Iranian Journal of Basic Medical Sciences
ijbms.mums.ac.ir

Non-coding RNAs related to PD1/PD-L1 signaling with potential diagnostic, prognostic, and therapeutic value in the tumorigenesis of brain cancers

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ARTICLE INFO

Article type:
Review

Article history:
Received: Jan 25, 2026
Accepted: May 18, 2026

Keywords:
Brain neoplasms
Immune evasion
MicroRNAs
Non-coding RNAs
PD-1/PD-L1

ABSTRACT

Brain cancers are among the most aggressive malignancies associated with significant global morbidity and mortality. Cancer immunotherapy has emerged as a promising novel approach for the treatment of brain cancer through regulating the PD-1/PD-L1 signaling and disrupting tumor immune escape. Several targeted therapies have been developed to inhibit the PD-1/PD-L1 route, but reduced therapeutic responses and drug resistance remain a major challenge that needs to be addressed. Notably, non-coding RNAs (ncRNAs), which include microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs), exert crucial effects on cell proliferation, invasion, and immune escape in the tumor microenvironment (TME). It has been shown that ncRNAs reduce tumor formation and progression by regulating the PD-1/PD-L1 pathway and by down-regulating key transcription factors, including NF-κB, JAK, and STAT. Therefore, identifying novel regulatory ncRNAs and their associated target genes offers promising opportunities for developing therapeutic interventions against brain cancer. This review highlights recent advances in understanding the regulatory role of ncRNAs on the PD-1/ PD-L1 pathway in brain cancer tumorigenesis.

▶ Please cite this article as:
Behnam-Rassouli R, Entezari F, Ghorbanzadeh M, Reyhani A, Nassiri MR, Golab F, Rahmani F. Non-coding RNAs related to PD1/PD-L1 signaling with potential diagnostic, prognostic, and therapeutic value in the tumorigenesis of brain cancers. Iran J Basic Med Sci 2026; 29: 1174-1183. doi: https://dx.doi.org/10.22038/ijbms.2026.94213.20304

Introduction

Brain tumors are among the most aggressive cancers and the leading cause of cancer-related death worldwide (1). Despite recent advances in diagnostic and therapeutic methods, patients are often diagnosed at advanced stages, with a dismal prognosis and poor survival outcomes (2). Emerging evidence suggests that brain cancer pathogenesis involves multiple cellular processes that facilitate tumor cell immune escape (3). In this context, studies have shown that programmed cell death protein 1 (PD-1) and its ligand, programmed cell death ligand 1 (PD-L1), trigger immunosuppressive signaling pathways that enable cancer cells to evade immune surveillance (4).

PD-1 is a key inhibitory receptor induced on activated T cells, which functions as a central regulator of immune activation (5). Upon binding its ligands (PD-L1 or PD-L2), PD-1 recruits phosphatases like SHP2 to primarily attenuate CD28-mediated stimulatory signaling, thereby limiting the secondary signals required for full T-cell activation (6, 7). This targeted inhibition down-regulates the PI3K/Akt/mTOR and Ras/MAPK signaling pathways, resulting in diminished cytokine secretion, metabolic activity, and cell proliferation (5, 8). *In vivo*, PD-1 expression rises on recently activated T cells to maintain peripheral tolerance and prevent tissue injury. Accordingly, disruption of this pathway in chronic inflammation or after therapeutic checkpoint blockade enhances T-cell activation, improves antitumor efficacy, but increases the risk of immune-mediated pathological complications (9, 10). This dual role underscores PD-1 as a pivotal modulator of immune balance, making it a central focus of both basic immunology and clinical intervention (11).

PD-L1 (CD274) represents a key immunoregulatory checkpoint in the brain tumor microenvironment, where it suppresses antitumor immune activity and facilitates immune evasion (12). In glioblastoma cells, PD-L1 expression is frequently increased and correlates with higher tumor grade and unfavorable clinical outcomes. Enhanced PD-L1 levels are associated with greater proliferative capacity, invasive behavior, and migratory potential of malignant cells. PD-L1 can interact with PD-1 receptors on nearby immune cells, thereby modifying immune responses within the tumor microenvironment (13).

Myeloid cells, including microglia and infiltrating

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macrophages, further contribute to this immunosuppressive environment through STAT3-dependent up-regulation of PD-L1 (14). The interaction between PD-L1 and PD-1 receptors on tumor-infiltrating lymphocytes (TILs), particularly $CD4^+$ and $CD8^+$ T cells, inhibits T-cell responses, reduces cytokine production and proliferation, thereby promoting immune tolerance within the tumor microenvironment (15, 16).

PD-1 and PD-L1 expression levels were reported to be modulated by several molecular mechanisms, including oncogenic signaling pathways and genetic and/or epigenetic alterations (14, 15). Epigenetic changes in cancer cells enhance the expression of various noncoding RNAs and proinflammatory cytokines, including NF-κB, IFN-γ, and TNF-α, which regulate PD-L1 on cancer cells (16, 17). In recent years, several PD-1/PD-L1 inhibitors have been developed to ameliorate anticancer immune responses in various human malignancies, including gastrointestinal, gynecological, and renal cancers. Accordingly, several PD-1/PD-L1 axis monoclonal antibodies were approved for cancer treatment, including nivolumab, atezolizumab, durvalumab, and pembrolizumab (18-20). However, resistance to antibody therapy in some cancer patients has complicated the treatment process. Therefore, fully identifying the PD-1/PD-L1 pathway regulatory mechanisms is crucial for developing novel and effective antitumor drugs in cancer immunotherapy (21, 22). In line with this, recent studies demonstrate that the PD-L1 mRNA is widely expressed in multiple tissues under normal conditions, but its corresponding protein is selectively expressed in specific tissues (23, 24). These observations suggest that ncRNAs modulate the PD1/PDL1 expression by transcriptional, posttranscriptional, and epigenetic mechanisms (25, 26). In the present study, we summarized recent findings about the regulatory role of ncRNAs on the PD-1/PD-L1 axis in brain cancers.

Role of ncRNAs in regulating immune checkpoints, myeloid polarization, cytokine profile, and T-cell responses

The central nervous system (CNS) tumor microenvironment is a highly complex and dynamic milieu composed of malignant cells, resident immune populations such as microglia, infiltrating macrophages, and diverse lymphocyte subsets, each contributing to immune regulation through distinct roles. Within this environment, ncRNAs function as key regulators of immune dynamics by shaping myeloid cell polarization, cytokine signaling networks, and T-cell activity (27, 28). A central aspect of ncRNA function is their regulation of myeloid cell polarization, specifically controlling the functional shift between pro-inflammatory (M1-like) and immunosuppressive (M2-like) phenotypes. They achieve this by modulating major signaling pathways, including NF-κB, STAT family proteins, and C/EBP transcription factors. Through these pathways, ncRNAs influence PD-L1 expression and facilitate immune evasion, establishing a mechanistic link between inflammatory signaling and immune checkpoint regulation (29, 30).

Importantly, regulation of the PD-1/PD-L1 axis by ncRNAs is highly cell type–specific, reflecting the unique immunological landscape of CNS tumors. In tumor cells, ncRNAs play a prominent role in promoting immune resistance. For example, in glioma, ncRNAs such as CRNDE, HOTAIR, and linc00346 enhance PD-L1 transcription by activating STAT3 and NF-κB signaling pathways (31-35). Conversely, in meningioma, circ_0004872 acts as a negative regulator of PD-L1 by interacting with EIF4A3 and modulating the miR-190a-3p/PTEN axis. These tumor-intrinsic ncRNA mechanisms collectively promote immune evasion by increasing PD-L1 expression on cancer cells, thereby suppressing cytotoxic T-cell–mediated antitumor responses (36).

Beyond tumor cells, ncRNA-mediated regulation of PD-L1 also extends to microglia and tumor-associated macrophages, key myeloid populations in brain tumors. For instance, linc00346 has been associated with elevated PD-L1 expression in macrophages and neutrophils (33), while linc01271 correlates with enrichment of M1-type macrophages (37). These findings indicate that ncRNAs not only regulate immune checkpoint expression but also influence the polarization and functional states of myeloid cells, thereby contributing to either pro-inflammatory or immunosuppressive microenvironmental conditions.

ncRNAs also exert significant regulatory effects on tumor-infiltrating lymphocytes, including effector T cells and regulatory T cells (Tregs). miR-138 has been shown to reduce PD-1 and CTLA-4 expression in effector T cells, thereby promoting the restoration of antitumor immunity (38). In Tregs, miR-214-5p modulates PD-1 expression and alters their suppressive function across multiple malignancies (39). In contrast, lncNDEPD1 stabilizes PDCD1 transcripts in $CD8^+$ T cells, sustaining PD-1 expression and contributing to T-cell exhaustion (40). Together, these mechanisms highlight the role of ncRNAs in determining lymphocyte responsiveness to PD-L1 signaling and in shaping the extent of T-cell dysfunction within the tumor microenvironment.

Cytokine-mediated feedback loops add another layer of regulation, through which ncRNAs amplify or attenuate PD-L1 induction. The IFN-γ/JAK/STAT signaling axis is a dominant pathway driving inducible PD-L1 expression (41, 42). ncRNAs that modulate components of this pathway can significantly alter PD-L1 expression across multiple cell types. For instance, ncRNAs that suppress inhibitors of STAT1 signaling can enhance cellular sensitivity to IFN-γ, thereby increasing PD-L1 induction. Conversely, ncRNAs that promote anti-inflammatory cytokines such as IL-10 and TGF-β favor M2-like macrophage polarization and sustained immunosuppression (43, 44).

Noncoding RNAs in PD-1/PD-L1 pathway

Genomic sequencing findings indicate that about 2% of the human genome is translated into proteins, and other RNA molecules that do not encode proteins are identified as ncRNAs (45). Based on their length and other structural characteristics, ncRNAs are mainly divided into three groups, including microRNAs, long non-coding RNAs, and circular RNAs (46). MiRNAs are identified as a class of endogenous small ncRNAs (20-25 nucleotides) that post-transcriptionally modulate gene expression of certain mRNAs by interacting with their 3'-untranslated regions (UTRs) (47). LncRNAs, another group of ncRNAs with at least 200 nucleotides, have been found to participate in various cellular processes by acting as competing endogenous RNAs (ceRNAs) for certain miRNAs and regulating their target genes. CircRNAs, as a structurally stable group of ncRNAs, have circular structures that make them more resistant to degradation by nuclease enzymes. Like lncRNAs, circRNAs function as miRNA sponges and modulate their expression at various transcriptional levels (46). Emerging evidence indicates that ncRNAs function as tumor suppressors or oncogenes and exert critical effects on brain tumor initiation and progression by modulating

several cellular processes, such as proliferation, invasion, and apoptosis (46, 48). Further studies have demonstrated the role of ncRNAs in tumorigenesis by regulating immune-related signaling pathways, such as the PD-1/PD-L1 pathway, suggesting their potential as promising targets for cancer therapy (25, 49).

Interplay between ncRNAs and PD-1/PD-L1 signaling in gliomas

Gliomas comprise several types of tumors in the CNS and are classified based on their specific tumor characteristics. GBM, the most aggressive type of glioma, accounts for 80 percent of brain cancers, with an unfavorable prognosis and a lower survival rate (47). Glioma tumorigenesis is a complex process driven by genetic and epigenetic alterations that modulate several signaling pathways, induce tumor growth, and regulate anti-cancer immune responses, such as the PD1/PDL1 route (50). Recent studies on the molecular mechanisms involved in glioma pathogenesis revealed that various ncRNAs enhance tumor initiation and progression by promoting oncogenes and/or inhibiting tumor suppressors in cancer patients (47, 51). PD-L1 (CD274) is one of the most studied oncogenes that causes T-cell dysfunction and hampers anti-cancer immune responses. Expression of PD-L1 has been linked to tumor invasiveness and glioma grading in cancer patients (52). In individuals with glioma, the PD-L1 expression is modulated via several lncRNAs, like colorectal neoplasia expressed (CRNDE), lncRNA RP11-571M6.8, lncRNA 01271, NEAT1, HOTAIR, and lncRNA linc00346 (53-55).

The oncogenic lncRNA CRNDE is up-regulated in various human malignancies, such as glioma, gastric, and colorectal cancer (56). LncRNA CRNDE promotes glioma cell growth and progression by activating mTOR signaling and up-regulating PD-L1 transcription. Experimental evidence indicates that CRNDE promotes glioma cell invasion and metastasis by inhibiting the miR-384/PIWIL4/STAT3 axis. Silencing CRNDE expression promotes autophagy and increases drug sensitivity in GBM patients. These findings suggest that CRNDE can be considered as an adverse prognostic marker in patients with gliomas (53). Similarly, the overexpression of lncRNA RP11-571M6.8 is reported to be associated with lower immunosuppressive scores and decreased survival rate in GBM patients. Further studies indicate that lncRNA RP11-571M6.8 exerts its immunosuppressive effects by inhibiting Treg infiltration and modulating the expression levels of immune checkpoint proteins, including PD-1, PD-L1, and CTLA-4 (57, 58). LincRNA 01271 is another PD-L1-related lncRNA whose expression is positively correlated with adverse prognosis and aggressive clinicopathological features in GBM. Patients with up-regulated linc01271 were found to have a higher abundance of M1-subtype macrophages in the TME, resulting in immune escape, tumor growth, and progression (59). Further investigations indicate that down-regulation of linc01271 suppresses glioma cell proliferation and migration, suggesting its potential as a target for cancer immunotherapy (60). Linc00346 is another oncogenic lncRNA whose expression is increased in glioma patients and influences glioma grading. Increased expression of linc00346 is correlated with the up-regulation of PD-L1 in macrophages and neutrophils, and hampers immune responses (33). Further results on the role of linc00346 in down-regulating lymphocyte-activating genes demonstrate that this lncRNA may serve as an unfavorable prognostic indicator for gliomas (60). To further evaluate the tumor-promoting effects of lncRNAs, it has been shown that some lncRNAs participate in tumor growth and immune evasion by promoting the activity of the transcription factor NF-kB and up-regulating PD-L1 in various cancers like breast, lung, and gliomas (55, 61). For instance, the expression of lncRNA NEAT1 has been reported to correlate with GBM patients' responses to PD-1/PD-L1 inhibitors. It has been shown that NEAT1 inhibits ubiquitin regulatory X domain-containing protein 1 (UBXN1), a key NF-κB signaling repressor, resulting in up-regulation of NF-κB and enhanced PD-L1 transcription in GBM patients (54). Further results on the oncogenic mechanism of lncRNA NEAT1 in human cancers indicate that NEAT1 repression diminishes T cell apoptosis by regulating the miR155/Tim-3 axis (62). Further observations suggest that *NEAT1*-knockout mice demonstrated abnormal differentiation of T regulatory cells (Tregs) and T helper cells (54). Therefore, these findings demonstrate that NEAT1 attenuates immune responses by suppressing various immune cells, including Tregs and Th cells, in the TME.

The HOX antisense intergenic RNA (HOTAIR) is another NF-kB-related lncRNA whose expression is elevated in multiple solid tumors and associated with malignant features and adverse prognosis in cancer patients. Wang *et al.* demonstrated that HOTAIR elevates NF-κB activity, thereby causing immune evasion by up-regulating PD-L1 transcription in glioma cells (55). Further investigations demonstrate that HOTAIR suppresses UBXN1 and promotes NF-κB phosphorylation and nuclear accumulation, resulting in immune escape and tumor development in GBM (55). Therefore, these results suggest that NF-κB-related lncRNAs can be considered promising targets for the treatment and management of gliomas.

In addition to the oncogenic lncRNAs described earlier, several miRNAs contribute to glioma progression by regulating the PD-1/PD-L1 signaling pathway. For example, enhanced expression of miR-10b-5p has been reported in GBM patients and is associated with a dismal prognosis and unfavorable clinicopathological features (63). The oncogenic miR-10b-5p induces GBM cell invasion and aggressiveness by negatively regulating the Ten-eleven translocation 2 (TET2). It has been reported that TET2 functions as a negative regulator, suppressing PD-L1 transcription by recruiting histone deacetylase enzymes to the PD-L1 promoter region (63). Taken together, the immunosuppressive effect of miR-10b-5p in inducing the PD-L1 transcription and tumor aggressiveness suggests its potential as a promising target in GBM treatment.

Similarly, miR-33a-5p is another onco-miRNA whose expression is linked to radiation resistance and adverse clinical outcomes in GBM patients. Further studies on the oncogenic mechanisms of miR-33a-5p revealed that this miRNA regulates radiation resistance-related pathways, such as STAT3 signaling, and reduces PTEN activity in GBM cells (64). PTEN, a potent tumor suppressor, regulates cell proliferation and metastasis in various human malignancies, including GBM (65, 66). Xia *et al.* demonstrate that PD-L1 inhibitors enhance radiosensitivity by repressing miR-33a-5p and activating the PTEN tumor suppressor in GBM cells. These observations highlight the importance of the miR-33a-5p/PTEN axis as a novel target for GBM therapy (64). Recent studies have also demonstrated a direct correlation between miR-155 levels and PD-L1 expression in high-grade gliomas. miR-155 has been reported to elevate resistance to radiation and chemotherapy by activating the

transcription factor NF-kB. Elevated expression of miR-155 diminishes T cell activity and immune responses and prevents the elimination of malignant cells (67). These findings demonstrate that miR-155 mediates drug resistance and immune evasion by stimulating NF-kB and PD-L1 in human gliomas.

Among miRNAs associated with human malignancies, repression of certain miRNAs has been linked to glioma tumorigenesis and development. For example, the tumor-suppressor miR-138 has been reported to be down-regulated in various cancers, including glioma, head and neck squamous cell carcinoma (HNSCC), thyroid carcinoma, and renal cell carcinoma (68-70). Wei *et al.* demonstrated that ectopic expression of miR-138 reduces tumor formation and metastasis by suppressing the cytotoxic T-lymphocyte-associated molecule 4 (CTLA-4) and PD-1 at the post-transcriptional level in gliomas. CTLA-4 inhibits the activity of T cells and regulatory T cells (Tregs), thereby reducing anti-tumor responses (38). These findings suggest that miR-138 may be a promising target for glioma therapy. lncNDEPD1 is another regulatory ncRNA that targets PD-1 in CD8+ T cells at the post-transcriptional level. Cheng *et al.* demonstrated that lncNDEPD1 prevents PDCD1 mRNA degradation and induces PD-1 expression by sponging miR-3619-5p (40).

Interplay between ncRNAs and PD-1/PD-L1 signaling in head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) encompasses various malignancies originating from the mucosal epithelial cells of the oral cavity, larynx, and pharynx, which can significantly impact patients' quality of life. Immunotherapeutic inhibition of PD-1/PD-L1 axis has increased anti-tumor immune responses and improved clinical outcomes in a limited group of HNSCC patients (71). Therefore, investigating the modulatory mechanisms of the PD-1/PD-L1 axis and identifying novel therapeutic targets offers a promising avenue for improving cancer treatment. Accumulating evidence indicates that up-regulated PD-L1 in HNSCC has a pivotal role in regulating cell proliferation, invasion, and apoptosis (71, 72). PD-L1 expression is primarily induced by inflammatory factors such as IFN-γ secreted by T cells. IFN-γ up-regulates PD-L1 in HNSCC cells by inducing JAK2 and STAT1 transcription factors (73). Further studies on the molecular mechanisms underlying PD-L1 induction indicate that certain ncRNAs promote tumor formation and metastasis by regulating the IFN-γ/JAK2/STAT1 signaling pathway in HNSCC cells (74, 75). Zhang *et al.* demonstrated that IFN-γ can down-regulate miR-382-3p, a negative regulator of PD-L1 expression, at the post-transcriptional level. The tumor suppressor miR-382-3p has been reported to be down-regulated in various cancers, such as colorectal cancer and HNSCC, and its expression inhibits tumor initiation and progression. Further results revealed that oncogenic circ_0000052 functions as a ceRNA for miR-382-3p and suppresses its regulatory effects on the PD-L1 expression in HNSCC. Knockdown of circ_0000052 attenuates tumor formation and propagation (74). Therefore, these findings suggest that the circ_0000052/miR-382-3p/PD-L1 pathway may be a promising candidate for HNSCC therapy. Similarly, the tumor suppressor miR-375 has been reported to inhibit IFN-γ-stimulated PD-L1 expression in HNSCC. Decreased miR-375 expression is associated with poor clinical outcomes and aggressive features in HNSCC patients. It has been shown that miR-375 suppresses PD-L1 expression by targeting JAK2 and inactivating JAK2/STAT1 signaling in HNSCC and gastric cancer (76).

miR-34a is another anti-cancer miRNA whose down-regulation has been reported in various human malignancies, including HNSCC, breast, and colorectal cancers (77). Ectopic expression of miR-34a suppresses tumorigenesis by inhibiting MET signaling and down-regulating PD-L1 at post-transcriptional levels. Elevated expression of proto-oncogene MET is reported in various cancers, such as gastric, lung, hepatocellular, and breast cancers (78). MET activates MAPK signaling and facilitates tumor initiation and metastasis. Increased expression of miR-34a-5p down-regulates MET and suppresses HNSCC carcinogenesis by reducing cell proliferation and epithelial-mesenchymal transition (EMT). Additionally, restoration of miR-34a-5p promotes anti-tumor immunity by stimulating T helper (Th1 cells) and CD8 T cells in TME (77). To further investigate the regulatory effects of miRNAs on HNSCC tumorigenesis, it has been found that the overexpression of let-7a/7b miRNAs induces PD-L1 degradation by targeting T-cell factor 4 (TCF-4) and repressing the β-Catenin/STT3 axis (79). The STT3 protein causes PD-L1 accumulation in cancer stem cells and reduces anti-tumor immune responses. Up-regulation of let-7a/7b miRNAs reduced immune tolerance by increasing infiltrating T cells in TME. Yu *et al.* reported that down-regulation of the let-7 family induces tumor development and immune evasion in HNSCC (79). These observations highlight the contribution of let-7a/7b miRNAs to enhancing anti-tumor immunity against HNSCC.

Further studies on the role of ncRNAs in HNSCC pathogenesis revealed that various lncRNAs implicated in tumorigenesis by targeting certain miRNAs. For instance, the oncogenic lncRNA HOTAIR has been shown to be up-regulated in multiple cancers, such as laryngeal squamous cell carcinoma (LSCC), and to facilitate tumor formation and development by targeting miR-30a-5p (80). The tumor suppressor miR-30a-5p, a negative regulator of cell proliferation and invasion, has been reported to be down-regulated in various cancers, including gastric, hepatocellular, and renal cancers (81). Increased expression of miR-30a-5p suppresses PD-L1 and glucose-regulated protein 78 (GRP78) implicated in tumor growth, angiogenesis, and drug resistance. Further results indicate that HOTAIR mediates cell proliferation and immune evasion by targeting miR-30a-5p and modulating GRP78 and PD-L1 (80).

The lncRNA IFITM4P is another cancer-related ncRNA that is up-regulated in oral squamous cell carcinoma (OSCC). IFITM4P promotes immune escape in OSCC by up-regulating PD-L1 primarily at the post-transcriptional level, while also enhancing NF-κB activity and inhibiting PTEN to drive transcriptional PD-L1 expression (82). Therefore, IFITM4P may be considered a novel therapeutic target for OSCC therapy.

Among all lncRNAs that contribute to tumorigenesis, suppression of multiple lncRNAs has also been linked to HNSCC growth and development. For example, down-regulation of lncRNA lncMX1–215 was reported in HNSCC patients, which is related to tumor aggressive features and adverse health outcomes. Ma *et al.* demonstrated that treatment with IFNα induced immunosuppression and elevated the expression of lncMX1–215, resulting in decreased tumor growth and metastasis (83). Up-regulated lncMX1–215 mediates anti-cancer immune responses by reducing the expression of PD-L1 and galectin-9 in HNSCC cells (83). Therefore, the IFNα/lncMX1–215/PD-L1 axis may

be investigated as a promising therapeutic route for HNSCC.

Interplay between ncRNAs and PD-1/PD-L1 signaling in meningioma

Meningioma is the most common intracranial brain tumor in adults, which is classified into three different stages (benign, atypical, and anaplastic). The recommended therapeutic methods for meningioma include surgery and radiotherapy, but their effectiveness in preventing recurrence and improving patients' overall survival remains limited (84). Therefore, investigating the molecular mechanisms underlying meningioma tumorigenesis is of great importance for advancing therapeutic methods. Emerging data demonstrate the pivotal role of immune checkpoints in tumor initiation and progression by regulating anti-tumor immune responses (85, 86).

PD-L1 is a key immune checkpoint whose expression is modulated by multiple regulatory mechanisms in brain tumors. Eukaryotic translation initiation factor 4A3 (EIF4A3) is one of the main translational factors that accelerate tumorigenesis by activating PD-L1 and immune escape in TME (36). Up-regulated EIF4A3 positively correlates with the PD-L1 expression and enhances cancer cell proliferation, metastasis, and angiogenesis in various cancers, like GBM, meningiomas, cervical, hepatocellular, and breast cancers (87, 88). It has been reported that hsa_circ_0004872 functions as a tumor-suppressive circRNA and competitively interacts with EIF4A3 to inhibit PD-L1 expression at the post-transcriptional level. The expression of hsa_circ_0004872 is down-regulated in meningiomas and is associated with aggressive tumor features and poor survival in patients (89). Ectopic expression of hsa_circ_0004872 alleviates tumor cell invasion and contributes to anti-tumor immune responses by regulating the EIF4A3/PD-L1 route in meningioma cells. Further studies on the tumor-suppressive effect of hsa_circ_0004872 indicate that this circRNA inhibits cell proliferation and promotes apoptosis by sponging miR-190a-3p in meningioma (89). It has been reported that miR-190a-3p induces malignant tumor behaviors by suppressing the tumor suppressor PTEN and activating the PI3K/AKT signaling pathway in meningioma (90).

The tumor suppressor PTEN was shown to be inversely related to PD-L1 expression and to be regulated by miR-21, miR-221/222, and miR-19a, thereby contributing to tumor aggressiveness and drug resistance in glioma and meningiomas (91-93). Restoration of hsa_circ_0004872 regulates the miR-190a-3p/PTEN route and prevents meningioma progression (89). These findings suggest that hsa_circ_0004872, PD-L1, and PTEN may serve as promising targets for the treatment of meningioma.

Interplay between ncRNAs and PD-1/PD-L1 signaling in pituitary adenoma

Pituitary adenoma (PA) is a common non-malignant tumor originating from the pituitary gland and ranks as the third most prevalent intracranial tumor after gliomas and meningiomas. Recent studies indicate that the development of pituitary adenomas may be related to the activation of oncogenes or the inhibition of tumor suppressor genes, and that ncRNAs exert critical effects on tumor initiation and propagation (94, 95). PD-L1, as one of the main oncogenic factors elevated in PA, is found to be up-regulated by various transcription factors, like JAK2/STAT and NF-kB 96). Several miRNAs are implicated in PA tumorigenesis by modulating JAK/STAT transcription factors. For example, decreased levels of miR-216a-5p and miR-652-3p have been linked to tumor growth and invasiveness in PA. Up-regulation of these tumor suppressive miRNAs hampers JAK/STAT activity, attenuates tumor aggressiveness, and improves clinical outcomes in PA patients (96).

To further investigate the molecular mechanism underlying PA pathogenesis, it has been reported that circMFN2 functions as an onco-circRNA that facilitates PA invasion and progression by activating the transcription factor NF-κB (97). The tumor-promoting effect of circMFN2 in PA was highlighted by its ability to sponge miR-146a-3p. The tumor suppressor miR-146a-3p inhibits NF-kB and alleviates PA aggressiveness (97). Down-regulation of NF-kB inhibits various proteins involved in cell proliferation, invasion, and metastasis, including cyclin D1, VEGF, E-cadherin, N-cadherin, and PD-L1 (78-100). Therefore, these observations suggest that circMFN2 promotes PA tumorigenesis through targeting the miR-146a-3p/NF-kB pathway.

ncRNA panel as biomarkers for brain cancer diagnosis

Early and accurate diagnosis of cancer at an early stage provides opportunities for earlier and minimally invasive interventions, thereby increasing patient survival and improving clinical outcomes. Emerging evidence suggests that ncRNAs may serve as potential diagnostic biomarkers in multiple cancers, including brain, lung, and gastrointestinal cancers. For instance, ANRIL (antisense noncoding RNA in the *INK4* locus) is considered an oncogenic lncRNA up-regulated in lung, breast, gastrointestinal, and brain cancers (101, 102). Elevated expression of ANRIL is associated with tumor aggressive features and poor prognosis in GBM patients, suggesting the role of ANRIL as a potential prognostic biomarker for screening patients suspected of GBM (103). To further investigate the diagnostic potential of lncRNAs in brain cancers, Tan *et al.* demonstrated that the expression of long noncoding RNA *HOX* Transcript Antisense Intergenic RNA (HOTAIR) is significantly up-regulated in GBM patients and correlated with high-grade brain tumors (104). In a study, HOTAIR serum levels were assessed pre- and post-surgical resection in patients with GBM. A significant reduction in HOTAIR serum level was observed at the two-week postoperative evaluation, supporting its potential as a novel diagnostic biomarker for GBM (104).

In addition to the above-mentioned lncRNAs, multiple miRNAs were identified as non-invasive diagnostic and prognostic biomarkers for brain cancers. For example, miR-21 is the first identified oncogenic miRNA, up-regulated in multiple human cancers and correlated with tumor formation and progression (105). To further evaluate the diagnostic accuracy of miRNA-21 as a potent biomarker in patients with suspected glioma, it has been shown that miR-21 possesses significant diagnostic accuracy for glioma, comparable to the conventional MRI and PET imaging, and could be integrated with these imaging approaches to enhance diagnostic precision (105). To further identify a prognostic biomarker in brain cancer, it has been found that the serum level of miR-205 is significantly lower in glioma patients compared with healthy volunteers (106). It has been reported that serum levels of miR-205 increase following surgical intervention but then decrease again during GBM recurrence. Further results indicate that elevated serum miR-205 is linked to improved overall survival in GBM, particularly in patients with advanced pathological grades, as those with higher miR-205 concentrations survived longer than patients with lower miRNA levels. These findings clearly suggest that serum miR-205 levels may

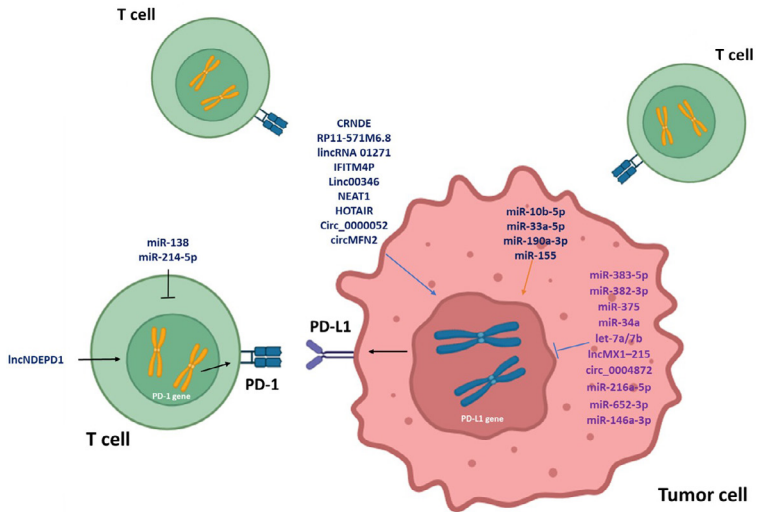

Figure 1. The interplay between lncRNAs and miRNAs in regulating the PD1/PD-L1 signaling pathway in the tumorigenesis of brain cancers

serve as a novel prognostic biomarker for GBM, particularly in patients with advanced pathological grades (106). These findings revealed that ncRNAs may serve as diagnostic and/or prognostic biomarkers in brain cancers.

Conclusion

This study summarizes current findings on the role of ncRNAs in the development of brain tumors by modulating the PD-1/PD-L1 immune checkpoint axis. The PD-1/PD-L1 interaction significantly affects tumor cell growth, invasiveness, and metastasis by repressing anti-tumor immune responses. As shown in Figure 1, numerous PD-1/PD-L1 signaling-associated ncRNAs are dysregulated in brain malignancies and may function as tumor suppressors or oncogenes, contributing to tumor initiation and progression (Tables 1 and 2). By modulating transcription

Table 1. Oncogenic ncRNAs

ncRNAs	Cancer	Target cells	Mechanism	Function	Ref.
lncRNA CRNDE	Glioblastoma	Tumor cells	Sponging miR-384 and regulating PIWIL4/STAT3 axis	Promotes glioma cell growth and drug resistance	53
lncRNA RP11-571M6.8	Glioblastoma	T-lymphocytes	Regulation of PD-L1 and CTLA-4	Inhibits immune cell infiltration	57
lincRNA 01271	Glioblastoma	Macrophages	PD-L1 up-regulation	Induces immune escape and tumor growth	37
linc00346	Glioblastoma	Macrophages and neutrophils	PD-L1 up-regulation	Inhibits immune responses	33
lncRNA NEAT1	Glioblastoma	T-lymphocytes	Sponging miR-155 and promoting NF-kB and PD-L1	Induces T cell apoptosis and Inhibits immune responses	54
lncRNA HOTAIR	Glioblastoma	Tumor cells	Suppresses UBXN1 and promotes NF-kB and PD-L1	Induces immune escape and tumor development	55
miR-10b-5p	Glioblastoma	Tumor cells	Inhibits TET2 and promotes PD-L1	Induces GBM cell invasion and aggressiveness	63
miR-33a-5p	Glioblastoma	Tumor cells	Regulates STAT3 and inhibits PTEN	Promotes radiation resistance	37
miR-155	Glioblastoma	Tumor cells	Stimulates NF-kB and PD-L1	Elevates drug resistance and immune evasion	67
Circ_0000052	Head and neck squamous cell carcinomas	Tumor cells	Sponging miR-382-3p and promoting PD-L1	Promotes tumor formation and propagation	74
lncRNA HOTAIR	Laryngeal squamous cell carcinoma	Tumor cells	Targeting miR-30a-5p and modulating GRP78 and PD-L1	Enhanced cell proliferation and immune evasion	80
lncRNA IFITM4P	Oral squamous cell carcinoma	Tumor cells	Up-regulates PD-L1 by stimulating NF-kB and inhibiting PTEN	Induces immune escape	82
miR-190a-3p	Meningioma	Tumor cells	Suppresses PTEN and activates PI3K/AKT signaling	Induce tumor growth and aggressiveness	89
circMFN2	Pituitary adenoma	Tumor cells	Sponging miR-146a-3p and promotes NF-kB	Induces PA invasion and progression	97

Table 2. Tumor suppressive ncRNAs

ncRNAs	Cancer	Target Cells	Mechanism	Function	Ref.
miR-138	Glioma	T-lymphocytes	Suppressing CTLA-4 and PD-1	Reduces tumor formation and metastasis	38
miR-382-3p	Head and neck squamous cell carcinomas	Tumor cells	Down-regulates PD-L1	Inhibits immune escape	74
miR-375	Head and neck squamous cell carcinomas	Tumor cells	Suppresses PD-L1 and inactivates JAK2/STAT1	Inhibits immune escape	76
miR-34a-5p	Head and neck squamous cell carcinomas	T-lymphocytes	Inhibits MET signaling and represses PD-L1	Reduces cell proliferation and EMT	77
let-7a/7b	Head and neck squamous cell carcinomas	T-lymphocytes	Reduces PD-L1 targeting TCF-4 and repressing β-Catenin/STT3 axis	Promotes immunity by increasing T cells	79
lncMX1–215	Head and neck squamous cell carcinomas	Tumor cells	Down-regulates PD-L1 and galectin-9	Decreases tumor growth and metastasis	83
circ_0004872	Meningioma	Tumor cells	Sponging miR-190a-3p and down-regulates PD-L1	Alleviates tumor invasion and induces immune responses	89
miR-216a-5p miR-652-3p	Pituitary adenoma	Tumor cells	Inhibits JAK/STAT activity	Inhibits tumor growth and aggressiveness	96
miR-146a-3p	Pituitary adenoma	Tumor cells	Inhibits NF-kB and PD-L1	Inhibits tumor growth and aggressiveness	97

factors and signaling pathways such as NF-κB, JAK, and STAT, these ncRNAs can regulate PD-1/PD-L1 axis activity, influencing downstream cellular processes such as epithelial-mesenchymal transition (EMT), proliferation, and invasion.

Importantly, the regulatory impact of ncRNAs on the PD-1/PD-L1 axis extends beyond tumor cells to multiple cellular compartments within the tumor microenvironment. ncRNA-mediated mechanisms act in a cell type–specific manner, influencing not only malignant cells but also microglia, tumor-associated macrophages, and infiltrating lymphocytes. The dynamic interplay among these cellular populations—coordinated in part by ncRNAs—shapes the overall immunosuppressive landscape of the CNS tumor microenvironment and determines the extent of immune evasion.

Taken together, these observations position ncRNAs as critical modulators of immune checkpoint regulation and tumor–immune interactions in brain cancers. Targeting ncRNAs involved in PD-1/PD-L1 signaling is a promising therapeutic strategy that could enhance antitumor immunity and improve clinical outcomes for individuals with brain cancers.

Authors' Contributions

R BR and F E contributed to manuscript preparation and discussed the study results; F E, M G, and A R contributed to data collection and processing; FR contributed to study design and supervised the study; M N, F G, and F R edited, proofread, and managed the study. All authors approved the final version of the manuscript.

Funding

This research was partly supported by Mashhad University of Medical Sciences (Farzad Rahmani).

Acknowledgment

This study was supported by grants awarded by Mashhad University of Medical Sciences (Grant No. 4042460).

Conflicts of Interest

The authors declare no conflicts of interest.

Declaration

We acknowledge the use of [ChatGPT (OpenAI)] for language editing and proofreading during the preparation of this manuscript. The AI-generated suggestions were carefully reviewed and modified by the authors, who take full responsibility for the final content.

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