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REVIEW

PDCD4: A Double-Edged Sword in Neurological Diseases

Conghui Li[1,2] · Kang Zheng[1] · Mengsheng Qiu[1] · Junlin Yang[1]

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Abstract
Programmed Cell Death 4 (PDCD4) is a multifunctional regulator with critically divergent, context-dependent roles: it acts as a tumor suppressor in neuro-oncology but a pathogenic driver in neuroinflammatory and degenerative conditions. Elucidating this functional duality is clinically relevant because PDCD4 dysregulation directly contributes to disease progression in both contexts. Its dual role is governed by disease-specific molecular environments, differential downstream mRNA targeting, and dynamic regulation of its expression and interactions. In gliomas, PDCD4 is frequently downregulated via promoter methylation, non-coding RNA inhibition (e.g., miR-*21*), and signaling pathway dysregulation (e.g., FAT1-STAT1 axis)—compromising key anti-tumor functions including cell cycle arrest, apoptosis induction, negative regulation of autophagy-lysosomal activity, and reversal of therapy resistance. Conversely, in conditions such as neural injury, neurodegenerative diseases, and mood disorders, PDCD4 is pathologically upregulated. Here, it exacerbates damage by driving the activation of pro-inflammatory pathways (e.g., MAPK/NF-κB, NLRP3 inflammasome), inducing neuronal death (apoptosis/ferroptosis), and impairing repair processes such as axonal growth by suppressing neurotrophic factors like brain-derived neurotrophic factor (BDNF). A multilayered regulatory network centered on miRNA-mediated control (notably miR-*21*), and expanded by epigenetic modifications and competitive endogenous RNA mechanisms, orchestrates its context-specific expression and activity. Current research gaps include an incomplete understanding of regulatory synergies, cell-type-specific functions, and key molecular interactions. Future studies employing multi-omics and cell-specific tools are needed to decipher these mechanisms and develop targeted therapeutic strategies.

Keywords PDCD4 · Neurological diseases · Dual role · Glioma · Neurodegenerative diseases

Introduction

Programmed Cell Death 4 (PDCD4) initially garnered significant attention due to its downregulated expression in various solid tumors such as lung cancer, breast cancer, and colorectal cancer, as well as its key tumor suppressor function mediated by mechanisms including inhibiting translation initiation and regulating cell cycle and apoptosis [1–4]. However, for many years, its potential roles in non-neoplastic diseases—particularly those of the nervous system which are characterized by dysregulated cell death, inflammation, and stress responses—remained a significant and unexplored gap in knowledge. Notably, these are the very processes that PDCD4 modulates to exert its tumor-suppressive effects, highlighting a compelling yet unexplored mechanistic link to neurological pathologies. With the advancement of research, the important role of PDCD4 in the nervous system has become increasingly evident, and its functions exhibit remarkable disease context dependency [5, 6]. This review systematically summarizes the expression profiles, regulatory networks, and molecular mechanisms of PDCD4 in various neurological disorders such as glioma, stroke, Alzheimer's disease (AD), Parkinson's disease (PD), and depression, aiming to provide a systematic perspective for understanding the multifunctionality of PDCD4 in the nervous system and offer insights for the future development of PDCD4-targeted diagnostic and therapeutic strategies for neurological diseases. Furthermore, we aim to synthesize these findings into a coherent conceptual framework that

✉ Junlin Yang
yjl8121@hznu.edu.cn

[1] College of Life and Environmental Sciences, Key Laboratory of Organ Development and Regeneration of Zhejiang Province, Hangzhou Normal University, Hangzhou 311121, China

[2] College of Life Sciences, Zhejiang University, Hangzhou 310058, China

explains the conditional determinants of PDCD4's dual functionality in the nervous system.

Literature Search and Selection Strategy

To ensure a comprehensive and unbiased synthesis of the role of PDCD4 in neurological diseases, this review employed a systematic approach for literature identification, screening, and analysis. Primary electronic databases, including PubMed, Web of Science Core Collection, and Scopus, were searched from their inception up to January 2026, supplemented by queries in Google Scholar for additional citation tracking. The search strategy combined keywords related to the target molecule, such as "Programmed cell death 4" or "PDCD4," with terms covering major neurological contexts including glioma, cerebral ischemia, spinal cord injury (SCI), brain injury, AD, PD, neuroinflammation, neuropathic pain, and depression. Literature selection adhered to predefined criteria, prioritizing English-language original research or authoritative reviews that centrally investigated the expression, regulation, function, or clinical relevance of PDCD4 in neurological disorders or pertinent models while excluding non-peer-reviewed publications and studies where PDCD4 was not a primary focus. The screening process involved independent assessment of titles, abstracts, and full texts by two authors, with discrepancies resolved through discussion or consultation with a senior author. Following the final selection of studies, key data pertaining to the experimental model, PDCD4 expression dynamics, regulatory mechanisms, and functional outcomes were extracted. The extracted information was then thematically synthesized and organized according to major disease categories—neuro-oncology, acute neural injury, neurodegenerative diseases, inflammation-related disorders, and mood dysfunction—to construct a coherent narrative highlighting PDCD4's context-dependent dual roles. This synthesis further involved identifying core regulatory networks and convergent effector pathways across different conditions, with findings systematically summarized in tables and integrated into schematic figures to illustrate the overarching molecular mechanisms and conceptual framework.

Gene Characteristics, Protein Functions, and Regulatory Mechanisms of PDCD4

The core functions of PDCD4 are evolutionarily conserved. It was first cloned from mouse cells in 1995 [7], and subsequently, homologous genes have been identified in humans, rats, chickens, and other species. The amino acid sequence of PDCD4 shows extremely high conservation, with 92% sequence identity and 96% homology between humans and mice, and up to 72% homology with lower species such as elephant sharks [8, 9], underscoring its pivotal role in regulating cellular physiology. The human PDCD4 gene is localized to the chromosome 10q24 region. Initially identified as a nuclear antigen gene [10], it is widely expressed in normal human tissues, with its encoded protein displaying cell-type-specific localization (either in the nucleus or cytoplasm). However, in various malignant tumors such as nervous system malignancies, PDCD4 often exhibits loss or downregulation of expression due to dysregulation [11–13].

The PDCD4 protein, composed of 469 amino acid residues, contains two MA3 domains homologous to those in eukaryotic translation initiation factor 4G (eIF4G) [14]. These domains bind eukaryotic translation initiation factor 4 A (eIF4A) to inhibit its RNA helicase activity, thereby blocking translation—a core mechanism through which PDCD4 regulates cellular functions [15, 16]. In addition, PDCD4 harbors two phosphorylation sites (Ser67 and Ser457), two positively charged amino acid clusters, and two nuclear export signals (NES) (Fig. 1A). Ser67 can be phosphorylated by Akt or p70S6K, after which it is recognized by β-TRCP to mediate its ubiquitination and degradation, while the positively charged amino acid clusters are involved in RNA binding and the NES regulates the nucleocytoplasmic shuttling of the protein [17]. Additionally, PDCD4's PABP (Poly(A)-Binding Protein) binding site enhances the translation inhibitory effect through interaction with PABP (Fig. 1A), and this evolutionarily conserved interaction highlights its significance for PDCD4 function [18].

PDCD4 exerts its functions through three primary mechanistic pathways, as summarized in Fig. 1B–G. First, it inhibits translation initiation via both eIF4A-dependent and independent mechanisms. In the eIF4A-dependent mode, PDCD4 preferentially inhibits the translation of mRNA containing complex secondary structures in the 5′ UTR (such as those encoding growth factors and signaling pathway components [19]). Here, PDCD4 binds to eIF4A via its MA3 domain, locking eIF4A in an inactive state and disabling its RNA helicase activity to unwind the 5′ non-translated regions of mRNA from genes like Sin1 and cyclin D1 [20] (Fig. 1B). Concurrently, its MA3 domain competes with eIF4A for binding sites, thereby blocking the formation of the eIF4F complex (eIF4A + eIF4G + eIF4E) and inhibiting cap-dependent translation [21] (Fig. 1C). In the eIF4A-independent mode, PDCD4 directly binds to the coding region of target mRNAs (e.g., c-Myb) via positively charged amino acid clusters, physically obstructing ribosome progression [18] (Fig. 1D), or to the internal ribosome entry sites (IRES) of anti-apoptotic genes like *Bcl-xL* [22] (Fig. 1E). Second, PDCD4 modulates transcription by directly interacting with key transcription factors. For instance, it binds to the AP-1 subunit c-Jun to inhibit its transactivation capacity, which in turn prevents the recruitment of coactivator P300 and reduces AP-1's binding to oncogene promoters such as *Plaur*

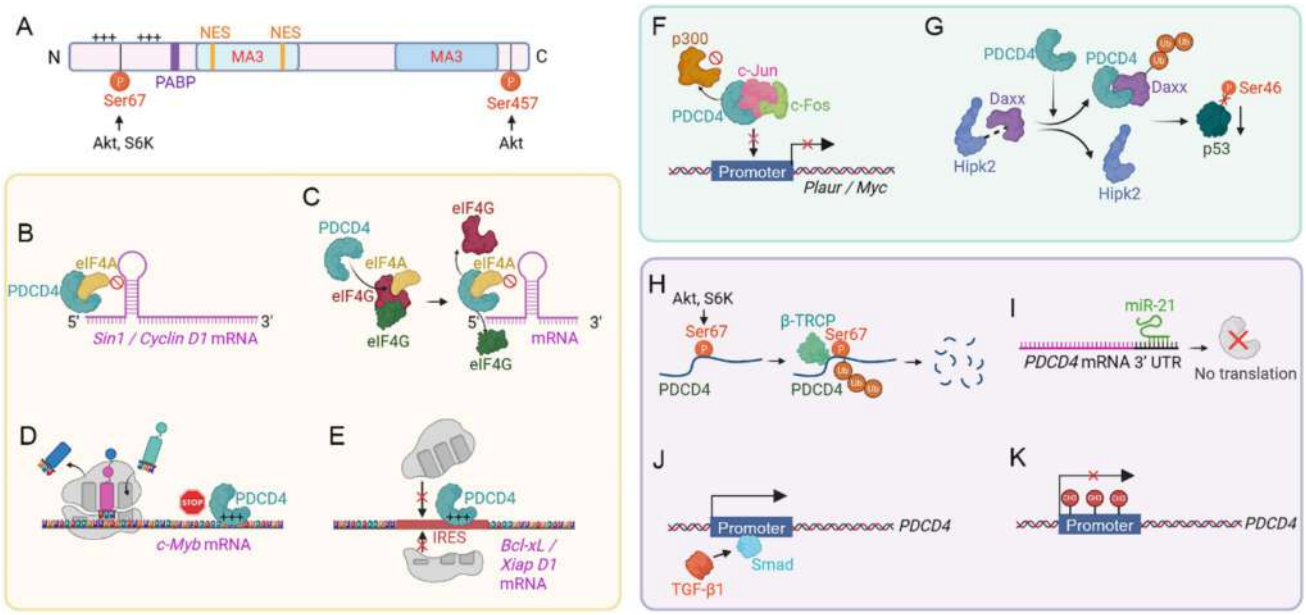

Fig. 1 Schematic diagram of the PDCD4 protein structure, functional mechanisms, and molecular regulatory pathways. **A** Structure of the PDCD4 protein. PABP, poly(A)-binding protein-binding site; MA3, eIF4G-homologous domain; NES, nuclear export signal; + + +, positively charged amino acid cluster (RNA-binding site). **B** eIF4A-dependent translational inhibition: PDCD4 (via its MA3 domains) binds to and locks eIF4A in an inactive conformation, preventing the unwinding of structured 5′ UTRs (e.g., in Sin1 mRNA), thereby blocking cap-dependent translation initiation. **C** Disruption of eIF4F complex assembly: The MA-3 domain of PDCD4 competes with eIF4G for binding to eIF4A, preventing the formation of the functional eIF4F (eIF4E-eIF4G-eIF4A) complex. **D** eIF4A-independent translation elongation block: PDCD4 directly binds to the coding sequence of target mRNAs (e.g., c-Myb) via its positively charged amino acid clusters, physically obstructing the progression of the scanning ribosome. **E** Internal ribosome entry site (IRES)-mediated translation inhibition: PDCD4 binds to the IRES element within the 5′ UTR of specific anti-apoptotic mRNAs (e.g., Bcl-xL), blocking the recruitment of the ribosome and inhibiting IRES-dependent translation. **F** Transcriptional repression via AP-1 inhibition: PDCD4 interacts with the transcription factor c-Jun (an AP-1 subunit), inhibiting its transactivation capacity. This prevents the recruitment of the coactivator p300 and reduces AP-1 binding to target gene promoters (e.g., Plaur), leading to transcriptional downregulation. **G** Modulation of P53 activity via the Daxx-Hipk2 axis: PDCD4 binds to the scaffold protein Daxx via its N-terminus. This interaction disrupts the Daxx-Hipk2 complex, promotes Daxx degradation, and subsequently inhibits Hipk2-mediated phosphorylation of P53 at Ser46, thereby attenuating P53 activity. **H** Post-translational regulation via ubiquitin-proteasomal degradation: Phosphorylation of PDCD4 at Ser67 by kinases such as Akt or p70S6K creates a recognition motif for the E3 ubiquitin ligase β-TRCP, leading to PDCD4 polyubiquitination and subsequent degradation by the proteasome. **I** Post-transcriptional repression by miRNAs: Specific microRNAs (most prominently miR-*21*) bind to complementary sequences within the 3′ untranslated region (3′ UTR) of PDCD4 mRNA, leading to translational repression and/or mRNA destabilization. **J** Transcriptional activation via the TGF-β/Smad pathway: The cytokine TGF-β1 activates its receptor, leading to the phosphorylation and nuclear translocation of Smad proteins (Smad2/3/4 complex). This complex binds to specific response elements in the PDCD4 promoter, driving its transcription. **K** Epigenetic silencing via promoter hypermethylation: In pathological conditions (e.g., glioma), the CpG island in the PDCD4 gene promoter undergoes DNA methylation catalyzed by DNA methyltransferases (DNMTs). This methylation recruits repressive complexes, leading to a closed chromatin state and transcriptional silencing of PDCD4

and *Myc* (Fig. 1F), and ultimately inhibits transcription [23]. In inflammatory microenvironments, PDCD4 binds to the p65 subunit of NF-κB, inhibiting its nuclear translocation and blocking the transcription of pro-inflammatory and pro-oncogenic genes such as *IL-6* and *TNF-α* [24]. Third, PDCD4 regulates cellular processes via specific protein interactions, such as forming a complex with polyadenylate-binding protein (PABP), a key factor in mRNA stabilization, thereby enhancing the inhibition of *c-Myb* mRNA translation elongation. This interaction is evolutionarily conserved [18]. Additionally, PDCD4 also binds to the central domain of the scaffold protein Daxx via its N-terminus, disrupting the interaction between Daxx and the kinase Hipk2 and promoting Daxx proteasome degradation, which ultimately inhibits Hipk2-mediated phosphorylation of P53 Ser-46, thereby suppressing P53 activity [25] (Fig. 1G).

PDCD4 expression is regulated at multiple levels. At the post-translational level, Akt or p70S6K mediates the phosphorylation of PDCD4 at Ser67, which triggers the β-TRCP-mediated ubiquitin–proteasome degradation pathway, ultimately leading to reduced PDCD4 levels [17] (Fig. 1H). At the post-transcriptional level, miRNA plays a crucial regulatory role, among which miR-*21* inhibits the translation of PDCD4 mRNA by binding to its 3′ untranslated region (3′

Table 1 Key miRNAs and ceRNAs regulating PDCD4 in neurological diseases

Regulator type	Regulator	Disease context	Core mechanism	Functional outcome	Refs
Direct miRNA regulators	miR-*21*	Glioma	Binds to PDCD4 3′ UTR	Promotes tumor proliferation	[33, 34]
	miR-*21*	Neuroinflammation	Binds to PDCD4 3′ UTR	Promotes microglial activation and inflammation	[35]
	miR-*21*	SCI, Cerebral Ischemia	Binds to PDCD4 3′ UTR	Aggravates apoptosis, inhibits axonal repair	[32, 36, 37]
	miR-*96*	Glioma	Binds to PDCD4 3′ UTR	Induces radioresistance	[41, 42]
	miR-*503*	Glioma	Binds to PDCD4 3′ UTR	Mediates temozolomide chemoresistance	[31]
	miR-*183-5p*	Amyotrophic Lateral Sclerosis (ALS)	Binds to PDCD4 3′ UTR	Promotes motor neuron apoptosis	[40]
	miR-*183-5p*	Diabetic Intracerebral Hemorrhage	Binds to PDCD4 3′ UTR	Aggravates neuroinflammation (NLRP3 activation)	[38]
	miR-*212*	AD	Downregulated by Aβ, binds to PDCD4 3′ UTR	Aggravates Aβ-induced neurotoxicity and apoptosis	[39]
	miR-*141-3p*	Traumatic Brain Injury (TBI)	Binds to PDCD4 3′ UTR	Promotes neuronal apoptosis and neuroinflammation	[44]
	miR-*150-5p*	AD	Binds to PDCD4 3′ UTR (inversely correlated with PDCD4 in PBMCs)	Potential peripheral biomarker/regulatory factor	[45]
Indirect regulators (ceRNAs)	lncRNA MEG3	Ischemic Brain Injury (IBI)	Sponges miR-*21*	Upregulates PDCD4, aggravates neuronal death	[32]
	circ_0007290	IBI	Sponges miR-*496* (targets PDCD4)	Upregulates PDCD4, aggravates neuronal injury	[43]
	lncRNA HOTAIR	Glioma	Recruits PRC2 for epigenetic silencing of PDCD4	Downregulates PDCD4, promotes tumor proliferation	[30]

UTR) (Fig. 1I). Furthermore, more than 80 miRNAs (such as miR-*182*, miR-*499*, etc.) have been predicted to target PDCD4 mRNA [26–28]. At both transcriptional and epigenetic levels, TGF-β1 upregulates the transcriptional level of PDCD4 through its receptor-mediated Smad signaling pathway [12] (Fig. 1J). In 47% of glioma tissues, methylation occurs at the 5′ CpG island of PDCD4 (Fig. 1K), which suppresses its transcription, and DNA methyltransferase inhibitors can restore PDCD4 expression while inhibiting glioma cell proliferation, indicating that its methylation status is closely associated with poor patient prognosis [29].

The miRNA-Centric Regulatory Network of PDCD4 in Neurological Contexts

Building on the general regulatory mechanisms outlined above, the expression and function of PDCD4 in the nervous system are orchestrated by a complex, multilayered network centered on microRNAs. This network serves as a pivotal determinant of PDCD4's context-dependent dual roles, integrating both conserved and disease-specific regulators [30–32]. As summarized in Table 1, miR-*21* emerges as a major negative regulator. Its overexpression in gliomas and neuroinflammatory conditions suppresses PDCD4 to promote oncogenesis or inflammation [33–35]; conversely, its downregulation—along with that of other miRNAs such as miR-212 and miR-183-5p—in neural injury and degenerative diseases relieves the inhibition of PDCD4, leading to its pathogenic accumulation [32, 36–40]. Additional miRNAs, including miR-96 and miR-503, are upregulated in gliomas to confer radio- and chemoresistance through PDCD4 downregulation [31, 41, 42]. The regulatory complexity is further amplified by competitive endogenous RNA (ceRNA) mechanisms, in which lncRNAs (e.g., MEG3, HOTAIR) and circRNAs (e.g., circ_0007290) sponge miRNAs to indirectly modulate PDCD4 levels [30, 32, 43]. This intricate, condition-dependent miRNA network functions as a molecular

switch that precisely controls PDCD4 abundance, toggling between its tumor-suppressive and neuro-destructive states according to the disease context. Detailed manifestations of this network in specific neurological disorders are discussed in the following sections.

PDCD4 as a Tumor Suppressor in Gliomas: Expression Patterns, Regulatory Hubs, and Translational Prospects

PDCD4 functions as a key tumor suppressor in gliomas—the most extensively studied malignant neurotumor—with its dysregulation tightly linked to tumorigenesis, progression, therapeutic resistance, and patient outcomes [5, 46, 47]. Its context-dependent loss of function in gliomas is orchestrated by multilayered regulatory mechanisms, while its tumor-suppressive effects span cell-autonomous and tumor microenvironment (TME)-modulating pathways. This section systematically summarizes PDCD4's expression profiles, convergent regulatory hubs, context-specific functions, and translational potential, with a focus on glioma subtype heterogeneity and clinical applicability.

Expression Patterns of PDCD4 in Gliomas

PDCD4 is consistently downregulated in most human glioma cohorts and cell lines and even absent in most gliomas, with expression levels inversely correlated with malignancy grade and unfavorable prognosis [29, 48]. This downregulation is most prominently driven by epigenetic silencing, with promoter hypermethylation being a well-validated mechanism: in a cohort of 120 primary human glioma samples (WHO Grade II–IV) analyzed by methylation-specific PCR (MSP) and bisulfite sequencing, 47% of the total samples exhibited hypermethylation of the PDCD4 5′ CpG island [29]. This modification correlates with reduced PDCD4 mRNA and protein levels regardless of partial or complete methylation [48], and is more prevalent in IDH-wildtype gliomas—an aggressive subtype with poor prognosis—compared to IDH-mutant tumors [49].

Clinically, PDCD4 methylation status serves as a prognostic marker: in a retrospective study of 85 high-grade glioma (HGG) patients, PDCD4-positive expression (associated with low promoter methylation) correlated with a median overall survival (OS) of 15.2 months, compared to 8.7 months in PDCD4-negative (highly methylated) patients (log-rank $p = 0.003$). Multivariate Cox regression further confirmed PDCD4 as an independent favorable prognostic factor (HR = 0.42, 95% CI: 0.23–0.77) [29].

At the cellular level, glioma cell lines (U251, U87, A172) exhibit markedly lower PDCD4 mRNA and protein levels compared to normal astrocytes [30, 48, 50, 51], with U251 cells showing near-complete loss of PDCD4 expression in some studies [51]. This deficiency is consistent across pathological subtypes, suggesting PDCD4 downregulation is an early event in gliomagenesis [50]. Notably, recent single-cell RNA-seq analyses have revealed cell-type-specific PDCD4 expression within glioma tissues: while tumor cells show minimal PDCD4 levels, infiltrating immune cells (e.g., macrophages) retain partial expression, highlighting the need to distinguish cell-autonomous vs. TME-derived PDCD4 functions [49].

Convergent Regulatory Hubs of PDCD4 in Gliomas

PDCD4 expression in gliomas is governed by three interconnected, convergent regulatory hubs—epigenetic silencing, miRNA-mediated repression, and PI3K/Akt-driven degradation—with crosstalk between pathways amplifying its downregulation. Notably, the atypical cadherin FAT1 drives PDCD4 downregulation via STAT1-mediated transcriptional suppression [52], a signaling axis that links cell adhesion to PDCD4's tumor-suppressive function. Consistent with this, FAT1 also acts as an upstream regulator of oncogenic and inflammatory pathways via PDCD4 [53], reinforcing the role of FAT1-PDCD4 crosstalk in glioma progression.

Epigenetic silencing serves as the primary regulatory hub for PDCD4 downregulation in gliomas. The 5′ CpG island hypermethylation, catalyzed by DNA methyltransferases (DNMTs), directly suppresses PDCD4 transcription [29], and treatment with DNMT inhibitors (e.g., decitabine) restores PDCD4 expression and inhibits glioma cell proliferation [29]. Additionally, the long non-coding RNA (lncRNA) HOTAIR recruits the Polycomb Repressive Complex 2 (PRC2) to the PDCD4 promoter, inducing H3K27me3 modification and further reinforcing transcriptional silencing [30]. This epigenetic crosstalk is particularly relevant in inflammatory TMEs, where HOTAIR is upregulated via immune cell-derived cytokines, linking TME stress to PDCD4 silencing [49].

Beyond epigenetic modifications, miRNA-mediated repression constitutes another key regulatory layer. miR-*21* emerges as the most well-validated repressor, with high expression in gliomas enabling direct binding to the PDCD4 3′ UTR to inhibit translation, thereby promoting tumor proliferation, invasion, and angiogenesis [33, 34]. Two additional miRNAs—miR-*96* and miR-*503*—contribute to therapeutic resistance: miR-*96* downregulates PDCD4 to enhance DNA repair and radioresistance [41, 42], while miR-*503* (upregulated via TGF-β1/Smad2/3 signaling) mediates temozolomide chemoresistance [31]. These miRNAs are often co-upregulated in EGFR-amplified gliomas [49], suggesting a subtype-specific regulatory network. The miRNA-PDCD4 axis is further modulated by competitive endogenous RNA (ceRNA) mechanisms: lncRNA MEG3

sponges miR-*21* to indirectly upregulate PDCD4, while circRNA circ_0007290 targets miR-*496* to relieve PDCD4 repression [30, 43]. However, HOTAIR acts as a ceRNA antagonist by sponging miR-*148a* (a PDCD4 activator), further suppressing PDCD4 expression [49].

Post-translational degradation of PDCD4 is predominantly driven by the PI3K/Akt/p70S6K pathway. Akt or p70S6K phosphorylates PDCD4 at Ser67, creating a recognition motif for the E3 ubiquitin ligase β-TRCP, which triggers polyubiquitination and proteasomal degradation [17]. This pathway is hyperactivated in gliomas due to loss of PTEN or gain-of-function mutations in PI3K, ensuring sustained PDCD4 downregulation [51]. Additionally, heterogeneous nuclear ribonucleoprotein C (hnRNPC) amplifies this degradation by two mechanisms: promoting pri-miR-21 maturation (to enhance miRNA-mediated repression) and directly activating Akt/p70S6K signaling [54]. The PI3K-Akt-PDCD4 axis also intersects with TME stressors, such as hypoxia and oxidative stress, which activate ion channel-mediated signaling (e.g., TRPM2) to further enhance PDCD4 degradation. Additionally, CLEC19A, another tumor suppressor in glioblastoma, exerts its tumor-suppressive effects by inhibiting the PI3K/AKT/NF-κB signaling pathway [55]. Its regulatory pathway exhibits crosstalk and synergy with the PDCD4-mediated PI3K/Akt-PDCD4 degradation axis, further confirming the core regulatory role of this pathway in the malignant progression of glioblastoma. This also provides a theoretical basis for the development of combined targeted therapeutic strategies against PDCD4 and CLEC19A-related pathways [55].

Context-Dependent Functions: Tumor Cell Autonomy vs. TME Modulation

PDCD4 exerts its tumor-suppressive effects through both cell-autonomous mechanisms (directly inhibiting glioma cell proliferation, survival, and plasticity) and TME-modulating functions (regulating immune cell activity and extracellular matrix remodeling), with these dual roles critical for understanding its impact on glioma progression and therapeutic response.

PDCD4's cell-intrinsic tumor-suppressive effects are mediated by four key pathways. It reduces glioma cell clonogenicity and anchorage-independent growth by arresting the cell cycle at G0/G1 (via inhibiting cyclin D1 translation) and upregulating pro-apoptotic proteins (BAX, Caspase-3) while downregulating anti-apoptotic Bcl-xL [42, 51, 56]. It also inhibits invasion and angiogenesis by binding the NF-κB p65 subunit to block its nuclear translocation, reducing expression of MMP-9 and VEGF—key mediators of aggressive dissemination [24], a mechanism particularly relevant in HGG [16]. Additionally, PDCD4 negatively regulates autophagy by binding to eIF4A and ATG5 mRNA via its MA3 domains, inhibiting ATG5 translation and formation of the ATG12-ATG5 complex [57]; autophagy dysregulation in PDCD4-deficient gliomas promotes nutrient recycling and survival under TME stress, exacerbating malignancy [57]. Finally, PDCD4 sensitizes glioma cells to chemoradiotherapy: its downregulation relieves repression of Bcl-xL translation, leading to chemoresistance [56], while overexpression restores sensitivity to temozolomide (via inhibiting Bcl-xL) and radiation (via blocking miR-*96*-mediated DNA repair) [31, 42].

Beyond cell-intrinsic roles, PDCD4 also modulates glioma progression indirectly by shaping the TME, with a well-characterized function in tumor-associated macrophages (TAMs). In TAMs, PDCD4 binds the 5′ UTR of TFEB (transcription factor EB) mRNA to suppress its translation, reducing lysosomal biogenesis and activity [58]. This impairs macrophage phagocytosis of glioma cells and antigen presentation, promoting immune evasion [58]. PDCD4 deficiency in TAMs further enhances secretion of pro-inflammatory cytokines (IL-6, TNF-α), which activate the PI3K/Akt pathway in glioma cells to further suppress PDCD4 expression—creating a pro-tumor inflammatory loop [49]. Additionally, PDCD4 interacts with immunomodulatory lncRNAs (e.g., LINC00346) to regulate TME immune cell infiltration, with low PDCD4 correlated with increased myeloid-derived suppressor cell (MDSC) recruitment [49]. These tumor-suppressive functions of PDCD4 in gliomas, including their underlying mechanisms and key regulatory molecules, are systematically summarized in Table 2. Notably, the TME remodeling process is further orchestrated by the crosstalk between ion channel-mediated stress responses and inflammation-related lncRNA networks. For instance, the ion channel TRPM2 is significantly upregulated in high-grade gliomas, where it mediates oxidative stress-induced Ca^{2+} influx and promotes tumor cell proliferation, invasion, and immune evasion by regulating inflammatory signaling cascades [59]. Concurrently, inflammation-related lncRNAs such as LINC00346 are involved in modulating TME immune cell infiltration (e.g., recruitment of myeloid-derived suppressor cells) and reinforcing pro-tumor inflammatory loops [60]. Together, these findings highlight that ion channel-driven stress responses and lncRNA-mediated inflammatory regulation jointly shape glioma progression and immune microenvironment remodeling, providing novel non-classical therapeutic targets beyond traditional oncogenic pathways [59, 60].

Translational Feasibility and Model/Subtype Considerations

Harnessing PDCD4's tumor-suppressive functions for glioma therapy requires addressing subtype heterogeneity, developing targeted delivery systems, and integrating

Table 2 Tumor-suppressive roles of PDCD4 in gliomas

Biological function	Key mechanism	Critical molecules/pathways	Level of evidence	Refs
Inhibition of proliferation & induction of apoptosis	Arrests G0/G1 cycle; upregulates pro-apoptotic proteins; blocks NF-κB nuclear translocation	Cyclin D1, BAX, Caspase-3, Bcl-xL; NF-κB p65	Strong (in vitro + in vivo validation)	[24, 42, 51]
Suppression of invasion & angiogenesis	Inhibits NF-κB-mediated invasion/angiogenesis-related factor expression	MMP-9, VEGF; NF-κB p65	Moderate (in vitro + clinical sample correlation)	[24]
Negative regulation of autophagy-lysosomal function	Inhibits ATG5 translation (autophagosome formation); suppresses TFEB-mediated lysosomal biogenesis	eIF4A, ATG5, TFEB; ATG12-ATG5 complex	Moderate (in vitro validation + partial in vivo evidence)	[57, 58]
Enhancement of chemo/radio-sensitivity	Relieves Bcl-xL translation repression (chemo); blocks miR-*96*-mediated DNA repair (radio)	Bcl-xL, miR-*96*, miR-*503*	Strong (multiple preclinical models + mechanism validation)	[31, 42, 56]

PDCD4-related biomarkers into clinical decision-making, with recent advances accelerating translational progress.

Three promising therapeutic strategies have emerged to restore PDCD4 function or target its regulatory hubs. miRNA-targeted therapy, such as miR-*21* antisense oligonucleotides (ASOs) delivered via T7-peptide-decorated exosomes…, effectively downregulates miR-*21* and restores PDCD4 expression in preclinical models [61]; similarly, miR-*96/503* inhibitors enhance radio- and chemosensitivity by upregulating PDCD4 [31, 42]. Epigenetic restoration using DNMT inhibitors (e.g., decitabine) reverses PDCD4 promoter methylation and inhibits glioma proliferation [29], with combination with temozolomide synergizing to enhance efficacy, particularly in methylation-high, IDH-wildtype gliomas [16]. TME-targeted interventions, including PI3K/Akt pathway inhibitors (e.g., copanlisib) and HOTAIR-targeting agents, block PDCD4 degradation and modulate TME immune function [30, 49], while macrophage-specific PDCD4 activation (via TFEB agonists) enhances anti-tumor immunity [58].

Translational success also requires accounting for glioma subtype heterogeneity and model limitations. PDCD4 downregulation is more pronounced in IDH-wildtype, EGFR-amplified, and mesenchymal-subtype gliomas [49], which exhibit higher miR-*21*/HOTAIR expression and PI3K/Akt activation, necessitating subtype-stratified therapeutic strategies. Most preclinical studies use U251/U87 cell lines, which fail to recapitulate subtype-specific biology; patient-derived organoids (PDOs) and immunocompetent mouse models (e.g., GL261) are better suited to validate PDCD4-targeted therapies. Biomarker integration, including PDCD4 methylation status, miR-*21/96/503* levels, and TFEB expression, can be combined with computational pathology features (e.g., histomorphometric analysis) to develop composite biomarkers for patient stratification [62]; notably, Jiang et al. [62] demonstrated that computational pathology approaches can reliably link histological morphology to molecular signatures (e.g., IDH mutation) in gliomas, providing a feasible framework for integrating PDCD4-related biomarkers with morphological features.

Key barriers to clinical translation include blood-brain barrier penetration, off-target effects, and adaptive resistance. Novel delivery systems (e.g., RVG peptide-conjugated siRNAs, extracellular vesicles) are being developed to enhance brain-targeted delivery of PDCD4 activators [61], while combining PDCD4-targeted therapies with immune checkpoint inhibitors (e.g., anti-PD-1) may overcome adaptive resistance by reversing TME immune suppression [49].

Current Limitations and Future Directions

Despite significant progress, several gaps remain in our understanding of PDCD4's role in gliomas. The overlapping

effects of epigenetic silencing, miRNA repression, and PI3K/Akt degradation (e.g., whether methylation enhances miRNA binding) are not fully elucidated [30, 54], and PDCD4's role in astrocytes, oligodendrocyte precursor cells, and other TME components requires further investigation using cell-type-specific knockout models [49]. Large-scale, multicenter studies are needed to confirm PDCD4's prognostic and predictive value across glioma subtypes, particularly in combination with other molecular markers (e.g., IDH, EGFR) [16].

Future research should prioritize integrating multi-omics data (transcriptomics, methylomics, proteomics) with spatial transcriptomics and computational pathology to map PDCD4's regulatory network in human gliomas [62]. Computational pathology has been validated to effectively bridge morphological and molecular characteristics of gliomas [62], which may provide a novel approach to dissect PDCD4's context-specific regulatory mechanisms in human tissues.

Neural Injury: PDCD4-Mediated Pathological Mechanisms and Therapeutic Implications

Neural injury, encompassing ischemic, traumatic, and metabolic-induced damage, is characterized by a cascade of neuroinflammation, abnormal cell death, and impaired repair—processes where PDCD4 acts as a key pathogenic driver in preclinical models [63–65]. Its pathological upregulation across injury types exacerbates neuronal loss, amplifies inflammation, and hinders regeneration, while targeted modulation of PDCD4 or its regulatory networks confers neuroprotection. Below, we systematically summarize PDCD4's expression patterns, cell-type-specific functions, regulatory mechanisms, and translational potential, organized by injury subtype to enhance clarity.

IBI/Stroke

IBI and stroke are the most extensively studied neural injury contexts for PDCD4, with its expression dynamically linked to injury severity and repair outcomes. In mouse middle cerebral artery occlusion (MCAO) models, PDCD4 levels are elevated in the ipsilateral cortex, showing strong co-localization with Iba-1 (a microglial marker) and weak association with astrocytes—indicating preferential activation in microglia [66]. In rat MCAO/reperfusion (MCAO/R) models, PDCD4 upregulation correlates with increased pro-inflammatory cytokines (TNF-α, IL-1β) and apoptotic markers (cleaved-Caspase-3), while Kudiezi injection (a traditional Chinese medicine) alleviates brain damage by downregulating PDCD4 [67]. Clinically, peripheral blood PDCD4 mRNA levels in cerebral ischemia patients are significantly higher than in healthy controls and positively correlate with neurological deficit scores and poor prognosis, highlighting its potential as a diagnostic and prognostic biomarker [68].

PDCD4 exerts cell-specific pathogenic effects in IBI: neurons undergo apoptosis and ferroptosis due to PDCD4-mediated suppression of antioxidant defenses [68], and PDCD4 activation of the MAPK/NF-κB pathway further exacerbates injury [67]; SMAD1 directly binds the PDCD4 promoter to enhance PDCD4's transcription, further promoting neuronal death [68]. Microglia are activated by PDCD4 to release pro-inflammatory factors (IL-1β, IL-6) via a PDCD4-MAPK-NF-κB positive feedback loop, while transcription factor Klf4 binds the PDCD4 promoter to amplify this pro-inflammatory response [35, 66]. Macrophages indirectly modulate PDCD4 function through cytokine secretion: macrophage-derived factors upregulate lncRNA HOTAIR, which sponges miR-*148a* (a PDCD4 activator) to reinforce PDCD4 silencing in adjacent neurons—creating a paracrine regulatory loop [49].

The regulatory network of PDCD4 in IBI is centered on non-coding RNAs and transcription factors. miR-*21* downregulation relieves its inhibition on PDCD4, mediating neuronal apoptosis, while miR-*21* overexpression reduces ischemia-induced neuronal death [32, 37]. LncRNA MEG3 and circRNA circ_0007290 act as ceRNAs to sponge miR-21 and miR-*496*, respectively, indirectly upregulating PDCD4 and exacerbating ischemic damage [32, 43]. In diabetic intracerebral hemorrhage (a severe IBI subtype), miR-*183-5p* targets PDCD4, and bone marrow mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) deliver this miRNA to suppress PDCD4-mediated NLRP3 inflammasome activation and neuroinflammation [38].

Therapeutic strategies targeting PDCD4 in IBI show promise, as evidenced by the following approaches: engineered EVs loaded with miR-*128-3p* downregulate PDCD4 to improve post-stroke neurological recovery [66]; furthermore, acupuncture inhibits REST to upregulate miR-*21-3p*, thereby suppressing PDCD4 and achieving neuroprotective effects comparable to nimodipine [69]; additionally, DNMT inhibitors reverse PDCD4 epigenetic silencing in ischemia-resistant brain regions, though this requires further validation [16]. Beyond PDCD4 targeting, mangiferin, a natural phytochemical, alleviates post-stroke cognitive impairment by modulating lipid metabolism (e.g., glycerophospholipid, sphingolipid, and linoleic acid metabolism) [70].

SCI

PDCD4 exhibits spatiotemporally specific expression in SCI, with its role shifting from pro-injury in early phases to repair-related in later stages. In contusive SCI rat models, PDCD4 expression peaks 3 days post-injury, and tetramethylpyrazine improves functional recovery by upregulating

miR-*21* to inhibit PDCD4 [36]. In complete transection SCI models, PDCD4 is rapidly upregulated after injury, and passive cycling exercise reduces its levels via miR-*21* induction, suppressing neuronal apoptosis [71]. Notably, PDCD4 expression is not altered in the acute phase of some SCI models but is markedly downregulated in the chronic phase, suggesting a context-dependent role in neural repair [72].

Cell-specific functions of PDCD4 in SCI are well-defined: neurons experience impaired axonal growth due to PDCD4-mediated suppression of growth-associated protein 43 (GAP-43) and β-III tubulin synthesis, neurons exhibit impaired axonal growth due to PDCD4-mediated suppression of GAP-43 and β-III tubulin synthesis, and the core mechanism of this process is that PDCD4 blocks the expression of neurite growth-related genes through translational inhibition [73]. Studies have confirmed that PDCD4 can directly bind to the mRNA coding regions or 5′UTR regions of key neurite growth genes, inhibiting their translation initiation or elongation, thereby regulating axonal regeneration at the post-transcriptional level [73]; while PDCD4 knockdown or miR-*21* overexpression can relieve this inhibition and restore neurite outgrowth [72, 73]. While PDCD4 knockdown or miR-*21* overexpression restores neurite outgrowth [72]. Microglia activated by SCI secrete IL-6 and TNF-α, which upregulate PDCD4 in neurons via the PI3K/Akt pathway—creating a pro-inflammatory loop that exacerbates damage [74]. Macrophages infiltrating the injury site contribute to PDCD4 regulation by secreting TGF-β1, which activates the Smad2/3 pathway to upregulate miR-*503*, indirectly suppressing PDCD4 and mitigating apoptosis [31].

Regulatory mechanisms of PDCD4 in SCI are dominated by miRNA-mediated control. miR-*21* directly targets PDCD4 to promote axonal repair, and acupuncture enhances this axis to improve cognitive function [69, 72]. LncRNA MEG3 sponges miR-*21* to upregulate PDCD4, and its knockdown alleviates SCI-induced neuronal apoptosis [74]. Therapeutic interventions targeting these networks include MSC-EV delivery of miR-*21* mimics and intrathecal injection of PDCD4 siRNA, both of which reduce apoptosis and enhance functional recovery [71, 74].

Other Neural Injuries

PDCD4's pathogenic role extends to diverse neural injury subtypes, with consistent upregulation linked to damage severity and poor outcomes. For instance, in diabetic encephalopathy (a metabolic-induced neural injury), quercetin activates the Nrf2/HO-1 signaling pathway by binding to KEAP1, and upregulates ferroptosis-inhibitory proteins such as GPX4 and SLC7A11, reduces lipid peroxidation and iron deposition in the hippocampus, thereby inhibiting neuronal ferroptosis and ameliorating cognitive impairment [75]. In chronic sciatic nerve injury rats, PDCD4 expression progressively increases in the spinal cord, aligning with the development of neuropathic pain; lncRNA DGCR5 overexpression reduces PDCD4 levels and pro-inflammatory factor (TNF-α, IL-6) release, alleviating hyperalgesia [76]. In retinal ischemia–reperfusion injury models, PDCD4 is upregulated in retinal ganglion cells; TNF-α-stimulated gingival MSC-derived exosomes inhibit PDCD4 via the MEG3/miR-*21a-5p* axis [77], while LncRNA H19 promotes PDCD4 expression by sponging miR-*21* to induce microglial pyroptosis and neuronal apoptosis [78]. In bupivacaine-induced dorsal root ganglion (DRG) injury, PDCD4 expression increases in a dose-dependent manner; transfection of miR-*101-3p* mimics inhibits PDCD4 to mitigate neurotoxicity, while knockdown of lncRNA MALAT1 (a protective ceRNA) enhances neurotoxicity despite inhibiting PDCD4 via miR-*101-3p* upregulation [79]. Beyond anesthetic-induced injury, ethanol-mediated neurotoxicity in fetal alcohol syndrome (FAS) involves time- and dose-dependent PDCD4 upregulation, and the PDCD4 protein binds eIF4A to block cap-dependent translation, causing neurodevelopmental defects; PDCD4 knockdown reverses this, making it a potential FAS target [80]. Collectively, PDCD4 acts as a conserved pathogenic mediator in diverse non-specific neural injuries, with targeted inhibition showing consistent neuroprotective potential.

Cell-specific effects in these injuries are conserved: neurons undergo apoptosis or ferroptosis due to PDCD4-mediated suppression of anti-apoptotic proteins (Bcl-2) and antioxidant pathways [79]; microglia are activated by PDCD4 to release pro-inflammatory cytokines, amplifying pain and tissue damage [76]; macrophages in the peripheral nerve microenvironment secrete EVs containing PDCD4-targeting miRNAs, providing a paracrine protective mechanism [77].

Regulatory networks in these injuries mirror those in IBI and SCI, with miR-*21*, lncRNA MEG3, and circRNAs as key modulators. Therapeutic strategies include natural products (e.g., ursolic acid) that target the miR-*141-3p*/PDCD4/PI3K/Akt axis [44] and gene therapy approaches (e.g., AAV (adeno-associated virus)-shPDCD4) that reduce neuropathic pain [81].

Translational Feasibility and Model Considerations

These pathological roles of PDCD4 in diverse neural injuries, along with their core mechanisms and therapeutic interventions, are systematically summarized in Table 3.

Translating PDCD4-targeted therapies for neural injury requires addressing subtype heterogeneity and delivery challenges. Promising strategies include the following: (i) BBB-penetrating EVs loaded with PDCD4 siRNA or miR-*21* mimics, which have shown efficacy in preclinical IBI models [38, 66]; (ii) natural products and traditional medicines (e.g., Kudiezi injection, tetramethylpyrazine) that

modulate PDCD4 with favorable safety profiles [36, 67]; and (iii) non-pharmacological interventions (acupuncture, passive exercise) that regulate the miR-*21*-PDCD4 axis, offering low-risk adjunct therapies [69, 71].

Model limitations must be addressed to advance translation: most preclinical studies use young, healthy animal models, while clinical neural injury often affects aged individuals with comorbidities (e.g., diabetes, hypertension) [38, 68]. Patient-derived organoids (PDOs) of the central nervous system, which recapitulate human tissue complexity, are emerging as valuable tools to validate PDCD4-targeted therapies [62]. Additionally, subtype-specific regulation (e.g., PDCD4's stronger upregulation in diabetic IBI vs. non-diabetic IBI) necessitates stratified therapeutic approaches [16].

Current gaps in knowledge include the stage-specific molecular mechanisms of PDCD4 in SCI, its role in astrocytes and oligodendrocytes, and the synergistic effects of PDCD4 with other injury-related pathways (e.g., Nrf2, P53) [68, 74]. Future research should employ cell-type-specific knockout models and multi-omics technologies to decipher these mechanisms, while large-scale clinical studies are needed to validate PDCD4 as a prognostic biomarker and therapeutic target across neural injury subtypes.

In summary, PDCD4 is a conserved pathogenic driver in neural injury, with cell-type-specific functions (neuronal death, microglial activation, macrophage-mediated paracrine regulation) and subtype-specific regulatory networks. Targeting PDCD4 or its upstream modulators (miRNAs, lncRNAs) holds significant translational potential, and addressing model limitations and subtype heterogeneity will accelerate the development of effective neuroprotective therapies.

Neurodegenerative Diseases

Neurodegenerative diseases are a group of chronic progressive disorders characterized by progressive neuronal loss, functional degeneration, and abnormal protein deposition in the central nervous system [82, 83]. With an irreversible course and no effective cure, they severely threaten the health of the elderly and impose a heavy social and family burden. Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are the three most common clinical subtypes. AD is primarily marked by β-amyloid (Aβ) senile plaques, tau neurofibrillary tangles, and progressive cognitive decline [84]; PD is characterized by selective loss of substantia nigra dopaminergic neurons and α-synuclein (α-syn) aggregation, mainly affecting motor function [85]; ALS involves progressive motor neuron death leading to muscle atrophy and limb weakness, with a poor prognosis [86]. Recent studies have demonstrated that PDCD4 is deeply involved in the pathological processes of these three diseases, though the evidence strength and mechanistic clarity vary across conditions.

AD

PDCD4 expression is abnormally elevated in AD models, closely correlating with pathological damage and neuronal apoptosis. In $A\beta_{1-42}$-treated SH-SY5Y cells (an in vitro AD model), PDCD4 protein and mRNA levels are significantly increased, showing a positive correlation with apoptosis severity [87]. Similarly, $A\beta_{25-35}$-induced SH-SY5Y and IMR-32 neurons exhibit PDCD4 overexpression, which is negatively correlated with miR-*212* expression, suggesting miRNA-mediated regulation of PDCD4 in AD [39].

Clinical investigations into PDCD4 as a peripheral AD biomarker have yielded context-dependent findings, underscored by the importance of standardized reporting of sample compartments and detection methods: plasma/serum studies show PDCD4 protein levels (detected by ELISA) are elevated in AD patients compared to healthy controls [39], suggesting that PDCD4 may be released from damaged neurons or activated immune cells into the circulation, serving as a potential biomarker of ongoing neurodegeneration, while PBMC studies demonstrate reduced PDCD4 mRNA (detected by qPCR) and protein (detected by flow cytometry) levels in the PBMCs of AD patients [45], reflecting intracellular transcriptional/post-transcriptional silencing in specific immune subsets (e.g., monocytes).

This discrepancy reflects distinct biological and technical underpinnings: (1) cellular vs. circulating pools: PBMC expression reflects immune cell-intrinsic regulation, while plasma levels represent extracellular leakage from stressed tissues; (2) disease stage and immune phenotype: PBMC downregulation may associate with early immune dysfunction, whereas plasma elevation correlates with progressive neurodegeneration; (3) technical standardization: differences in assay targets (mRNA vs. protein) and PBMC subpopulation purity further contribute to variability [39, 45]. Resolving these discrepancies requires future studies that standardize sample types (e.g., isolated $CD14^+$ monocytes, plasma exosomes), employ single-cell RNA-seq of PBMC subpopulations, and correlate peripheral PDCD4 measures with CNS pathology across defined AD stages [45].

PDCD4's dysregulation in AD is primarily mediated by miRNA targeting. Transfection of miR-*21* mimetics downregulates PDCD4 expression in an Aβ-dependent manner, suggesting Aβ may modulate PDCD4 by regulating miR-*21* [87]. Dual luciferase reporter assays confirm that miR-*212* directly binds the PDCD4 3′ UTR, and its mimetics reduce PDCD4 protein levels to alleviate Aβ-induced neurotoxicity [39]. Additionally, miR-*150-5p* inhibits PDCD4 transcription by binding its 3′ UTR, and its levels in AD patients'

Table 3 The role and molecular mechanisms of PDCD4 in neural injury

Neural injury	Model/subject	Role of pdcd4	Key mechanism	Key regulators/interventions	Level of evidence	Refs
IBI/stroke	MCAO mice; oxygen–glucose deprivation (OGD)/R-treated neurons	Exacerbates neuroinflammation	Activates MAPK/NF-κB pathway	PDCD4 siRNA; MAPK pathway inhibitor	Moderate (in vitro + in vivo validation)	[66]
	MCAO/R rats; OGD/R-treated astrocytes	Aggravates cerebral injury	SMAD1 enhances astrocyte activation via PDCD4	SMAD1 silencing; PDCD4 shRNA	Moderate (in vitro + in vivo validation)	[67]
	Clinical cerebral ischemia patients (blood); OGD cells	promotes neuronal ferroptosis	Regulates ferroptosis-related protein expression	Ferroptosis inhibitor (Fer-1); PDCD4 siRNA	Strong (in vitro + clinical correlation)	[68]
	MCAO mice; OGD-treated N2a cells	Exacerbates neuronal injury and cognitive impairment	ceRNA axis upregulates PDCD4 expression	miR-*21* mimics; MEG3 siRNA	Moderate (in vitro + in vivo validation)	[32]
	MCAO rats; clinical samples	Alleviates IBI via downregulating PDCD4	Acupuncture inhibits PDCD4 by regulating the REST/miR-*21-3p* axis	Acupuncture intervention; miR-*21-3p* mimics	Strong (in vivo + clinical validation)	[69]
	MCAO/R rats; OGD/R-treated neurons	Exacerbates neuronal apoptosis and neuroinflammation	ceRNA axis upregulates PDCD4	MSC-EVs (miR-*183-5p*); circ_0007290 siRNA	Moderate (in vitro + in vivo validation)	[38]
SCI	Contusive SCI rats; LPS-treated microglia	Promotes microglial inflammation and neuronal apoptosis	Activates PI3K/Akt pathway via microglial IL-6 secretion	PDCD4 siRNA; PI3K pathway inhibitor	Moderate (in vitro + in vivo validation)	[36]
	Complete transection SCI rats	Inhibits axonal repair and functional recovery	Suppresses GAP-43/β-III tubulin synthesis	miR-*21* mimics; PDCD4 silencing	Moderate (in vivo validation + mechanism)	[71]
	Contusive SCI rats; primary neurons	Aggravates SCI-induced neuroinflammation and pain	Regulates NF-κB-mediated pro-inflammatory cytokine release	Tetramethylpyrazine; PDCD4 shRNA	Moderate (in vitro + in vivo validation)	[72]
	SCI rats; OGD-treated astrocytes	Exacerbates astrocyte activation and scar formation	miR-*21* targets PDCD4 to inhibit astrocyte proliferation	miR-*21* agomir; PDCD4 silencing	Moderate (in vitro + in vivo validation)	[74]
TBI	TBI mice; primary cortical neurons	Promotes neuronal apoptosis and neuroinflammation	Regulate the PDCD4/PI3K/Akt signaling pathway to inhibit apoptosis	Ursolic acid; miR-*141-3p* upregulation	Moderate (in vivo validation + mechanism)	[44]
Metabolic/other injuries	Diabetic intracerebral hemorrhage rats	Aggravates neuroinflammation and brain edema	Activates NLRP3 inflammasome to promote pro-inflammatory factor release	AAV-shPDCD4; NLRP3 inhibitor (MCC950)	Moderate (in vivo + mechanism validation)	[76]
	Chronic sciatic nerve injury rats	Mediates neuropathic pain and neuronal hypersensitivity	Inhibits autophagy + activates MAPK pathway to enhance pain	lncRNA DGCR5; autophagy activator	Moderate (in vivo + mechanism validation)	[38]
Organ-specific neural injury	Retinal ischemia–reperfusion mice	Exacerbates retinal neuronal death	lncRNA H19/MEG3 ceRNA axis upregulates PDCD4	lncRNA H19 siRNA; miR-*101-3p* mimics	Preliminary (single in vivo model)	[77]
	Retinal ischemia–reperfusion rats	Aggravates neuroinflammation	Induces microglial pyroptosis	PDCD4 siRNA; pyroptosis inhibitor	Preliminary (single in vivo model)	[78]
	Bupivacaine-induced DRG injury	Mediates DRG neuronal apoptosis	Promotes Caspase-3/Bax expression; inhibits Bcl-2	miR-*101-3p* mimics; PDCD4 silencing	Moderate (in vitro + single in vivo model)	[79]

peripheral blood are inversely correlated with PDCD4 expression, indicating potential as a regulatory target [45].

Pathologically, PDCD4 mediates neuronal damage by suppressing the PI3K/Akt/GSK-3β signaling pathway; overexpression of PDCD4 inhibits this pathway in neurons, while downregulation restores its neuroprotective function and reduces Aβ-induced damage [87]. Notably, ferroptosis is a key pathogenic driver of AD-related cognitive impairment, characterized by iron overload-induced Fenton reaction, glutathione depletion, GPX4 dysfunction, and excessive lipid peroxidation—these processes form a vicious cycle with Aβ aggregation and tau hyperphosphorylation to exacerbate neuronal loss [88]. Therapeutic strategies targeting ferroptosis (e.g., iron chelators, GPX4 activators, and lipid peroxidation inhibitors) have shown promise in alleviating AD-related cognitive deficits [88]. As a candidate gene for late-onset AD, PDCD4 is localized to the AD-susceptible chromosomal region 10q24 and has been experimentally validated to directly interact with core AD seed genes PSEN2 and APOE at the protein level (via co-immunoprecipitation assays [89]). This physical interaction between PDCD4 and the core AD-associated proteins PSEN2 and APOE is hypothesized to participate in the regulation of Aβ neurotoxicity—consistent with PDCD4's upregulation in AD patient brain tissues and its membership in the "translation elongation" functional module (involved in protein translation inhibition [89]). While the specific functional consequences of the PDCD4-PSEN2/APOE interaction (e.g., on Aβ production or clearance) have been proposed but not fully elucidated, the direct physical binding between these molecules has been confirmed by experimental evidence, providing a molecular link between PDCD4 and AD core pathological pathways. Notably, the 10q24 region where PDCD4 is located is a well-recognized susceptibility locus for late-onset AD (MIM:605,526), further supporting PDCD4's potential involvement in AD pathogenesis [89].

PD

In Parkinson's disease (PD), a neurodegenerative disorder characterized by dopaminergic neuronal loss in the substantia nigra, PDCD4 expression is significantly upregulated in both MPTP-induced mouse models and MPP + -treated dopaminergic cell models (e.g., SK-N-SH, MN9D cells) [90, 91]. MPP + -induced dopaminergic neuronal injury is aggravated by PDCD4 upregulation: PDCD4 blocks autophagy (via regulating LC3, Beclin1, and p62, potentially targeting ATG5-related pathways) to promote cell apoptosis, inflammation, and oxidative stress; PDCD4 knockdown alleviates injuries, while 3-MA reverses the effects [90]. Beyond autophagy regulation, PDCD4 also exacerbates PD-related neuronal damage by inhibiting the PI3K/Akt/mTOR signaling pathway, which is essential for mitochondrial homeostasis and cell survival—knockdown of PDCD4 activates this pathway to ameliorate mitochondrial injury and suppress apoptosis, an effect abrogated by the PI3K inhibitor LY294002 [91]. In AAV9-mediated α-syn overexpression PD mice, striatal PDCD4 levels are positively correlated with α-syn aggregation, implying involvement in α-syn-related pathological processes [92]. Collectively, these findings indicate that PDCD4 contributes to PD pathogenesis through multiple complementary mechanisms, highlighting its potential as a therapeutic target for PD.

MiRNA-mediated targeting is a key regulatory mechanism for PDCD4 in PD. PDCD4 silencing activates the PI3K/Akt/mTOR pathway, reversing apoptosis and mitochondrial damage to protect dopaminergic neurons [91], highlighting the pathway's role in PDCD4-mediated PD pathology. PDCD4's pathogenic mechanisms in PD are multifaceted, with experimentally validated components and reasonably inferred causal links: directly validated mechanisms: PDCD4 blocks autophagy in dopaminergic neurons by downregulating ATG5 expression (inhibiting autophagosome formation) [90]; PDCD4 binds the 5′ UTR of TFE3/TFEB mRNA via its MA3 domains, suppressing their translation (without affecting their transcription or protein stability) and reducing downstream lysosomal enzyme CTSD production (impairing lysosomal degradation capacity) [92].

Beyond autophagy and PI3K/Akt/mTOR pathways, PDCD4's pathogenic role in PD is further consolidated by its regulation of lysosomal biogenesis via TFE3/TFEB. PDCD4-mediated TFE3/TFEB translation suppression and subsequent lysosome dysfunction directly reduce the clearance of abnormally folded α-syn, promoting its aggregation—this causal link is validated by rescue experiments showing that TFE3/TFEB silencing abrogates the α-syn clearance effect of PDCD4 knockout [92]. Notably, a blood-brain barrier-penetrating RVG polypeptide-modified siRNA targeting PDCD4 (RVG-siPdcd4) has been developed, which efficiently downregulates brain PDCD4 expression via intraperitoneal injection, restores TFE3/TFEB-CTSD signaling, reduces α-syn aggregation, and improves motor deficits without obvious systemic side effects [92].

ALS: Preliminary Cell Model Evidence

Current understanding of PDCD4's role in ALS is supported by in vitro, in vivo, and clinical evidence. miR-*183-5p*, a neuron-enriched and stress-inducible miRNA, is dynamically regulated in ALS: it is elevated in pre-symptomatic/early-symptomatic SOD1-G93A transgenic mice (stress compensation) and reduced in late stages (neuronal degeneration), while it is significantly downregulated in ALS patients' peripheral blood [40]. In NSC-34 motor neuron-like cells and primary neurons, reduced miR-*183-5p* expression is associated with elevated PDCD4 and RIPK3 protein levels, which align with changes in apoptosis

Table 4 The role and molecular MECHANISM of PDCD4 in neurodegenerative diseases

Disease	Model/subject	Role of PDCD4	Key mechanism	Key regulators/interventions	Level of evidence	Refs
AD	Aβ-treated SH-SY5Y cells; AD patients (plasma)	Enhances Aβ neurotoxicity	Suppresses PI3K/Akt/GSK-3β pathway	miR-*21* mimics	Strong (in vitro + clinical correlation)	[87]
	Aβ-treated IMR-32 cells; AD patients (PBMCs)	Promotes neuronal apoptosis	Regulates apoptotic signaling	miR-*212* mimics; PBMCs PDCD4 detection	Moderate (in vitro + clinical correlation)	[39]
	Aβ-treated SH-SY5Y cells	Exacerbates Aβ-induced neuronal injury	Interacts with PSEN2; enhances Aβ generation	PSEN2 silencing; PDCD4 siRNA	Moderate (in vitro + mechanism validation)	[45]
	AD patients ($CD14^+$ monocytes); in vitro validation	Potential peripheral diagnostic biomarker	Regulates inflammatory response	Standardized $CD14^+$ monocyte detection	Strong (in vitro + clinical validation)	[89]
PD	MPP^+-treated SK-N-SH cells	Exacerbates dopaminergic neuronal loss	Inhibits PI3K/Akt/mTOR signaling pathway	PDCD4 siRNA; PI3K/Akt pathway activator	Moderate (in vitro + mechanism validation)	[90]
	MPTP-induced PD mice; MPP^+-treated MN9D cells	Promotes α-syn aggregation	Blocks autophagy	PDCD4 shRNA; autophagy activator	Strong (in vitro + in vivo + mechanism validation)	[91]
	α-syn overexpression mice	Impairs mitochondrial homeostasis	Suppresses TFE3/TFEB translation	RVG-siPdcd4; TFEB activator	Strong (in vitro + in vivo + mechanism validation)	[92]
ALS	NSC-34/primary neurons; SOD1-G93A mice; ALS patients (peripheral blood)	Collaborative promotion of motor neuron apoptosis with RIPK3	miR-*183-5p* co-targets PDCD4/RIPK3	miR-*183-5p* mimics	Moderate (in vitro + in vivo + clinical marker correlation)	[40]

(cleaved Caspase-3) and necroptosis (p-MLKL) markers [40]. Database predictions and dual luciferase reporter assays confirm that miR-*183-5p* specifically binds the wild-type 3′ UTR of both PDCD4 and RIPK3; overexpression of miR-*183-5p* reduces PDCD4/RIPK3 levels, alleviates stress-induced (TNF-α/H_2O_2/tunicamycin) motor neuron death via synergistically inhibiting apoptosis and necroptosis, providing a potential therapeutic direction [40].

Pathologically, PDCD4 mediates motor neuronal apoptosis in ALS, while RIPK3 drives necroptosis—two key cell death pathways in ALS pathogenesis. miR-*183-5p* coordinates these pathways by co-targeting PDCD4 and RIPK3, highlighting its role as a nodal regulator of motor neuron survival under stress [40]. Notably, miR-*183-5p* is rapidly induced by multiple stressors (oxidative, ER, inflammatory stress) in neurons, functioning as an immediate stress-response mediator that couples stress sensing to cell death suppression [40]. This stress-inducible property enables it to compensate for ALS-related cellular stress in early disease stages.

Translational Feasibility and Model Considerations

These pathological roles of PDCD4 in AD, PD, and ALS—along with their core molecular mechanisms, regulatory factors, and therapeutic interventions—are systematically summarized in Table 4.

Harnessing PDCD4-targeted strategies for neurodegenerative diseases requires addressing disease-specific heterogeneity, evidence gaps, and model limitations. Promising interventions include miRNA mimics (e.g., miR-*21*, miR-*212*, miR-*183-5p*) to downregulate PDCD4, and targeted delivery systems (e.g., RVG peptide-conjugated siRNA) to enhance brain penetration [91, 93]. For AD, integrating PDCD4-related biomarkers (plasma/serum protein, PBMC mRNA) with multi-omics data may enable stratified diagnosis, but the standardization of sample types and detection methods is critical [39, 45]. In PD, optimizing PDCD4 silencing to restore autophagy/lysosome function shows preclinical potential, but validating the direct causal link between PDCD4 and α-syn aggregation in vivo is essential [92].

Model limitations must be addressed to advance translation: most studies rely on cellular or partial animal models, lacking validation in aged or comorbid models that better recapitulate clinical realities [89, 91]. ALS research remains confined to cellular models, with no in vivo or clinical validation. Future multicenter clinical cohort studies should elucidate PDCD4 expression patterns in key brain regions and peripheral samples across disease stages, establishing correlations with progression. Proteomic technologies can dissect PDCD4's interaction network with core pathological molecules (Aβ, α-syn), while large-animal model validation of

targeted delivery systems will promote clinical translation. Current gaps include the following: (1) unclear brain region-specific PDCD4 dynamics and PDCD4-PSEN2/APOE interaction details in AD; (2) undefined direct mechanisms linking PDCD4-mediated autophagy/lysosome dysfunction to α-syn aggregation in PD; (3) lack of in vivo and clinical validation of PDCD4's role in ALS [40, 89, 91]. Addressing these will clarify PDCD4's utility as a diagnostic biomarker and therapeutic target for neurodegenerative diseases.

Inflammation-Related Neurofunctional Disorders

Inflammation-related neurofunctional disorders encompass two major categories: neuroinflammation and neuropathic pain [94]. Both are characterized by dysregulated inflammatory signaling pathways as their core pathological mechanism, severely impacting patients' quality of life. Neuroinflammation is marked by microglial activation and excessive release of inflammatory mediators, leading to neuronal damage and neurological dysfunction; neuropathic pain arises from inflammation-induced peripheral or central sensitization, featuring a long course and high treatment difficulty [35, 81]. Recent studies have demonstrated that PDCD4 is deeply involved in the pathological processes of these diseases, with distinct cell-type-specific functions and context-dependent causal roles.

Neuroinflammation

In neuroinflammation, PDCD4 exerts cell-type-specific roles: microglia act as core pro-inflammatory cells, while neurons are targets of inflammatory damage, and it functions as an upstream pathogenic factor [35]. PDCD4 is specifically upregulated in activated microglia (BV2 cell line) and damaged neurons (HT22 cell line) (not astrocytes) in LPS-induced neuroinflammation models, with its expression peaking at day 1 [35]. Microglial PDCD4 drives inflammation via a PDCD4-MAPK (p38/ERK/JNK)-NF-κB positive feedback loop: it activates the phosphorylation of p38, ERK, and JNK, promotes the phosphorylation and nuclear translocation of NF-κB p65, thereby enhancing the release of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, iNOS) and reactive oxygen species (ROS); silencing PDCD4 significantly inhibits these inflammatory responses, whereas neuronal PDCD4 silencing does not affect microglial activation [35]. Neuronal PDCD4 induces apoptosis via the intrinsic pathway (upregulating BAX and Cleaved-PARP), and its upregulation is dependent on TNF-α secreted by activated microglia [35]. PDCD4's upstream role in neuroinflammation is supported by temporal and functional evidence: LPS induces microglial PDCD4 upregulation at 12 h (preceding inflammatory factor peaks at 24 h), and its silencing blocks inflammatory pathway activation [35]. A positive feedback loop exists between PDCD4 and MAPK/NF-κB pathways, though PDCD4's initial activation is TLR4-dependent and independent of these pathways [35]. PDCD4 is regulated differently by anti-inflammatory interventions: Oxycodone (a semi-synthetic opioid analgesic) alleviates LPS-induced neuroinflammation in human HMC3 microglia via the CREB (cAMP response element binding protein)/miR-*181c*/PDCD4 axis [95]. Mechanistically, oxycodone promotes CREB phosphorylation, and activated CREB directly binds to the MIR181C promoter to transcriptionally upregulate miR-*181c*; miR-*181c* then specifically binds the 3′ UTR of PDCD4 to inhibit its expression [95]. This axis ultimately reduces the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-8) and downregulates iNOS expression, with oxycodone showing no cytotoxicity at concentrations of 2.5–20 μg/mL [95]. In contrast, molecular hydrogen exerts anti-inflammatory effects in LPS-activated retinal microglia by upregulating PDCD4 via inhibiting miR-*21*, a context-dependent anti-inflammatory role of PDCD4 specific to retinal microglia that differs from its pro-inflammatory function in central nervous system microglia [96]. Mechanistically, hydrogen-saturated medium (1.0×10^{-6} concentration, non-cytotoxic) modulates a set of inflammation-related miRNAs: it downregulates miR-*21* and miR-*9*, while upregulates miR-*199* [96]. Beyond regulating PDCD4 via miR-*21* suppression, this intervention also reduces the expression of Myd88 and IKK-β (key molecules in the TLR4-Myd88-NF-κB pathway) without affecting NF-κB p65 levels [96], reflecting PDCD4's context-dependent role in neuroinflammation.

Neuropathic Pain

Similar to its neuroinflammatory role, PDCD4 mediates neuropathic pain primarily via spinal dorsal horn neurons (core effectors), with microglia as auxiliary initiators [81]. In CCI models, PDCD4 expression in the spinal cord is significantly upregulated from day 7 post-surgery, persisting until day 21 (synchronized with pain behavior progression) [81]. PDCD4 is predominantly localized in spinal dorsal horn neurons, with minor colocalization in microglia and no association with astrocytes ($GFAP^+$) [81]. It promotes pain sensitization through two interconnected mechanisms: (1) inhibiting autophagy (downregulating Beclin1 and LC3B, upregulating autophagic substrate p62); (2) activating the MAPK pathway (enhancing phosphorylation of ERK, JNK, and p38) and promoting neuroinflammation (elevating IL-1β, IL-6, and TNF-α at both mRNA and protein levels, validated by qRT-PCR and ELISA) [81]. Neuron-specific silencing of PDCD4 via intrathecal injection of AAV-shPDCD4 alleviates mechanical allodynia and thermal hyperalgesia [81]. The causal link between PDCD4 and neuropathic pain is further confirmed by rescue experiments: the autophagy

Table 5 The role and molecular mechanism of PDCD4 in inflammation-related neurological dysfunction

Dysfunction type	Model/subject	Role of PDCD4	Key mechanism	Key regulators/interventions	Level of evidence	Refs
Neuroinflammation	LPS-induced neuroinflammatory mice	Promotes neuroinflammation and neuronal apoptosis	PDCD4-MAPK-NF-κB loop induce neuronal apoptosis	PDCD4-shRNA	Strong (in vitro + in vivo validation)	[35]
	LPS-stimulated BV2 microglia	Regulates microglial activation and pro-inflammatory factor release	PDCD4-MAPK-NF-κB loop amplifies inflammation	PDCD4-shRNA	Moderate (only in vitro validation)	[35]
	LPS-stimulated HMC3 human microglia	Promotes pro-inflammatory factor secretion	The p-CREB-miR-*181c* axis downregulates PDCD4 to reduce pro-inflammatory factors	Oxycodone	Moderate (only in vitro validation)	[95]
	LPS-activated retinal microglia	Upregulates PDCD4 to mediate anti-inflammatory effects	PDCD4 couples with Myd88/IKK-β downregulation	Hydrogen-saturated medium	Preliminary (single in vitro model)	[96]
Neuropathic pain	Chronic Constriction Injury (CCI) mice	Promotes pain maintenance and mediates pain sensitization	Inhibits autophagy; activates MAPK pathway	AAV-shPDCD4	Strong (in vivo validation + mechanism verification)	[81]

inhibitor 3-MA not only reverses the analgesic effect of PDCD4 inhibition but also abrogates its regulatory effects on autophagy (restoring Beclin1/LC3B/p62 levels) and neuroinflammation (reversing the reduction of pro-inflammatory cytokines) [81]. Microglia express low PDCD4 only in the early post-injury phase, inducing neuronal PDCD4 upregulation via IL-6 but not contributing to pain maintenance [81]. Further clarification of its cell-autonomous functions requires cell-type-specific conditional KO models.

Translational Considerations and Conditional KO Validation Strategies

To clarify PDCD4's cell-type-specific roles and causality, future studies should use cell-type-specific conditional KO models. For neuroinflammation, CX3CR1-Cre^{+}; PDCD4$^{flox/flox}$ mice (microglia-specific KO) in LPS models (assessing microglial activation, cytokines, and neuronal apoptosis) are recommended, with expected reduced inflammation. Nestin-Cre^{+}; PDCD4$^{flox/flox}$ mice (pan-neuronal KO) should target neuronal apoptosis, predicted to decrease without affecting inflammation.

For neuropathic pain, Pirt-Cre^{+}; PDCD4$^{flox/flox}$ mice (dorsal horn neuron-specific KO) in CCI models (assessing pain thresholds and neuronal excitability) are expected to improve pain behaviors. CX3CR1-Cre^{+}; PDCD4$^{flox/flox}$ mice in CCI models will likely show transient early-phase pain relief, confirming microglia's auxiliary role.

Translational strategies for PDCD4-targeted therapies include cell-type-specific inhibitors, clinical sample validation, and combination with anti-inflammatory drugs (e.g., NLRP3 inhibitors) for synergistic effects. Current limitations include unvalidated PDCD4 target switching, unclear autophagy inhibition mechanisms, and lack of clinical PDCD4-prognosis data. Addressing these will deepen understanding and accelerate translation of PDCD4-targeted therapies.8.4 Summary.

Summary

PDCD4 primarily exerts pro-inflammatory and pro-nociceptive effects in inflammation-related neurofunctional disorders, with strict cell-type specificity and clear upstream causal roles (Table 5)—findings that are further supported by the proposed cell-type-specific conditional KO validation strategies. In neuroinflammation, microglial PDCD4 drives inflammation via the PDCD4-MAPK-NF-κB positive feedback loop, while neuronal PDCD4 mediates cell-autonomous apoptosis. In neuropathic pain, spinal dorsal horn neurons are the core effector cells, with PDCD4 promoting pain sensitization via MAPK activation and autophagy inhibition. Collectively, conditional KO models will further validate these cell-type-specific functions and causal relationships, while addressing current limitations will advance translational research, laying the foundation for targeted therapy development.

Emotional Dysfunction

Emotional dysfunction, primarily represented by depression, is a kind of mental disorder caused by multiple factors such as stress, neuroinflammation, impaired synaptic plasticity, and imbalance of neurotrophic factors. It features complex pathological mechanisms and significant individual differences in clinical treatment. With the global incidence rate increasing year by year, it has become a major public health concern that requires urgent attention. Abnormal BDNF and excessive activation of microglia are recognized as key pathological processes in depression [97, 98]. As a multifunctional regulatory protein, PDCD4 has been demonstrated to be deeply involved in these pathological processes in recent years.

Expression and Functional Characteristics of PDCD4 in Emotional Dysfunction

PDCD4 exhibits abnormal upregulation and brain region-specific expression in stress-induced depression models, closely associated with depression susceptibility. In the "double stress" model (neonatal LPS injection + adolescent unavoidable foot shock), hippocampal PDCD4 expression is higher than in single-stress groups, accompanied by more severe depressive/anxiety-like behaviors and social impairments—suggesting PDCD4 regulates depression susceptibility triggered by stress superposition [99]. Chronic restraint stress (CRS) upregulates hippocampal PDCD4 by inhibiting mTORC1-mediated phosphorylation (Ser67) and ubiquitin-proteasomal degradation, thereby reducing BDNF IIc protein levels (without affecting BDNF mRNA) and inducing depressive-like behaviors, synaptic spine loss, and anxiety-like phenotypes [100]. Notably, PDCD4 expression is also elevated in the hippocampus of patients with major depressive disorder (MDD), as verified by the GEO database, a finding that confirms its clinical relevance [100]. Systemic administration of RVG-9dR peptide-modified PDCD4 siRNA (RVG/siPdcd4) via tail vein injection—an approach enabling blood–brain barrier penetration and selective targeting of neurons and microglia—effectively silences PDCD4, upregulates BDNF, and downregulates pro-inflammatory cytokines (IL-6, IL-1β) [93]. Both global/neuronal-specific PDCD4 knockout and RVG/siPdcd4 delivery can prevent or rescue CRS-induced deficits; additionally, the TAT-eIF4A6 peptide, which disrupts the PDCD4-eIF4A complex, specifically promotes BDNF IIc translation and exerts rapid antidepressant effects [100].

Molecular Mechanisms of PDCD4 Mediating Emotional Dysfunction

PDCD4 participates in the pathogenesis of depression through two core molecular pathways, integrating translational regulation and neuroinflammatory modulation.

One key mechanism is the translational inhibition of BDNF in hippocampal neurons. RNA immunoprecipitation demonstrates PDCD4 directly binds BDNF mRNA in hippocampal tissue, selectively inhibiting translation of the BDNF IIc splice variant via an eIF4A-dependent pathway. The 5′ UTR Loop2 structure of BDNF IIc serves as a critical binding site, ensuring precise regulation of BDNF function [100]. CRS inhibits mTORC1 activity, reducing PDCD4 phosphorylation and ubiquitin-dependent degradation—leading to PDCD4 accumulation and subsequent BDNF downregulation. This forms a regulatory cascade: "stress → mTORC1 inhibition → PDCD4 accumulation → BDNF downregulation → depressive-like behaviors" [100]. Validation studies confirm CRS reduces BDNF protein levels only in wild-type mice (not PDCD4 knockout mice), and TrkB receptor inhibitors abolish the antidepressant effect of PDCD4 knockout—confirming the PDCD4-BDNF-TrkB pathway as a core mechanism [100]. Furthermore, RVG/siPdcd4 directly targets microglia to silence PDCD4, suppressing the release of IL-6 and IL-1β, which synergizes with BDNF upregulation to alleviate depressive-like behaviors [93].

The second mechanism involves regulation of microglia-mediated neuroinflammation. In LPS-induced depression-like mice, PDCD4 mRNA and protein levels are significantly elevated in the PFC, with increased intracellular PDCD4 expression in microglia [101]. Microglia-specific PDCD4 conditional knockout (mcKO) mice were generated by crossing Pdcd4-flox mice with Cx3cr1-Cre^{ERT2} mice, and knockout was induced via tamoxifen administration at 56 days after birth [101]. Microglia-specific PDCD4 knockout markedly improves depression-like behaviors via a mechanism where PDCD4 competes with Daxx (via its SIM2 domain) for PPARγ binding—inhibiting PPARγ nuclear translocation and reducing anti-inflammatory factor IL-10 transcription. Mechanistically, the IL-10 promoter contains multiple PPARγ response elements (PPREs), and PDCD4-mediated inhibition of PPARγ nuclear translocation blocks its binding to PPREs, thereby suppressing IL-10 expression and exacerbating neuroinflammation [101]. Notably, PDCD4 specifically regulates IL-10 expression without affecting the mRNA levels of pro-inflammatory cytokines such as

TNF-α, IL-1β, and iNOS, highlighting its selective role in balancing anti-inflammatory responses [101]. Treatment with PPARγ inhibitors or IL-10 neutralizing antibodies completely abolishes the antidepressant effect of PDCD4 knockout—validating the central role of the PDCD4-PPARγ-IL-10 pathway in inflammatory depression [101].

Unresolved Challenges and Future Research Directions

Despite significant progress, several critical challenges remain in understanding PDCD4's role in emotional dysfunction. First, the upstream signaling pathway driving LPS-induced PDCD4 upregulation in microglia is not fully elucidated, hindering comprehensive mapping of inflammation-induced PDCD4 regulatory networks. Second, the mechanisms underlying region-specific PDCD4 regulation (PFC vs. hippocampus) are unclear, limiting the development of brain region-targeted interventions. Third, existing interventions lack validation in primate models, and their clinical translation potential requires further evaluation. For example, RVG/siPdcd4 achieves non-invasive brain targeting with a well-tolerated dosing regimen (50 μg per injection, once every 2 days for 4 times), providing a feasible translational strategy [93].

To address these unresolved challenges, targeted studies are warranted: For LPS-induced PDCD4 upregulation in microglia, potential upstream drivers include TLR4-MyD88-NF-κB and MAPK pathways (canonical LPS-responsive cascades [101]), which can be validated via pathway inhibitors (e.g., TLR4 antagonist TAK-242, NF-κB inhibitor PDTC) and microglia-specific conditional KO mice (CX3CR1-Cre^{+}; PDCD4$^{flox/flox}$). For region-specific PDCD4 regulation in PFC vs. hippocampus, single-cell RNA-seq and spatial transcriptomics can dissect cell-type composition differences (e.g., neuronal subtype distribution) and region-specific regulators (e.g., transcription factors or non-coding RNAs [100]); Camk2a-Cre^{+}; PDCD4$^{flox/flox}$ (neuron-specific KO) and GFAP-Cre^{+}; PDCD4$^{flox/flox}$ (astrocyte-specific KO) mice will further clarify cell-autonomous contributions to regional PDCD4 dynamics. These approaches align with the core mechanisms of PDCD4 regulation summarized earlier, while filling key knowledge gaps.

Summary

PDCD4 plays a pivotal pro-depressive role in emotional dysfunction, mediating pathological processes through two interconnected pathways: translational inhibition of BDNF in hippocampal neurons and regulation of microglia-mediated neuroinflammation via the PDCD4-PPARγ-IL-10 axis (Table 6). Both stress and inflammatory models confirm its causal role, and clinical evidence validates its relevance in human depression. Intervention strategies targeting PDCD4 (e.g., hippocampal PDCD4 knockdown, brain-targeted PDCD4 siRNA [93], PDCD4-eIF4A interaction-blocking peptides) effectively improve depressive behaviors by upregulating BDNF and inhibiting neuroinflammation. Resolving upstream regulatory gaps and region-specific mechanisms through conditional KO models and multi-omics approaches will deepen understanding of PDCD4's regulatory network, promoting its development as a potential target for depression treatment.

Concluding Remarks

PDCD4, an evolutionarily conserved multifunctional regulatory protein, exerts a context-dependent role in neurological disorders, which is mediated by cell-type- and disease-stage-specific molecular mechanisms. (Fig. 2). In neuro-oncological contexts like glioma (Fig. 2A), PDCD4 functions as a tumor suppressor. Its expression is frequently downregulated through epigenetic silencing (e.g., promoter methylation), non-coding RNA interference (e.g., miR-*21* and miR-*96*), and protein signaling pathway modulation (e.g., the FAT1–STAT1 axis). These downregulations impair its tumor-suppressive functions, including cell cycle arrest, tumor cell apoptosis induction, negative regulation of autophagy-lysosome functions, and reversal of chemoradiotherapy resistance, making its expression level one of the important indicators for evaluating patient prognosis. Conversely, in neuropathological conditions such as neural injury, neurodegeneration, and mood disorders (Fig. 2B), PDCD4 is pathologically upregulated. Here, it functions as a pathogenic driver by promoting pro-inflammatory and pro-death signaling cascades (e.g., MAPK/NF-κB, NLRP3) while inhibiting reparative processes such as BDNF expression and axonal growth, thereby exacerbating disease progression.

The precise mechanism underlying PDCD4's functional duality in neurological disorders—tumor suppressor in glioma versus pathogenic driver in neural injury and degeneration—remains the field's central paradox. Current research has successfully mapped numerous associations, identifying key regulatory nodes like miR-*21* and effector pathways such as PI3K/Akt and MAPK/NF-κB. However, significant limitations persist. The field often relies on correlative data from reductionist models, leaving the synergistic hierarchy of its multi-layered regulation (epigenetic, transcriptional, post-translational) unresolved. Crucially, its cell-type-specific functions are conflated in heterogeneous tissues, and its purported "activation" of pathways often lacks proof of direct mechanistic causality, failing to distinguish whether PDCD4 is a proximal driver or a feedback loop component.

To resolve this, we propose a testable "functional switch" framework where PDCD4's role is dictated by integrated

Table 6 The role and molecular mechanism of PDCD4 in emotional dysfunction

Disease	Model/subject	Role of PDCD4	Key mechanism	Key regulators/interventions	Level of evidence	Refs
Depression	"Dual-hit" stress mice	Regulates depression susceptibility	PDCD4-BDNF-Akt-CREB pathway	PDCD4 shRNA	Moderate (in vivo validation)	[99]
	CRS-induced depressive mice	Mediates stress-induced depression	mTORC1-PDCD4-BDNF IIc pathway	PDCD4-KO; PDCD4 siRNA	Strong (in vivo + mechanism validation)	[100]
	CRS-induced depressive mice	Key driver of depressive-like behaviors	CRS-mTORC1-PDCD4-BDNF-TrkB pathway	siPdcd4; PDCD4-KO	Strong (in vivo + mechanism validation)	[93]
	LPS-induced depressive-like behavior mice	Participate in microglia-mediated neuroinflammation	PDCD4-PPARγ-IL-10 axis	PDCD4-CKO; PPARγ inhibitor; IL-10 neutralizing antibody	Strong (in vivo + mechanism validation)	[101]
	MDD patients (postmortem hippocampus)	Validates pathological association between PDCD4 and depression	PDCD4-BDNF axis	PDCD4 siRNA	Strong (clinical sample + in vitro validation)	[93, 99, 100]

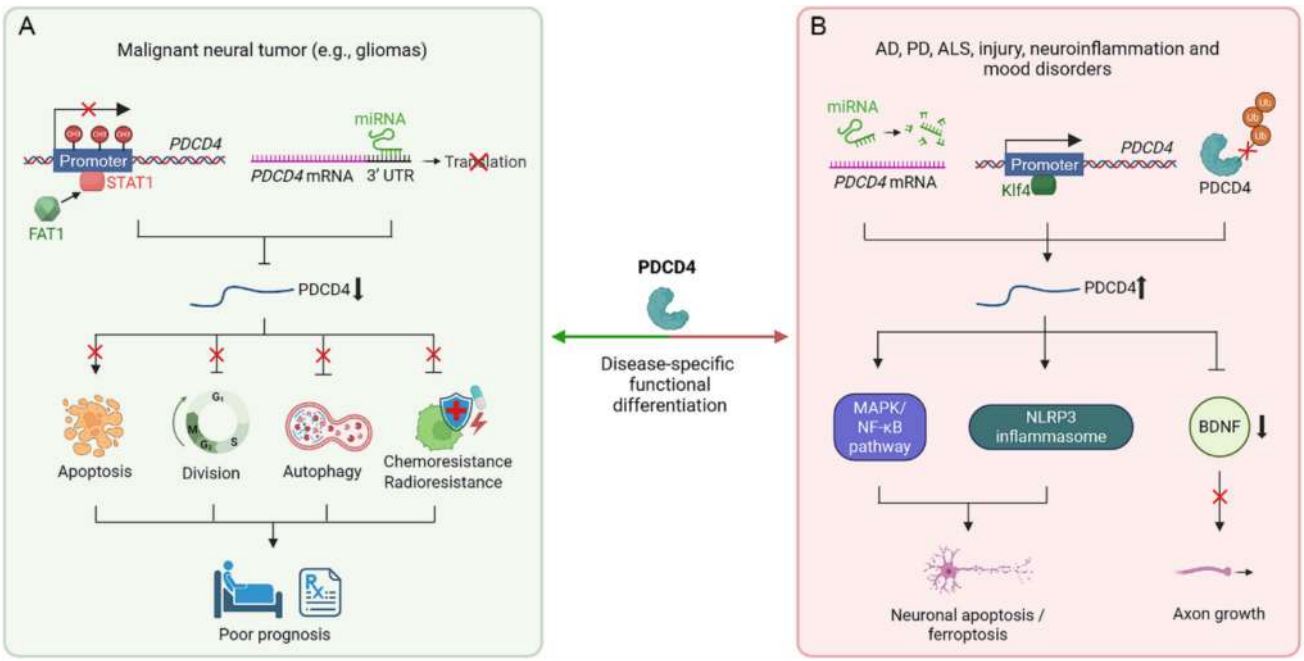

Fig. 2 Context-dependent dual roles of PDCD4 in neurological diseases. **A** In neuro malignant tumors represented by glioma, PDCD4 exerts a tumor-suppressive role, but its expression is often inhibited, resulting in the impairment of its core functions including promoting tumor cell apoptosis, inhibiting cell division, negatively regulating autophagy-lysosomal function, and enhancing chemo-radiotherapy sensitivity. **B** In diseases such as neural injury, neurodegenerative diseases, neuroinflammation, and emotional disorders, PDCD4 acts as a pathogenic factor by promoting the activation of the MAPK/NF-κB pathway, NLRP3 inflammasome in microglia, and inhibiting BDNF expression in neurons

contextual determinants: (1) The disease-specific signaling tone (pro-proliferative vs. inflammatory) dictates which mRNA pool (e.g., oncogenic vs. neuroprotective) is subject to repression; (2) Spatiotemporal dynamics, including expression thresholds and phosphorylation-regulated nucleocytoplasmic shuttling, control access to specific targets; (3) The condition-dependent interactome and PTM landscape (e.g., binding to eIF4A, Daxx, or PPARγ) fundamentally redirects its activity and stability.

Future research must transition from mapping associations to establishing causal mechanisms within this framework. A focused roadmap is essential: First, define the context-specific PDCD4 universe. Integrated multi-omics approaches—combining CLIP-seq, ribosome profiling, and spatial transcriptomics in disease models—are crucial. Equally important is the mining of existing and newly generated neurological patient NGS datasets. For example, reanalysis of public resources like The Cancer Genome Atlas (TCGA) for glioma or cohort data from neurodegenerative disease consortia (e.g., ADNI, PPMI) can reveal correlations between PDCD4 genetic/epigenetic variants, its expression quantitative trait loci (eQTLs), co-expression networks, and patient outcomes. This will dynamically map how the PDCD4 regulatory network operates in human disease contexts. Second, resolve causality and cellular crosstalk. Employing cell-type-specific genetic tools in immunocompetent, aged models, complemented by structural and biochemical studies, will delineate autonomous functions and distinguish direct modulation from indirect network effects. Finally, engineer precision modulation. Insights from the first two pillars must drive the rational design of next-generation therapeutics—such as miRNA modulators, cell-type-specific siRNAs, or small-molecule inhibitors—with optimized delivery routes (e.g., RVG peptide-conjugated carriers, exosomes) to enhance blood-brain barrier (BBB) penetration and minimize off-target effects. Safety considerations, including biodegradable carriers and cell-specific targeting to avoid normal neural tissue toxicity, will be critical for clinical translation of PDCD4-targeted strategies.

Abbreviations *AD*: Alzheimer's disease; *ALS*: Amyotrophic lateral sclerosis; *AP-1*: Activator protein 1; *ATG5*: Autophagy-related 5; *Aβ*: β-Amyloid; *BDNF*: Brain-derived neurotrophic factor; *Bcl-2*: B-cell lymphoma 2; *Bcl-xL*: B-cell lymphoma-extra large; *CCI*: Chronic constriction injury; *ceRNA*: Competitive endogenous RNA; *circRNA*: Circular RNA; *CpG*: Cytosine-phosphate-guanine; *CREB*: CAMP response element binding protein; *CRS*: Chronic restraint stress; *CTSD*: Cathepsin D; *Daxx*: Death domain-associated protein; *DGCR5*: DiGeorge syndrome critical region gene 5; *DNMT*: DNA methyltransferase; *DRG*: Dorsal root ganglion; *eIF4A*: Eukaryotic translation initiation factor 4A; *eIF4E*: Eukaryotic translation initiation factor 4E; *eIF4G*: Eukaryotic translation initiation factor 4G; *EVs*: Extracellular vesicles; *GSK-3β*: Glycogen synthase kinase-3 beta; *Hipk2*: Homeodomain-interacting protein kinase 2; *hnRNPC*: Heterogeneous nuclear ribonucleoprotein C; *HOTAIR*: HOX transcript antisense RNA; *IBI*: Ischemic brain injury; *IL-1β*: Interleukin-1 beta; *IL-6*: Interleukin-6; *IL-10*: Interleukin-10; *IRES*: Internal ribosome entry site; *Klf4*: Krüppel-like factor 4; *KO*: Knockout; *lncRNA*: Long non-coding RNA; *LPS*: Lipopolysaccharide; *MAPK*: Mitogen-activated protein kinase; *MCAO*: Middle cerebral artery occlusion; *MCAO/R*: Middle cerebral artery occlusion/reperfusion; *miRNA*: MicroRNA; *MMP-9*: Matrix metallopeptidase 9; MPP^+: 1-Methyl-4-phenylpyridinium; *MPTP*: 1-Methyl-4-phenyl-12,3,6-tetrahydropyridine; *mTOR*: mTOR-Mammalian target of rapamycin;; *mTORC1*: Mammalian target of rapamycin complex 1; *ncRNA*: Non-coding RNA; *NES*: Nuclear export signal; *NF-κB*: Nuclear factor kappa B; *NLRP3*: NLR family pyrin domain containing 3; *Nrf2*: Nuclear factor erythroid 2–related factor 2; *PABP*: Poly(A)-binding protein; *PBMCs*: Peripheral blood mononuclear cells; *PD*: Parkinson's disease; *PDCD4*: Programmed cell death 4; *PI3K*: Phosphoinositide 3-kinase; *PPARγ*: Peroxisome proliferator-activated receptor gamma; *PRC2*: Polycomb repressive complex 2; *PSEN2*: Presenilin 2; *ROS*: Reactive oxygen species; *RVG*: Rabies virus glycoprotein; *SCI*: Spinal cord injury; *shRNA*: Short hairpin RNA; *siRNA*: Small interfering RNA; *SOD1*: Superoxide dismutase 1; *STAT1*: Signal transducer and activator of transcription 1; *TFEB*: Transcription factor EB; *TFE3*: Transcription factor E3; *TGF-β1*: Transforming growth factor beta 1; *TNF-α*: Tumor necrosis factor-alpha; *TrkB*: Tropomyosin receptor kinase B; *UTR*: Untranslated region; *VEGF*: Vascular endothelial growth factor; *XIAP*: X-linked inhibitor of apoptosis protein; *α-syn*: α-Synuclein; *β-TRCP*: Beta-transducin repeat-containing protein

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare no competing interests.

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