. Chaumont-Dubel S, Dupuy V, Bockaert J, *et al.* The 5-HT6 receptor interactome: New insight in receptor signaling and its impact on brain physiology and pathologies. *Neuropharmacology*. 2020;172:107839.
doi: 10.1016/j.neuropharm.2019.107839
6. Ghia JE, Li N, Wang H, *et al.* Serotonin Has a Key Role in Pathogenesis of Experimental Colitis. *Gastroenterology*. 2009;137(5):1649-1660.
doi: 10.1053/j.gastro.2009.08.041
7. Pozhidaev IV, Paderina DZ, Fedorenko OY, *et al.* 5-Hydroxytryptamine Receptors and Tardive Dyskinesia in Schizophrenia. *Front Mol Neurosci*. 2020;13:63.
doi: 10.3389/fnmol.2020.00063
8. Teng LL, Lu GL, Chiou LC, *et al.* Serotonin receptor HTR6-mediated mTORC1 signaling regulates dietary restriction-induced memory enhancement. *PLoS Biol*. 2019;17(3):e2007097.
doi: 10.1371/journal.pbio.2007097
9. DeDeurwaerdere P, Di Giovanni G. Serotonergic modulation of the activity of mesencephalic dopaminergic systems: Therapeutic implications. *Prog Neurobiol*. 2017;151:175-236.
doi: 10.1016/j.pneurobio.2016.03.004
10. Illi A, Setälä-Soikkeli E, Viikki M, *et al.* 5-HTR1A, 5-HTR2A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression. *Neuroreport*. 2009;20(12):1125-1128.
doi: 10.1097/WNR.0b013e32832eb708
11. Thome J, Retz W, Baader M, *et al.* Association analysis of HTR6 and HTR2A polymorphisms in sporadic Alzheimer's disease. *J Neural Transm*. 2001;108(10):1175-1180.
doi: 10.1007/s007020170007
12. Wu X, Qiu F, Wang Z, *et al.* Correlation of 5-HTR6 gene polymorphism with vestibular migraine. *J Clin Lab Anal*. 2020;34(2):e23042.
doi: 10.1002/jcla.23042
13. Nedic Erjavec G, Grubor M, Zivkovic M, *et al.* SLC6A3, HTR2C and HTR6 Gene Polymorphisms and the Risk of Haloperidol-Induced Parkinsonism. *Biomedicines*. 2022;10(12):3237.
doi: 10.3390/biomedicines10123237
14. Kannen V, Bader M, Sakita JY, *et al.* The Dual Role of Serotonin in Colorectal Cancer. *Trends Endocrinol Metab*. 2020;31(8):611-625.
doi: 10.1016/j.tem.2020.04.008
15. Zhang W, Li L, Li J, *et al.* Systematic Analysis of Neurotransmitter Receptors in Human Breast Cancer Reveals a Strong Association With Outcome and Uncovers HTR6 as a Survival-Associated Gene Potentially Regulating the Immune Microenvironment. *Front Immunol*. 2022;13:756928.
doi: 10.3389/fimmu.2022.756928
16. Xu Y, Gu S, Bi Y, *et al.* Transcription factor PU.1 is involved in the progression of glioma. *Oncol Lett*. 2018;15(3):3753-3759.
doi: 10.3892/ol.2018.7766
17. Vasaiyar SV, Straub P, Wang J, *et al.* LinkedOmics: analyzing multi-omics data within and across 32 cancer types. *Nucleic Acids Res*. 2018;46(D1):D956-D963.
doi: 10.1093/nar/gkx1090
18. Plattner C, Finotello F, Rieder D. Deconvoluting tumor-infiltrating immune cells from RNA-seq data using quanTIseq. *Methods Enzymol*. 2020;636:261-285.
doi: 10.1016/bs.mie.2019.05.056
19. Becht E, Giraldo NA, Lacroix L, *et al.* Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression. *Genome Biol*. 2016;17(1):218.
doi: 10.1186/s13059-016-1070-5
20. Racle J, de Jonge K, Baumgaertner P, *et al.* Simultaneous enumeration of cancer and immune cell types from bulk tumor gene expression data. *eLife*. 2017;6:e26476.
doi: 10.7554/eLife.26476
21. Li T, Fan J, Wang B, *et al.* TIMER: A Web Server for Comprehensive Analysis of Tumor-Infiltrating Immune Cells. *Cancer Res*. 2017;77(21):e108-e110.
doi: 10.1158/0008-5472.CAN-17-0307
22. Youssef G, Miller JJ. Lower Grade Gliomas. *Curr Neurol Neurosci Rep*. 2020;20(7):21.
doi: 10.1007/s11910-020-01040-8
23. Dhawan S, Patil CG, Chen C, *et al.* Early versus delayed postoperative radiotherapy for treatment of low-grade gliomas. *Cochrane Database Syst Rev*. 2020;1(1):CD009229.
doi: 10.1002/14651858.CD009229.pub3
24. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med*. 2013;19(11):1423-1437.
doi: 10.1038/nm.3394
25. Liu Y, Cao X. Characteristics and Significance of the Pre-metastatic Niche. *Cancer Cell*. 2016;30(5):668-681.
doi: 10.1016/j.ccell.2016.09.011
26. Bagaev A, Kotlov N, Nomie K, *et al.* Conserved pan-cancer microenvironment subtypes predict response to immunotherapy. *Cancer Cell*. 2021;39(6):845-865.e847.
doi: 10.1016/j.ccell.2021.04.014

27. Wang Y, Wang Y, Xu C, *et al.* Identification of Novel Tumor-Microenvironment-Regulating Factor That Facilitates Tumor Immune Infiltration in Colon Cancer. *Mol Ther Nucleic Acids*. 2020;22:236-250.
doi: 10.1016/j.omtn.2020.08.029
28. Zhang X, Shi M, Chen T, *et al.* Characterization of the Immune Cell Infiltration Landscape in Head and Neck Squamous Cell Carcinoma to Aid Immunotherapy. *Mol Ther Nucleic Acids*. 2020;22:298-309.
doi: 10.1016/j.omtn.2020.08.030
29. Zhang H, Luo YB, Wu W, *et al.* The molecular feature of macrophages in tumor immune microenvironment of glioma patients. *Comput Struct Biotechnol J*. 2021;19:4603-4618.
doi: 10.1016/j.csbj.2021.08.019
30. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol*. 2019;19(6):369-382.
doi: 10.1038/s41577-019-0127-6
31. Xiang X, Wang J, Lu D, *et al.* Targeting tumor-associated macrophages to synergize tumor immunotherapy. *Signal Transduct Target Ther*. 2021;6(1):75.
doi: 10.1038/s41392-021-00484-9
32. Meng J, Jiang YZ, Zhao S, *et al.* Tumor-derived Jagged1 promotes cancer progression through immune evasion. *Cell Rep*. 2022;38(10):110492.
doi: 10.1016/j.celrep.2022.110492
33. Deng X, Lin D, Zhang X, *et al.* Profiles of immune-related genes and immune cell infiltration in the tumor microenvironment of diffuse lower-grade gliomas. *J Cell Physiol*. 2020;235(10):7321-7331.
doi: 10.1002/jcp.29633
34. Liu CC, Steen CB, Newman AM. Computational approaches for characterizing the tumor immune microenvironment. *Immunology*. 2019;158(2):70-84.
doi: 10.1111/imm.13101
35. Zeng D, Ye Z, Shen R, *et al.* IOBR: Multi-Omics Immuno-Oncology Biological Research to Decode Tumor Microenvironment and Signatures. *Front Immunol*. 2021;12:687975.
doi: 10.3389/fimmu.2021.687975
36. Riley RS, June CH, Langer R, *et al.* Delivery technologies for cancer immunotherapy. *Nat Rev Drug Discov*. 2019;18(3):175-196.
doi: 10.1038/s41573-018-0006-z
37. Rosenberg SA. IL-2: The First Effective Immunotherapy for Human Cancer. *J Immunol*. 2014;192(12):5451-5458.
doi: 10.4049/jimmunol.1490019
38. Lim M, Xia Y, Bettegowda C, *et al.* Current state of immunotherapy for glioblastoma. *Nat Rev Clin Oncol*. 2018;15(7):422-442.
doi: 10.1038/s41571-018-0003-5
39. Darvin P, Toor SM, Nair VS, *et al.* Immune checkpoint inhibitors: recent progress and potential biomarkers. *Exp Mol Med*. 2018;50(12):1-11.
doi: 10.1038/s12276-018-0191-1
40. Martin-Orozco N, Dong C. Inhibitory costimulation and anti-tumor immunity. *Semin Cancer Biol*. 2007;17(4):288-298.
doi: 10.1016/j.semcancer.2007.06.003
41. Chen L, Flies DB. Molecular mechanisms of T cell co-stimulation and co-inhibition. *Nat Rev Immunol*. 2013;13(4):227-242.
doi: 10.1038/nri3405
42. Hathcock KS, Laszlo G, Dickler HB, *et al.* Identification of an alternative CTLA-4 ligand costimulatory for T cell activation. *Science*. 1993;262(5135):905-907.
doi: 10.1126/science.7694361
43. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. *Annu Rev Immunol*. 2005;23:515-548.
doi: 10.1146/annurev.immunol.23.021704.115611
44. Mellor AL, Munn DH. IDO expression by dendritic cells: tolerance and tryptophan catabolism. *Nat Rev Immunol*. 2004;4(10):762-774.
doi: 10.1038/nri1457
45. Fallarino F, Grohmann U, Hwang KW, *et al.* Modulation of tryptophan catabolism by regulatory T cells. *Nat Immunol*. 2003;4(12):1206-1212.
doi: 10.1038/ni1003
46. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271(5256):1734-1736.
doi: 10.1126/science.271.5256.1734
47. Yin W, Jiang X, Tan J, *et al.* Development and Validation of a Tumor Mutation Burden-Related Immune Prognostic Model for Lower-Grade Glioma. *Front Oncol*. 2020;10:1409.
doi: 10.3389/fonc.2020.01409
48. Lin S, Xu H, Zhang A, *et al.* Prognosis Analysis and Validation of m6A Signature and Tumor Immune Microenvironment in Glioma. *Front Oncol*. 2020;10:541401.
doi: 10.3389/fonc.2020.541401
49. Pope B, Brown RD, Gibson J, *et al.* B7-2-positive myeloma: incidence, clinical characteristics, prognostic significance, and implications for tumor immunotherapy. *Blood*. 2000;96(4):1274-1279.

- doi: 10.1182/blood.V96.4.1274
50. Maeda A, Yamamoto K, Yamashita K, *et al.* The expression of co-stimulatory molecules and their relationship to the prognosis of human acute myeloid leukaemia: poor prognosis of B7-2-positive leukaemia. *Br J Haematol.* 1998;102(5):1257-1262.
doi: 10.1046/j.1365-2141.1998.00901.x
51. Qiu H, Tian W, He Y, *et al.* Integrated Analysis Reveals Prognostic Value and Immune Correlates of CD86 Expression in Lower Grade Glioma. *Front Oncol.* 2021;11:654350.
doi: 10.3389/fonc.2021.654350
52. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. *Nat Rev Drug Discov.* 2018;17(12):887-904.
doi: 10.1038/nrd.2018.169
53. Prager I, Watzl C. Mechanisms of natural killer cell-mediated cellular cytotoxicity. *J Leukoc Biol.* 2019;105(6):1319-1329.
doi: 10.1002/jlb.Mr0718-269r
54. Newman KC, Riley EM. Whatever turns you on: accessory-cell-dependent activation of NK cells by pathogens. *Nat Rev Immunol.* 2007;7(4):279-291.
doi: 10.1038/nri2057
55. Lanier LL. Up on the tightrope: natural killer cell activation and inhibition. *Nat Immunol.* 2008;9(5):495-502.
doi: 10.1038/ni1581
56. Lin A, Yan WH. Heterogeneity of HLA-G Expression in Cancers: Facing the Challenges. *Front Immunol.* 2018;9:2164.
doi: 10.3389/fimmu.2018.02164
57. Xu X, Zhou Y, Wei H. Roles of HLA-G in the Maternal-Fetal Immune Microenvironment. *Front Immunol.* 2020;11:592010.
doi: 10.3389/fimmu.2020.592010
58. Nuñez SY, Ziblat A, Secchiari F, *et al.* Human M2 Macrophages Limit NK Cell Effector Functions through Secretion of TGF- β and Engagement of CD85j. *J Immunol.* 2018;200(3):1008-1015.
doi: 10.4049/jimmunol.1700737
59. Taniguchi K, Karin M. NF- κ B, inflammation, immunity and cancer: coming of age. *Nat Rev Immunol.* 2018;18(5):309-324.
doi: 10.1038/nri.2017.142
60. Ramar V, Guo S, Wang G, *et al.* The Pivotal Role of NF- κ B in Glioblastoma: Mechanisms of Activation and Therapeutic Implications. *Int J Mol Sci.* 2025;26(16):7883.
doi: 10.3390/ijms26167883
61. Donders Z, Skorupska IJ, Willems E, *et al.* Beyond PDE4 inhibition: A comprehensive review on downstream cAMP signaling in the central nervous system. *Biomed Pharmacother.* 2024;177:117009.
doi: 10.1016/j.biopha.2024.117009
62. Qin Z, Huang Y, Li Z, *et al.* Glioblastoma Vascular Plasticity Limits Effector T-cell Infiltration and Is Blocked by cAMP Activation. *Cancer Immunol Res.* 2023;11(10):1351-1366.
doi: 10.1158/2326-6066.CIR-22-0872
63. Zhang N, Wei L, Ye M, *et al.* Treatment Progress of Immune Checkpoint Blockade Therapy for Glioblastoma. *Front Immunol.* 2020;11:592612.
doi: 10.3389/fimmu.2020.592612
64. Greenall SA, McKenzie M, Seminova E, *et al.* Most clinical anti-EGFR antibodies do not neutralize both wtEGFR and EGFRvIII activation in glioma. *Neuro Oncol.* 2019;21(8):1016-1027.
doi: 10.1093/neuonc/noz073
65. Grewal EP, Nahed BV, Carter BS, *et al.* Clinical progress in the development of CAR T cells to treat malignant glioma. *J Neurooncol.* 2025;171(3):571-579.
doi: 10.1007/s11060-024-04909-7
66. Birocchi F, Cusimano M, Rossari F, *et al.* Targeted inducible delivery of immunoactivating cytokines reprograms glioblastoma microenvironment and inhibits growth in mouse models. *Sci Transl Med.* 2022;14(653):eabl4106.
doi: 10.1126/scitranslmed.abl4106
67. Louis DN, Perry A, Wesseling P, *et al.* The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021;23(8):1231-1251.
doi: 10.1093/neuonc/noab106