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Protein tyrosine phosphatase receptor type kappa (*PTPRK*) revisited: evolving insights into structure, function, and pathology

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Abstract

Protein Tyrosine Phosphatase Receptor Type Kappa (PTPRK) is a membrane-bound tyrosine phosphatase encoded by the frequently deleted region of chromosome 6q, which plays a crucial role in regulating cell signaling, adhesion, and immune response. Structurally, PTPRK comprises with an extracellular domain involved in cell-cell adhesion, a transmembrane region, and two intracellular catalytic domains responsible for its phosphatase activity. Notably, PTPRK undergoes proteolytic cleavage by Furin and ADAM10, resulting in the generation of an extracellular E-subunit and a P-subunit. Further processing by γ-secretase releases the intracellular PIC, which plays a pivotal role in regulating β-catenin signaling within the nucleus. PTPRK is widely recognized for its tumor-suppressive properties across various cancers, including colorectal, lung, ovarian, and melanoma. Despite its function as a tumor suppressor, the expression and activity of *PTPRK* exhibit considerable variability across different cancer types and stages. It exerts its effects by dephosphorylating key signaling molecules such as EGFR, STAT3, CD133 and β-catenin, thereby inhibiting cancer cell proliferation, survival, and metastasis. Beyond its role in cancer, *PTPRK* is also involved in immune regulation, particularly in the development of CD4+T cells, and has been implicated in autoimmune diseases such as multiple sclerosis. In the nervous system, *PTPRK* is linked to neurite outgrowth and synaptic transmission, with genetic polymorphisms in PTPRK associated with an increased risk of neurodegenerative diseases like Alzheimer's disease. Given its extensive involvement in cancer biology, immune regulation, and neurodevelopment, *PTPRK* presents a promising therapeutic target. Strategies aimed at restoring its activity or targeting *PTPRK* might offer new approaches for current cancer therapies and overcome drug resistance. In this review, we elucidate the structural characteristics and functional roles of PTPRK in cellular signaling and disease pathogenesis. The variability of PTPRK suggests that the regulatory mechanisms governing its activity are intricate and worth further comprehensive investigation.

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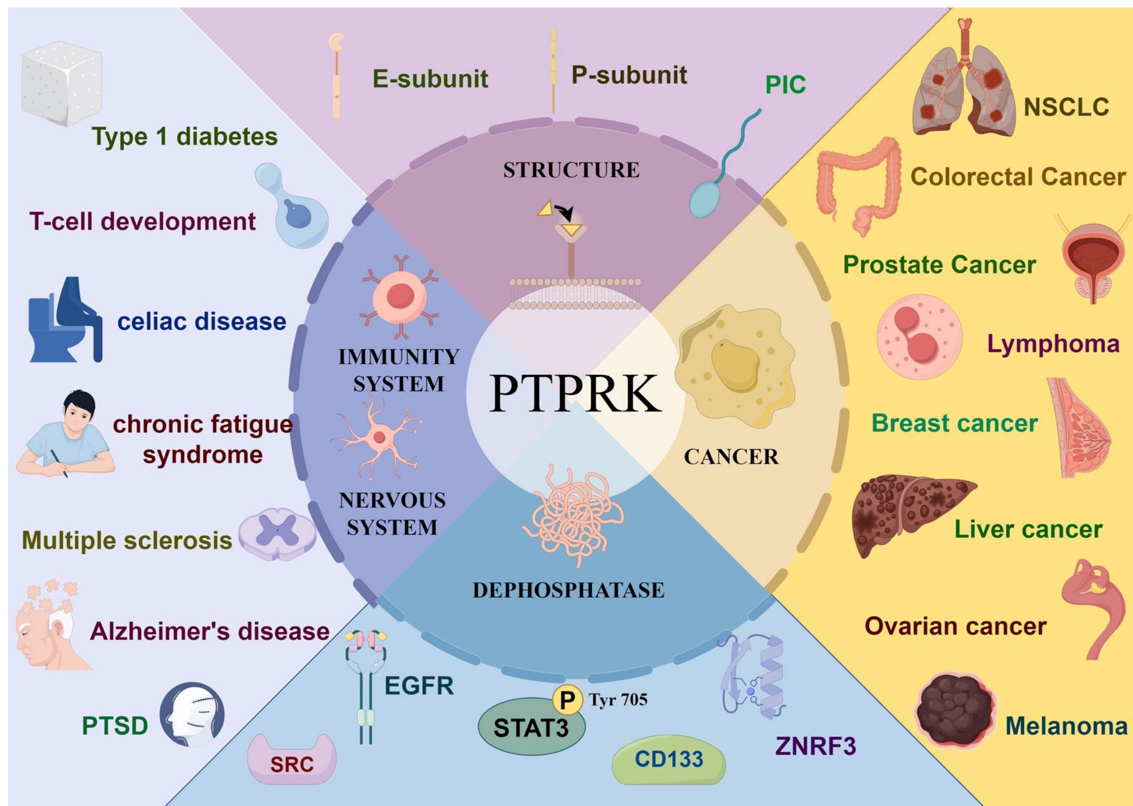
Graphical Abstract



Discovery and initial characterization

Receptor tyrosine phosphatases (PTPs) family garnered widespread attention upon their initial discovery and cloning, as they were believed to play a crucial role in receptor tyrosine kinase signaling [1]. Over the past decade, PTPs have become recognized as integral components of signal transduction in the central nervous systems of both vertebrates and invertebrates [2]. Based on phylogenetic analysis of phosphatase domains, PTPs are classified into 8 major subfamilies, 4 of which (R2A, R2B, R3, and R4) play indispensable roles in the development of the central nervous system [3]. PTPRK (*PTPRK*) belongs to the membrane-associated protein tyrosine phosphatase (PTP) R2A/IIb subfamily and shows the highest similarity to PTP-μ(PTPRM), PCP-2(PTPRU) and PTP-ρ(PTPRT) within this subfamily [4].

Although these four members share similar structures, their locations in the human genome are different. *PTPRT*, *PTPRK*, *PTPRM*, and *PTPRT* are located on human chromosomes 1, 6, 18, and 20, respectively [5]. Yang et al. successfully isolated and cloned the human *PTPRK* gene, initially named p55-7. This gene encodes a transmembrane protein consisting of 1440 amino acids and is highly conserved with the mouse PTPRK at the amino acid level, showing 98% homology [6].

Structure of PTPRK

Protein Tyrosine Phosphatase Receptor Type Kappa (*PTPRK*) is located in the 6q22-23 region of the human genome and it consists of a longest polypeptide chain containing 1440 amino acids [7]. According to the latest predictions from National Center for Biotechnology Information (NCBI), PTPRK now has 6 isoforms*PTPRK* shares the same structure as many members of this PTP subfamily, including intracellular catalytic domains (ICDs), extracellular domains (ECDs), and an transmembrane domain [8]. Specifically, the extracellular domain of PTPRK includes an architecture of MAM (meprin/A5/μ), a combination of immunoglobulin (Ig)-like domains and four fibronectin type III repeats [9] (Fig. 1A). The extracellular domain functions as a cell adhesion molecule-like domain, interacting with β- and γ-catenin at adherens junctions [10], thereby facilitating cell-cell adhesion [1]. The transmembrane regions serve to transmit signals from the extracellular domains to the intracellular domains [11]. The intracellular region of PTPRK comprises two phosphatase domains: a membrane-proximal domain (D1) and a membrane-distal domain (D2). These domains possess dephosphorylation activity and potential transcription regulator functions. Notably,, the D1 domain exhibits catalytic activity [12], whereas the D2

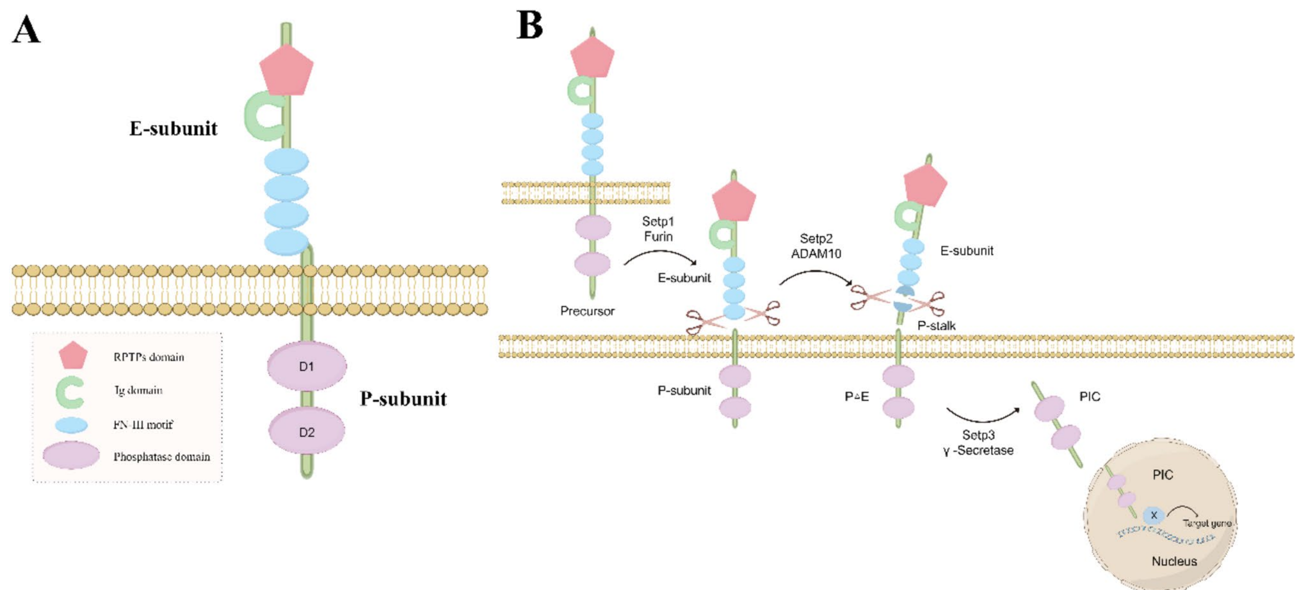


Fig. 1 Schematic diagram of PTPRK structure (**A**) and PTPRK intracellular clipping mode (**B**)

domain is highly conserved and exhibits limited catalytic function [13]. The PTPRK protein undergoes proteolytic cleavage through the action of three key enzymes: Furin, ADAM10, and γ-secretase. Initially, Furin processes a membrane-proximal dibasic sequence, resulting in the formation of two subunits: an extracellular E-subunit and a membrane-bound P-subunit, which contains the phosphatase domains. Subsequently, ADAM10 mediates a second cleavage that sheds the extracellular domain, leaving a membrane-bound fragment. This fragment is then subjected to final processing by γ-secretase, which releases the phosphatase intracellular portion (PIC) into the cytoplasm. This release facilitates its entry into the nucleus, where it regulates transcription, particularly that of β-catenin (Fig. 1B) [14]. Additionally, the D1 domain of the PTPRK monomer represents the first monomeric crystal structure identified within this family: the active site cysteine (Cys1083) is located within a highly conserved phosphate-binding loop [12].

There may be genome location and transcriptomic differences in PTPRK across different species. The human PTPRK has been mapped to chromosome 6 through DNA hybridization in mouse/human cell hybrids. In rats, PTPRK (NW 047547; incomplete) is located on chromosome 1, while in mice, it is found on chromosome 10, approximately 21 centimorgans from the centromere [2]. Alternative splicing of PTPRK exons 16, 17a, and 20a has been reported in various studies [14]. Jiang et al. have firstly cloned mouse PTPRK, a new member of the receptor protein tyrosine phosphatase family [7]. Forrest et al. have identified two novel forms of PTPRK from the full-length mouse cDNA sequence, which may produce two PTPRK splice variants: a secreted form and a membrane-bound form [15].

Extensive cancer studies elucidated that *PTPRK* genetic mutations or structural abnormalities of PTPRK in tumor cells will lead to biological function alterations. For instants, in malignant glioma cell lines, deletions or missense mutations in the *PTPRK* will elevate phosphorylation levels of EGFR and β-catenin, which will alleviate the sensitivity of glioma cells to chemotherapy [16]. In primary central nervous system lymphoma (PCNSL), patients with deletions in the *PTPRK* have higher mortality rates, a phenomenon similarly observed in melanoma [17]. In Hodgkin lymphoma (HL), the downregulation of PTPRK expression promotes enhanced survival and proliferation [18]. Furthermore, the loss of PTPRK phosphatase activity results in impaired cell-cell adhesion and increased tumor invasive ability [19]. In breast cancer and melanoma cell lines, the knockdown of PTPRK leads to increased cell proliferation, adhesion, and migration capabilities [20].

Functions of PTPRK

PTPRK is associated with T cell immunity

PTPRK is widely expressed in various tissues within the organism. In mice, PTPRK is primarily expressed in the thymus, liver, and kidneys [5, 21, 22]. The role of PTPRK in the immune function of animals has garnered significant attention from numerous scientists. It is noteworthy that PTPRK is highly expressed in the thymus of rats and is closely associated with the regulation of CD4+T cell development [22]. Both the PTPRK and THEMIS genes are deleted in the immunodeficient rats (Long-Evans Cinnamon, LEC) rat strain, and both are necessary for

the observed CD4 + T cell defects in this rat strain. Atsushi Asano et al. elaborated that the knockout of PTPRK in LEC rats leads to a helper T cell immunodeficiency [23]. In addition, Namjil and his scholars had built upon this foundation by demonstrating that the inhibition of PTPRK suppressed CD4 + T cell agonists (PMA and ionomycin) induced ERK1/2 phosphorylation in T cell hybrids and total thymocytes from LEC rats [24].

PTPRK is related to cell-cell adhesion

In human being, PTPRK is expressed in normal tissues such as the spleen, prostate, ovaries, brain, lungs, skeletal muscle, heart, placenta, liver, kidneys, and intestines [21], as well as in melanocyte and keratinocyte epidermal cell lines [25]. As mentioned above, PTPRK is widely expressed at high levels in organisms, and its extracellular segment (called MAM domain [26]), regulated by cell growth density [19], appears to determine the specificity of its interactions [27]. Besides, some researchers believe that members of the PTP family can maintain intact cell adhesion complexes by dephosphorylating adhesion proteins [28, 29]. In cell experiments and overexpression systems, it had demonstrated to directly perceive cell-cell contact and thereby might mediate contact inhibition of cell growth [30].

Within the cell membrane, PΔE and PIC co-localize and immunoprecipitated with β-catenin and plakoglobin/γ-catenin, and catalyze the dephosphorylation of β-catenin (some researchers inferred that β-catenin might be a substrate of PTPRK). Hence, tyrosine-phosphorylated β-catenin translocate to the nucleus and activates transcription to promote cell proliferation and migration [14].

There are also some sporadic evidences indicate that the full-length PTPRK is exactly opposite biological functions to that of the phosphatase activity of the intracellular fragments of PTPRK. Lacking full-length PTPRK expression, melanomas cells migration and proliferation are significantly accelerated: Luisa Novellino et al. demonstrated that full-length PTPRK could recruit β-catenin into the cell membrane and alter the it's cytoplasmic level, led to free β-catenin and E-cadherin rearranged intracellular localization. This, in turn, impedes the expression levels of nuclear β-catenin, ultimately reducing the expression of β-catenin downstream genes such as cyclin D1 and c-myc, thereby acting as a tumor suppressor [31].

In the rat induced pancreatitis model, the cell adhesion role of PTPRK has also been demonstrated: Before the termination of cell-cell adhesion, PTPRK interacts with E-cadherin, α/β-catenin and continuously dephosphorylating the cadherin/catenin complex on plasma membrane. This interaction regulates the formation and maintenance of the cadherin/catenin complex, as well as the reassembly and cell-cell contact in vivo.

Potential mechanism of PTPRK tyrosine dephosphorylates activity

PTPRK-Mediated EGFR dephosphorylation

Epidermal growth factor receptor (EGFR), as a key receptor tyrosine kinase (RTKs) in intracellular signaling pathways, plays a central role in the development and progression of various cancers [32]. The tyrosine phosphorylation of EGFR within cancer or normal cells must be strictly regulated, and one potential mechanism for this regulation is through dephosphorylation catalyzed by PTPs [11, 33–35]. As a member of the PTPs family, PTPRK might attenuates the activation of various signaling pathways induced by protein tyrosine phosphorylation by removing phosphate groups from intracellular proteins. PTPRK specifically dephosphorylates the epidermal growth factor receptor (EGFR), making it a major negative regulator of EGFR signaling. The expression level of PTPRK has been shown to be clearly associated with the proliferation of keratinocytes both in vitro and in vivo. Overexpression of PTPRK leads to EGFR dephosphorylation, inhibiting EGFR-induced cancer cell proliferation and ERBB receptor signaling, and ultimately suppressing the mitogenic effects mediated by transforming growth factor-β (TGF-β) [36]. Yi-ru Xu et al. detailed the mechanism the way how PTPRK affects EGFR. First, they have observed that in CHO cells (a kind of lacking endogenous EGFR cell line), EGFR exhibited abnormally high levels of tyrosine phosphorylation. Additionally, the loss of PTPRK expression in CHO cells increased EGFR phosphorylation. In vitro experiments demonstrated that PTPRK preferentially dephosphorylates the 1068 and 1174 sites on EGFR. Yi-ru Xu and his colleagues concluded that PTPRK acts as a tumor suppressor gene by dephosphorylating and inactivating EGFR [37]. Furthermore, N-acetylglucosaminyltransferase V (GnT-V) glycosylation has been validated to potentially reduce the full-length expression of PTPRK and increased its proteolytic cleavage vulnerability [38]. Cells with reduced full-length PTPRK might lost the ability to dephosphorylate the membrane-associated substrate EGFR, which leading to increased phosphorylation at the tyrosine 1068 site on EGFR and subsequent changes in downstream biological functions [39].

PTPRK-Mediated STAT3 dephosphorylation

Signal transducer and activator of transcription (STAT) proteins are a family of transcription factors activated by cytokines, growth factors, and other peptide ligands [40]. In normal cells, STAT activation is strongly restricted to prevent uncontrolled gene expression. However, in cancer cells, prolonged STAT activation can lead to

significant adverse effects, such as drug resistance and poor prognosis [41, 42]. STAT3 is the most strongly associated with promoting tumor growth and immunosuppression among the seven members of the STAT protein family (STATs 1–4, 5 A, 5B, and 6) [41, 43]. It is also the only member whose genetic deletion leads to embryonic lethality [43, 44]. Under various extracellular stimuli (such as cytokines, growth factors, etc.), STAT3 is constitutively activated and participates in the survival, growth, migration, drug resistance and immune escape of tumor cells [45]. STAT3 activation can be regulated through various post-translational mechanisms, including phosphorylation/dephosphorylation of serine or tyrosine residues [46], acetylation [47], or demethylation [48]. One of the primary mechanisms for negatively regulating STAT3 activity is the dephosphorylation of tyrosine residues, which are essential for STAT3 activation by protein tyrosine phosphatases (PTPs) [49]. It has been confirmed that seven PTPs can dephosphorylate STAT3: PTP receptor type T (PTPRT), PTP receptor type D (PTPRD), PTP receptor type K (PTPRK), Src homology region 2 (SH-2) domain-containing phosphatase 1 (SHP1), SH-2 domain-containing phosphatase 2 (SHP2), MEG2/PTP non-receptor type 9 (PTPN9), and T-cell PTP (TC-PTP)/PTP non-receptor type 2 (PTPN2) [50]. Among these, *PTPRK* is the only protein tyrosine phosphatase located on chromosome 6q region which contains a STAT3-specific motif [51]. Yun-Wen Chen et al. discovered a strong connection between low PTPRK expression and high levels of nuclear phosphorylated STAT3 at Tyr705 in primary nasal-type natural killer/T-cell lymphoma (NKTCL). They demonstrated that PTPRK binds to STAT3 and directly dephosphorylates and regulating STAT3 at Tyr705, thereby down-regulation of PTPRK leads to STAT3 activation, promoting the development of NKTCL [51]. Xu-ting Xu et al. identify that PTPRK is significantly negatively correlated with the expression of phosphorylated STAT3 at Tyr705 in non-small cell lung cancer (NSCLC). They demonstrated that PTPRK increases the expression of phosphorylated STAT3 at Tyr705 in NSCLC cells, highlighting that PTPRK plays a crucial role in NSCLC proliferation and metastasis by inhibiting STAT3 activity [52].

PTPRK-Mediated SRC dephosphorylation

Steroid receptor co-activator (SRC), a non-receptor protein tyrosine kinase, plays a crucial role in cell signal transduction [53]. It is regulated by growth factors, cytokines, and integrin receptors, and is involved in cellular processes such as survival, proliferation, and migration [54, 55]. Researchers has found that c-SRC mediates downstream signaling of the fibroblast growth factor (FGF) receptor in vascular endothelial cells (HECV). After knocking down PTPRK in these cells, the protein levels of c-SRC were increased, then enhancing FGF-induced endothelial cell migration [56]. Evidence in breast cancer also supports that PTPRK is a positive regulator of SRC. Interfering with PTPRK increases the inactivating phosphorylation of SRC at Tyr527 while reducing its phosphorylation at Tyr416. This disruption affects focal adhesion formation, F-actin assembly, TGF-β-induced FAK phosphorylation, and breast cancer cell migration [36]. Comparing to those with osteoarthritis, the fibroblast-like synoviocytes (FLS) in the rheumatoid arthritis (RA) patients exhibit higher levels of PTPRK expression [57]. Platelet-derived growth factor (PDGF) is a prominent growth factor promoting FLS invasiveness in the abnormal synovium of RA patients. PTPRK enhances PDGF-induced RA FLS migration by dephosphorylating SRC at Tyr527, thereby promoting the activation of downstream signaling of the platelet-derived growth factor receptor (PDGFR) [57].

PTPRK-Mediated CD133 dephosphorylation

CD133 is considered a molecular marker of cancer stem cells [58], and it has been demonstrated to undergo tyrosine phosphorylation via in vitro tyrosine kinase assays in human brain tumor cell lines [59]. As a tyrosine phosphatase, PTPRK had been demonstrated that it could combine with CD133 and form a PTPRK-CD133 complex. In vitro studies indicate that PTPRK's intracellular phosphatase domain binds to the C-terminal region of CD133 and catalyzes the dephosphorylation of CD133 at tyrosine-828 and tyrosine-852. This dephosphorylation regulates AKT signaling and plays an essential role in the progression of colorectal cancer [60]. Moreover, clinicopathologic data analysis suggested that low expression of PTPRK was significantly associated with poor prognosis in colon cancer patients with high expression of CD133 [60]. Matsushita et al. found that PTPRK knockout significantly promotes colonel tumor growth. Silencing PTPRK enhances the phosphorylation of CD133, AKT, and its downstream target such as Bad, while significantly reducing the sensitivity of high CD133-expressing colorectal cancer cells to the chemotherapy drug oxaliplatin [61].

PTPRK-Mediated ZNRF3 dephosphorylation

Zinc and ring finger protein 3 (ZNRF3), a transmembrane E3 ubiquitin ligase, can target WNT receptors, facilitating their ubiquitination and lysosomal degradation [62]. ZNRF3 acts as a negative regulator of WNT receptors under RSPO3, thereby inhibiting cancer development [62, 63]. Ling-Shih Chang et al. explored that PTPRK is an upstream positive regulator of ZNRF3, which consumes LRP 6 and FZD on the cell surface by promoting the lysosomal transport of ZNRF3 [64]. PTPRK could bind to ZNRF3 and dephosphorylate tyrosine on endocytosis signals, whereby reducing WNT receptors on the

cell surface, inhibiting WNT/b-catenin protein signaling, and ultimately inhibiting tumor occurrence [64].

Finally, *PTPRK* takes exerted on various cellular signaling pathways by dephosphorylating different substrate proteins, thereby leading to diverse biological functions. As a result, its role varies across different cell types depending on the specific substrates it targets (Table 1).

The relationship between PTPRK and human disease

PTPRK in disease of neurodegeneration

Tyrosine phosphorylation is vital for regulating cell proliferation and differentiation during the developmental processes of an organism. Accumulating evidence indicates that tyrosine phosphorylation controls biological events in nervous system development. *PTPRK* is widely expressed in the nervous system, but its specific role in neural development remains to be fully elucidated [65, 66]. Drosopoulos et al. demonstrated that PTPRK can recruit growth factor receptor-bound protein 2 (Grb2) to the neuronal cell membrane, triggering the MAPK cascade to stimulate neurite outgrowth. Meanwhile, after Grb2 inhibitory peptides and MEK1 inhibitors were used, they only suppressed approximately 60% of the PTPRK-induced neurite outgrowth response. This phenomenon suggests that PTPRK activates multiple intracellular signaling pathways involved in neurite growth [67]. However, some researchers have suspected that PTPRK phosphatase activity is not essential for neural development. Mice remained viable after knockdown of the PTPRK promotor, which the authors attributed to redundancy with other tyrosine phosphatases in PTPs family [21]. Author also confirmed that PTPRK is localized at synaptic junctions in neurons, further supporting the potential role of PTPRK at synaptic terminals in neural development or transmission [21].

PTPRK is associated with various neurological disorders, including Alzheimer's disease (AD), the most common cause for dementia. AD is an irreversible, chronic neurodegenerative disease that gradually impairs memory and cognitive abilities in affected patients [68]. Meanwhile, though a case-control dataset and a family-based study, Yang Chen et al. found that rs2326681 and rs7748155 (a kind of single nucleotide polymorphisms, SNPs) in the *PTPRK* are significantly associated with the risk of developing AD and the age at onset (AAO). These SNPs are identified as risk factors for both the occurrence and the timing of AD onset [69]. Therefore, SNPs of *PTPRK* are considered to connect genetic susceptibility to AD [70]. As above mentioned, *PTPRK* is up-regulated by TGF-β [36]. In mechanism, brain amyloid angiopathy caused by excessive production of TGF-β is usually associated with AD.

Other SNPs within the *PTPRK*, such as rs17461290 and rs11753871, have been also associated with psychiatric disorders including schizophrenia, depression, and bipolar disorder [71, 72]. Besides, *PTPRK* has been predicted as a potential genetic target for post-traumatic stress disorder (PTSD) [73].

Autophagy is involved in the pathological processes of AD, such as the removal of misfolded proteins, making it a novel therapeutic target for AD [74, 75]. A study utilizing the GEO database, based on metabolic and signaling pathways linked to high-fiber diets, identified *PTPRK* as a biomarker related to high-fiber diets, type 2 diabetes mellitus (T2-DM), and AD. The high-fiber diet might regulate autophagy homeostasis in the hippocampal-hypothalamic endocrine axis via the binding of the metabolite acetylaminobenzoic acid with the SPEG (striated muscle enriched protein kinase gene) protein [76]. Hence, *PTPRK* as a biomarker associated with high-fiber diets, T2-DM, and AD, warrants further investigation into its potential influence on metabolism and neurodegenerative diseases through the regulation of autophagy.

In conclusion, *PTPRK* act as optional participant in neural development and has been linked to various neurological disorders, including AD and psychiatric conditions like schizophrenia and bipolar disorder. While

Table 1 Mechanism of protein tyrosine phosphatase receptor type Kappa in dephosphorylation

Target Protein	Dephosphorylation Mechanism by PTPRK	Associated Pathways	Reference
EGFR	PTPRK dephosphorylates EGFR at specific tyrosine residues, inhibiting EGFR-induced signaling	**EGFR signaling**, **TGF-β signaling**	[36, 37, 39]
STAT3	PTPRK directly dephosphorylates STAT3 at Tyr705, inhibiting its activation and downstream oncogenic effects	**STAT3 signaling**	[51, 52]
β-catenin	PTPRK dephosphorylates β-catenin, reducing its nuclear translocation and transcriptional activation	**WNT/β-catenin signaling**	[14, 31]
SRC	PTPRK regulates SRC by dephosphorylating it at Tyr527, controlling cell migration and adhesion	**SRC signaling**, **TGF-β signaling**	[36, 56, 57]
CD133	PTPRK dephosphorylates CD133 at specific tyrosine residues, inhibiting AKT activation and promoting tumor suppression	**CD133-AKT signaling**	[60, 61]
ZNRF3	PTPRK dephosphorylates ZNRF3, promoting its activity in the inhibition of WNT signaling	**WNT/β-catenin signaling**	[62, 64]

its phosphatase activity supports neurite outgrowth, its exact role in the nervous system remains unclear.

PTPRK in disease of immune system

The human immune system is composed of specialized immune cells that work together to eliminate microbial pathogens, thereby protecting the organism. Immune cells widely use surface receptors to initiate signaling pathways. Some of these receptors could transmit signals via activating specific protein tyrosine kinases (PTKs), leading to the phosphorylation of various target proteins on tyrosine residues [77]. Abnormal growth, differentiation, and activation of immune cells can lead to inappropriate immune responses, finial leading to various diseases. Accumulative evidence suggests that dysfunctional protein tyrosine phosphatases (PTPs) can disrupt the balance between PTPs and PTKs, contributing to abnormal immune responses [78, 79]. Hence, PTPs bear a heavy responsibility in regulating multiple signaling pathways within both innate and adaptive immunity [80]. *PTPRK* is widely expressed across various tissues in the body, and its especially high expression in the thymus has garnered significant scientific attention regarding its function within the immune system [22].

PTPRK is highly associated with the regulation of T-cell development. As mentioned above, *PTPRK* has been shown to regulate the differentiation of CD4 + T cells in the immunodeficient rats (Long-Evans Cinnamon, LEC) [22, 81]. The deletion of *PTPRK* will produce T-helper cell immunodeficiency in LEC rats, meanwhile re-transfect *PTPRK* into LEC bone marrow cells could restore half of the missing CD4 + T cells in LEC rats [23]. However, CD4 + T cell development was reduced in bone marrow-derived stem cells transfected with the dominant-negative form of *PTPRK.* Both dominant-negative form of *PTPRK* and *PTPRK* siRNA were found to decrease the phosphorylation of c-Raf, MEK, and ERK 1/2 in T cell lines, imply that PTPRK can positively regulate the c-Raf/MEK/ERK1/2 signaling pathway required for CD4 + T cell development [24].

Multiple sclerosis (MS) is a chronic autoimmune disorder affecting the central nervous system. Genome-wide association studies have identified more than 100 common variants associated with MS, most of which are related to immune-related genes, particularly those involved in T cell development [82, 83]. One of the genome regions involved is located on chromosome 6q, which contains two genes critical for T cell development: Thymocyte Selection-Associated Molecule (THEMIS) and PTPRK. The SNP rs802734 was first identified in most association with multiple sclerosis (MS) in a 2011 genome-wide association study (GWAS), which was in 56 kb upstream of THEMIS and 11 kb downstream of PTPRK. It's also suggesting that *PTPRK* plays a key role in MS susceptibility.

Intriguingly, SNP rs802734 has also been confirmed to be associated with celiac disease (CD), highlighting its involvement in multiple autoimmune conditions [84]. It is well-known that CD is a common immune-mediated enteropathy. Research has shown that the SNP rs802734 can affect the expression of THEMIS but does not influence PTPRK expression in CD patients. In active CD patients, PTPRK is often observed to be low expressed in the intestinal mucosa. This low level of PTPRK is consistent with the permeability of the intestinal barrier increasing, which could be a key mechanism promoting the excessive proliferation of crypt cells in the gut [85].

Type 1 diabetes mellitus (T1-DM) is a disease caused by an autoimmune response targeting insulin-producing β-cells in the pancreas. Research has shown that polymorphisms in the *PTPRK* gene locus are also associated with the development of T1-D. Niina Sandholm et al. found that 58 SNPs were located within DNA fragments interacting with the promoter regions of PTPRK (naïve CD4 + T cells in fetal thymus) and THEMIS (in naïve CD8 + T cells) [86]. The authors also found that the insertion of rs138300818 created a common thymocyte regulatory motif, which simultaneously disrupted the RFX5/7 motif. This interference with PTPRK (and THEMIS) gene expression could contribute to protection against the development of early-onset type 1 diabetes (T1-D) [86].

In addition, there has been a study to explore the changes in the composition of T cell subsets in peripheral blood during the progression of dengue virus (DV) plasma leakage to shock. They found an increased frequency of CD4 + CD8 + double-positive T cell subsets detected in peripheral blood and significantly down-regulated *PTPRK* as a differential gene in CD8 + single-positive cells [87]. Similarly, a genomic analysis of peripheral blood in patients with chronic fatigue syndrome (CFS) identified six upregulated genes within the CD19 + cell population. Among them, *PTPRK* is showed significantly lower expression [88]. Previous studies have demonstrated that PTPRK, a TGF-β target gene, can be down-regulated by the Epstein-Barr virus (EBV), a well-known trigger factor for CFS [18]. This highlights the potential regulatory role of PTPRK in the pathogenesis of CFS [89].

In summary, *PTPRK* emerges as a central regulatory molecule in immune responses, with its dysregulation contributing to the pathogenesis of dozens of diseases. Its role in T-cell development and immune signaling pathways makes it a promising target for future research and potential therapeutic strategies in treating autoimmune diseases and related patients.

PTPRK in human Cancer

Hematologic malignancies

Association between PTPRK and Nasal-type natural killer/T-cell lymphoma (NKTCL) Nasal-type natural killer/T-cell lymphoma (NKTCL) is an aggressive lymphoma arising from NK cells or cytotoxic T cells [90], characterized by frequent deletions on chromosome 6q and constitutive activation of STAT3 [91]. The *PTPRK* encodes receptor-type tyrosine-protein phosphatase κ, which is the only protein tyrosine phosphatase (PTP) located on chromosome 6q21 among the three phosphatase that interact with STAT3 [92]. Chen and colleagues discovered that the loss of PTPRK is clearly associated with the development of nasal NK/T-cell lymphoma (NKTCL) and that its low expression correlates with reduced overall survival [51]. The expression of PTPRK protein is negatively correlated with the levels of nuclear phosphorylated STAT3 Tyr705 in NKTCL cell lines. Restoring PTPRK expression in NKTCL cell lines reduces the levels of nuclear phosphorylated STAT3 Tyr705, while PTPRK knockout produces the opposite effect. In vitro experiments demonstrated that restoring PTPRK inhibits tumor cell growth and triggers caspase-mediated apoptosis, whereas partial knockdown of PTPRK promotes tumor cell growth in NKTCL cells. The authors further concluded that the mRNA expression of PTPRK in NKTCL is frequently insufficient due to monoallelic deletion and transcriptional silencing caused by abnormal promoter hypermethylation. This insufficiency promotes lymphomagenesis by activating the oncogenic STAT3 protein in NKTCL cells. Apart from STAT3's Tyr705 site dephosphorylating, PTPRK can also target STAT3 activation at multiple levels to achieve tumor suppression in NKTCL. PTPRK could dephosphorylate JAK3 at the Tyr980 site and might provide an additional mechanism leading to constitutive JAK3 phosphorylation at Tyr980, especially in the absence of activating JAK3 mutations [93, 94].

Association between PTPRK and primary central nervous system lymphoma (PCNSL) Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of non-Hodgkin lymphoma (NHL) that is confined to the central nervous system [95]. According to previous statistical studies, it accounts for approximately 1% of all NHL cases and 5% of primary brain tumors [96]. In PCNSL, the events of Del 6q22 and BCL6 rearrangement are common and of significant importance, where the mutation of 6q21-23 loci on the long arm of chromosome 6 is mainly involved [93, 97–99]. Since *PTPRK* is located within the deleted region at 6q22, clinical data have indicated that both heterozygous loss at the *PTPRK* locus and the deficiency of PTPRK expression are associated with poorer prognosis. Patients with reduced PTPRK expression have higher mortality rates, suggesting that PTPRK may act as a tumor suppressor gene in PCNSL [100].

Association between PTPRK and acute lymphoblastic leukemia (ALL) Acute lymphoblastic leukemia (ALL) is the most common malignancy in childhood [101], representing a leading cause of disease-related mortality in children and adolescents. It is also a significant contributor to cancer-related deaths in adults, with over 150,000 new cases reported globally in 2019 [102]. ALL originates from the fault transformation and uncontrolled abnormal proliferation of B-cell precursors acute lymphoblastic leukemia (BCP-ALL) or T-lymphoid progenitors acute lymphoblastic leukemia (T-ALL) [103]. Aberrant DNA promoter methylation and tumor suppressor silencing are common epigenetic abnormalities in ALL and are highly associated to poor prognosis [104]. WS Stevenson et al. discovered that the PTPs are hypermethylated targets in acute lymphoblastic leukemia (ALL) and high-grade B-cell lymphomas. In his ALL cohort, methylation of the *PTPRK* promoter region was associated with decreased overall survival, and *PTPRK* was methylated in 63% of ALL cases. Restoring PTPRK levels reduced cell proliferation, inhibited colony formation, and increased sensitivity to cytotoxic chemotherapy drugs in leukemia cells. These biological changes were correlated with decreased levels of phosphorylated proteins such as ERK1/2, Akt, STAT3, and STAT5 [105].

Association between PTPRK and hodgkin lymphoma (HL) Hodgkin lymphoma, first portrayed by British pathologist Thomas Hodgkin in 1832 [106], is primarily characterized by malignant cells derived from B cells, which morphologically appear as multinucleated giant cells or large mononuclear cells (called Hodgkin and Reed-Sternberg, HRS) [107]. Epstein-Barr virus (EBV), a saliva transmitted gamma herpesvirus, is present in Hodgkin Reed-Sternberg (HRS) cells in cases from developing country [108]. Flavell et al. disclosed that PTPRK may have a potential HL suppressing gene function. On the one hand, In EBV-infected Hodgkin lymphoma (HL) cells, the virus encodes and translates the EBNA1 protein, which downregulates PTPRK gene expression by reducing Smad2 protein levels in the TGF-β signaling. On the other hand, EBV-infected HL cells secrete cytokines such as TGF-β, affecting immune cells and promoting an immunosuppressive tumor microenvironment (TME). The authors further demonstrated that overexpressing PTPRK in EBV-positive HL cells reduced cell survival and proliferation [18].

Solid tumors

Association between PTPRK and colorectal Cancer Colorectal cancer (CRC) is a malignant lesion occurring in the mucosal epithelium of the colon and a common malignant tumor of the gastrointestinal tract [109]. *PTPRK* is now commonly recognized as a tumor suppressor gene that plays a significant role in colorectal cancer [60, 61]. As previously mentioned, *PTPRK* acts as a binding chaperone of CD133 in colorectal cancer [60]. It interacts with the carboxyl-terminal region of CD133 through its intracellular phosphatase domain and dephosphorylates specific tyrosine residues, thereby inhibiting CD133-mediated AKT phosphorylation. The phenomenon of losing PTPRK could enhance the CD133/AKT axis, therefore activating the AKT-Bad pathway and preventing the death of colorectal cancer cells induced by chemotherapy drugs [61]. There is a study indicates that the cleavage of PTPRK protein is associated with colon cancer metastasis. In overexpressing N-acetylglucosaminyl transferase V (GNT-v) WiDr cells, PTPRK often undergoes abnormal glycosylation, making it highly susceptible to proteolytic cleavage. The cleaved PTPRK exhibits a reduced capacity to bind with normal ones, ultimately leading to increased migration of colon cancer cells [38].

The Cancer Genome Atlas Network has revealed that the vast majority of colorectal tumors exhibit activation of the WNT signaling pathway [110]. R-spondin (RSPOs) proteins, a family of four secreted glycoproteins, are well-known for their role as ligands that activate the WNT/β-catenin signaling pathway [111, 112]. RSPO3, a member of the RSPOs family, is a strong activator of the WNT/β-catenin signaling pathway [113, 114]. According to researcher Shigeki et al.'s work [113], PTPRK–RSPO3 fusions frequent in colorectal cancers. This abnormal fusion protein may activate the WNT signaling pathway through a mechanism distinct from the traditional mutations (such as those in the APC [115, 116]). There are two main types of fusion events: The first type involves the fusion of the first exon of PTPRK with the second exon of RSPO3 (PTPRK(e1)–RSPO3(e2)), which retains the full coding sequence of RSPO3 while replacing its secretion signal sequence with that of PTPRK. Another type involves the fusion of the seventh exon of PTPRK with the second exon of RSPO3 (PTPRK(e7)–RSPO3(e2)), which includes the first 387 amino acids of PTPRK along with RSPO3 amino acids 34–272, lacking its native signal peptide [117]. Overall, the PTPRK-RSPO3 fusion acts as a driver of tumor growth in colorectal cancer. Colorectal tumor which was PTPRK-RSPO3 fusion positive are sensitive to RSPO3-targeted therapies. The remedy target for RSPO3 blocking could inhibit tumor growth and promote colon tumor cell differentiation [118].

Association between PTPRK and NSCLC Lung cancer is the leading cause of cancer-related deaths worldwide [119], with a poor prognosis and a 5-year overall survival rate of only about 11.6% in 2018 oncology report [120], making it one of the deadliest malignancies in humans. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases, with the majority (60–80%) of patients diagnosed at an advanced stage [121]. Regardless of significant advancements in treatment methods in recent years, the prognosis remains poor, with a 5-year survival rate of only 15% [122]. Li-min Xu et al. discovered that PTPRK is a direct target of miR-1260b in lung cancer cells: PTPRK expression is significantly inversely correlated with miR-1260b levels in both A549 cell lines and non-small cell lung cancer (NSCLC) clinical tissue samples. miR-1260b directly targets the 3'-UTR region of PTPRK, suppressing its expression, which in turn promotes the migration and invasion of lung cancer cells [123].They also revealed that in NSCLC tissues, phosphorylated STAT3 (Tyr 705) levels are positively correlated with lymph node metastasis and conversely correlated with PTPRK expression. The down-regulated of PTPRK may promote tumorigenesis in NSCLC by activating STAT3 [52]. Those researches suggests that PTPRK is not only a prominent tumor suppressor gene but also a potential target for NSCLC diagnosis and therapy.

Association between PTPRK and prostate cancer (PC) Prostate cancer is one of the most common non-cutaneous tumors in men and the third leading cause of cancer-related deaths among males [124, 125]. Despite advances in treatment, there is still a lack of effective gene therapy options for prostate cancer [126]. While PTPRK is widely recognized as a tumor suppressor gene in most cancers, its role in prostate cancer appears to be more complex. Sun et al. [127] found that PTPRK was elevated in prostate cancer tissues. After knockout of PTPRK, they have observed that PC-3 cancer cell was increasing population of the apoptotic cell. Additionally, down-expression of PTPRK was also associated with increased tyrosine phosphorylation of c-Jun N-terminal kinase (JNK) and expression of caspase-3, caspase-8, and p53. In conclusion, the authors suggest that PTPRK knockdown promotes apoptosis and inhibits the growth of prostate cancer cells in vitro.

Besides, existing research has proved that miRNAs are closely associated with the development and progression of prostate cancer [128, 129]. Another study found that the overexpression of miRNA-627 weaken the proliferation and migration of prostate cancer cells and promotes apoptosis. Furthermore, miRNA-627 exerts its antitumor effects by inducing G0/G1 cell cycle arrest in prostate cancer cells and upregulating tumor suppressor genes such as MAP3K1, PTPRK, and SRA1 [130]. Therefore,

the miRNA-627/PTPRK signaling axis can inhibit the proliferation and migration of prostate cancer, thereby blocking its progression and providing a new therapeutic target for prostate cancer treatment.

Association between PTPRK and breast cancer (BC) The incidence of breast cancer ranks first among female malignant tumors [131, 132]. The role of *PTPRK* in breast cancer is not well understood. Sun et al. found that patients with advanced breast cancer with poor prognosis, especially those with breast cancer metastasis and death, had relatively low *PTPRK* expression levels. Reduced levels of *PTPRK* are associated with poor disease prognosis [20]. This suggests that *PTPRK* is a potential tumor suppressor in breast cancer. However, the inhibitory effect of *PTPRK* on the growth, adhesion and invasion of breast cancer cells remains unclear.

Association between PTPRK and hepatocellular carcinoma (HCC) The liver centrally governs systemic homeostasis by storing liposoluble vitamins and proteins, regulating lipid/hormone metabolism, and coordinating innate-adaptive immune crosstalk [133]. Hepatocellular carcinoma (HCC) incidence continues to rise globally, representing the end-stage consequence of diverse carcinogenic factors and serving as a primary indication for liver transplantation [134]. Recent work by Gilglioni et al. uncovered a dual regulatory role of PTPRK in obesity-associated hepatocellular carcinogenesis. They demonstrated significant upregulation of PTPRK expression in steatotic hepatocytes from high-fat diet-induced liver microenvironments, with this overexpression strongly correlating with dysregulated PPARγ signaling activation. They work have established the PTPRK-STAT1/c-Fos-PPARγ axis as molecular pathway linking metabolic dysregulation to hepatocarcinogenesis, proposing PTPRK as a potential therapeutic target for metabolic intervention in HCC management [135].

Association between PTPRK and ovarian cancer Globally, ovarian cancer is the seventh most common cancer and the eighth most fatal cancer in women, and patients are often diagnosed at an often advanced stage due to the lack of effective screening strategies [136]. Standard treatment for ovarian cancer includes surgery and platinum-based chemotherapy, however, late stage at diagnosis and the development of chemotherapy resistance are major causes for therapy failure [137]. The sequencing of drug-resistant cell lines indicates that the extracellular matrix (ECM) molecules were differentially expressed in drug-resistant ovarian cancer strains, suggesting a relatively clear relationship between the molecules involved in cell adhesion-mediated processes and the drug resistance of ovarian cancer [138]. The interaction between ECM molecules, such as collagen, and cell receptors activates intracellular signaling pathways like PI3K/AKT or mitogen-activated protein kinase (MAPK), leading to the activation of cytoplasmic proteins [139]. Since AKT and ERK 1/2 are substrates of PTPRK [105], the loss of PTPRK expression may result in the activation of these pathways, leading to increased gene expression and resistance to apoptosis [140]. Loss of PTPRK activity leads to higher resistance to different chemotherapy agents. Monika and co-workers found that the expression level of *PTPRK* was reduced in cisplatin, paclitaxel, doxorubicin, topotecan, vinnestine and methotrexate resistant ovarian cancer cell lines [141]. Mechanistically, the loss of PTPRK expression may be related to increased MDR1-mediated resistance, which is responsible for resistance to PAC, VIN, DOX, and TOP in the cell lines studied [141]. Another study found that in 15 drug-resistant ovarian cancer cell lines, *PTPRK* expression was downregulated, but its expression increased after piperine treatment. Re-expression of *PTPRK* in resistant cells following piperine treatment led to a reduction in cell adhesion-mediated drug resistance (CAM-DR) and resulted in tumor suppression [142].

Association between PTPRK and melanoma Melanoma is a highly malignant tumor originating from melanocytes, and cutaneous malignant melanoma ranks third among skin malignancies, accounting for approximately 6.8–20% [143]. Currently, there are no effective treatments for advanced-stage melanoma [143]. Compared to normal cells, melanoma cells exhibit increased expression of phosphorylated tyrosine residues [144], indicating potential abnormalities in the PTP family in melanoma [145]. The expression of PTP family member *PTPRK* is absent or downregulated in over 20% of melanoma cell lines. This loss may contribute to the abnormal tyrosine phosphorylation observed in melanoma [146]. Since *PTPRK* has been located on chromosome 6q22.2-3, a region commonly affected by chromosomal rearrangements in melanoma, the frequent deletion may play a significant role in tumor progression [147]. Luisa et al. discovered a novel MHC class II-restricted tumor antigen, where a mutation in *PTPRK* results in the altered presentation of an immunogenic epitope by the HLA-DRα/DRB1*1001 allele [17]. Berta Casar et al. predicted that changes in *PTPRK* expression could influence the melanoma process, especially in the case of dysregulation of RAS. The loss of *PTPRK* enhances RAS-ERK signaling pathway, which is an important driver of melanoma. Therefore, *PTPRK* acts as a RAS-driven factor in melanoma. It is worth noting that when carcinogenic RAS signals are emitted from the plasma membrane, rather than from the Golgi complex (GC), melanoma is might deteriorate [148].

Table 2 Mechanism of protein tyrosine phosphatase receptor type kappa in cancer

Cancer Type	Mechanism	Cellular/Molecular Function	Reference
Colorectal Cancer	PTPRK dephosphorylates **CD133**, inhibiting the **AKT** pathway;**PTPRK–RSPO3** fusions, activate the **WNT/β-catenin** pathway	**CD133-AKT, WNT/β-catenin**	[60, 113]
Non-Small Cell Lung Cancer	PTPRK downregulates **STAT3** phosphorylation (Tyr 705), inhibiting tumor proliferation and metastasis	**STAT3**	[123]
Prostate Cancer	PTPRK knockdown increases c-**JNK** and **caspase activation-3**,**-8**,**p53**, promoting apoptosis in cancer cells	**JNK**, **Caspase-3**, **Caspase-8**, **P53**	[127]
Nasal NK/T-Cell Lymphoma	PTPRK dephosphorylates **STAT3 (Tyr 705)**, inhibiting oncogenic signaling and inducing apoptosis	**STAT3**, **JAK3**	[51, 93, 94]
Hepatocellular carcinoma	PTPRK might dephosphorylates **STAT1/c-Fos** to activate **PPARγ**-driven metabolic reprogramming	**STAT1**, **c-Fos**	[135]
Ovarian Cancer	**Loss of PTPRK expression contributes to AKT** and **ERK1/2** pathway activation, promoting drug resistance	**AKT**, **ERK1/2**	[105]
Melanoma	**Loss of PTPRK enhances RAS-ERK** signaling, promoting tumor progression	**RAS-ERK**	[148]
Hodgkin lymphoma	Reducing **Smad2** protein levels in the **TGF-β signaling**	**Smad2**, **TGF-β**	[18]
Glioblastomas	Inhibition of cell growth and migration via suppressing **EGFR** and **β-catenin** signaling pathways	**EGFR**,**β-catenin**	[16]

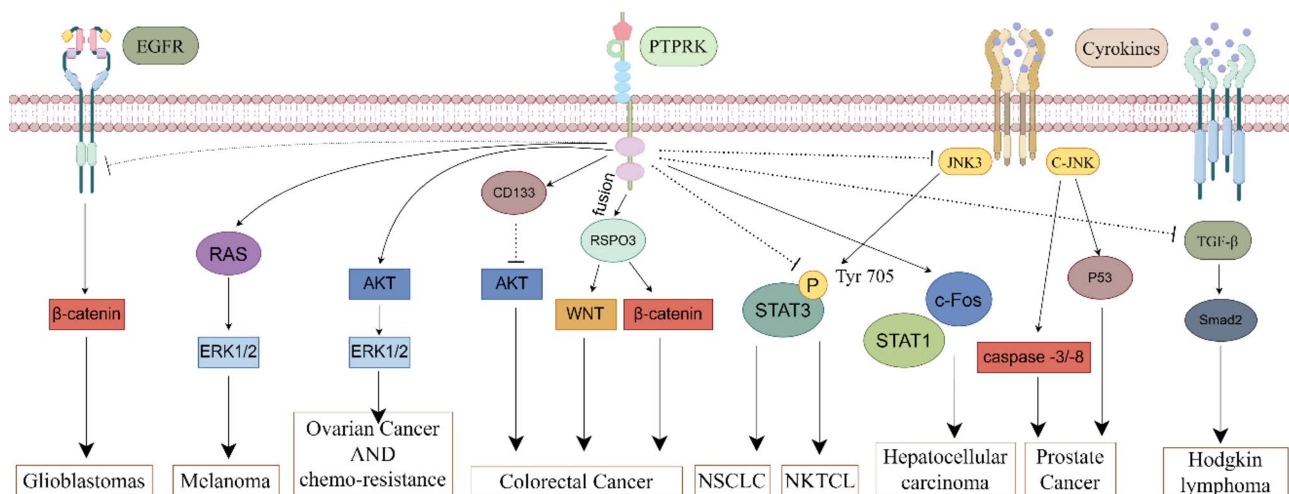


Fig. 2 PTPRK in Cancer Signaling Pathways

Association between PTPRK and glioblastomas (GBM) Globally, the incidence of glioblastomas is approximately 7 cases per 100,000 people annually, accounting for around 2% of all primary tumors. These GBM contribute to 7% of cancer-related life years lost before the age of 70 [149]. Malignant gliomas are the most common type of primary intracranial tumor. The prognosis for patients with GBM is often considered poor due to the early and widespread infiltration of tumor cells into the surrounding healthy brain tissue [150]. Malignant gliomas exhibit significant molecular distinctions in pivotal regulators of cell migration and dissemination, which contribute to their highly morphology diffuse and the difficulty in remedy [151]. Supreet Agarwal et al. was screened PTPRK might be a genomic alteration and it's an independent prognostic factor in malignant gliomas [16]. PTPRK mutations significantly alter its phosphatase activity and post-translational processing, leading to a marked reduction in phosphatase function. Subsequent studies revealed that this decreased phosphatase activity is due to changes in phosphatase domain-2 (D2), which was lacking intrinsic phosphatase activity, plays a regulatory role in controlling the enzymatic activity of phosphatase domain-1(D1). In malignant glioma cell lines (U251-MG), recombinant wild-type PTPRK inhibits cell growth and migration via suppressing EGFR and β-catenin signaling pathways, thereby enhancing the effectiveness of conventional glioma treatments. Besides, mutated PTPRK weakens its tumor-suppressive effects and alters the sensitivity of glioma cells to chemotherapy (Table 2, Fig. 2).

Discussion

The multifaceted roles of Protein Tyrosine Phosphatase Receptor Type Kappa (PTPRK) in cancer, immune regulation, and neurodegeneration underscore its biological significance, yet its functional complexity demands

nuanced interpretation. Our review has gathered *PTPRK* diverse roles in regulating cell proliferation, migration, protein phosphorylation and drug resistance across various cancers, as well as its contribution to immune regulation and neurodegeneration.

PTPRK, located on the frequently deleted chromosome 6q region, is a transmembrane tyrosine phosphatase. Structurally, PTPRK is composed of three main regions: an extracellular domain, a transmembrane region, and an intracellular catalytic domain. As the first sight of PTPRK function lies in its ability to mediate dephosphorylation of tyrosyl residues of substrate proteins, thereby mediating intracellular signaling processes including growth, differentiation, migration, and adhesion. As this review highlights, PTPRK's primary function is to mediate the dephosphorylation of key signaling molecules, serving as a counterbalance to the effects of protein tyrosine kinases (PTKs). This regulatory activity is crucial in maintaining normal cell functions and preventing abnormal cell proliferation.

Several critical signaling pathways were interacted with PTPRK dephosphorylation. For instance, the dephosphorylation of EGFR by PTPRK inhibits growth factor-mediated tumor proliferation, particularly in cancers such as colorectal and **NSCLC**. Similarly, by targeting STAT3, PTPRK prevents the persistent activation of transcription factors that can promote tumorigenesis and immune evasion. Moreover, PTPRK's ability to dephosphorylate β-catenin limits its role in cell migration and metastasis, highlighting the importance of phosphorylation regulation in maintaining cell-cell adhesion and preventing cancer cell dissemination. The balance between phosphorylation and dephosphorylation, facilitated by PTPRK, thus plays a crucial role in determining cellular outcomes. Dysregulation of this balance, loss of PTPRK could lead to enhanced oncogenic signaling and cancer progression. Consequently, restoring PTPRK function or mimicking its dephosphorylation effects may represent a promising therapeutic approach for cancers driven by aberrant phosphorylation.

PTPRK is essential for both immune cell signaling and neural development. In the immune system, it is vital for CD4 + T cell development, as seen in studies on immunodeficient rats, where loss of PTPRK consequence to deficiencies, highlighting its role in immune surveillance and potentially in immune-related cancers like **HL**. Emerging evidence suggests that PTPRK may also play a role in the nervous system, particularly in neurodevelopment and neurodegenerative diseases. While its precise function in neural cells remains less well-defined compared to its role in cancer and the immune system, studies have shown that PTPRK is involved in neurite outgrowth and synaptic transmission. Additionally, *PTPRK* has been linked to neurodegenerative diseases such as **AD**, where SNPs in the *PTPRK* have been associated with an increased risk of disease onset. This indicates that *PTPRK* could serve as a novel biomarker or therapeutic target in the treatment of neurodegenerative diseases.

Moreover, PTPRK has been implicated in modulating the response to chemotherapy. Downregulation of PTPRK activity has been linked to increased drug resistance to many chemotherapies in cancers such as ovarian and colorectal cancer. This chemoresistance is partly due to enhanced activation of survival pathways, including the AKT and WNT/β-catenin signaling cascades. Understanding this mechanism could provide our insights into improving therapeutic strategies by restoring or mimicking PTPRK's function in chemo-resistant patients.

Intriguingly, while PTPRK is widely recognized as a tumor suppressor across multiple malignancies, emerging evidence reveals its functional complexity in prostate cancer. Paradoxically, studies in this context have demonstrated that PTPRK may exhibit oncogenic properties by promoting tumor proliferation. This mechanistic dichotomy strongly supports the existence of context-dependent regulatory mechanisms, likely mediated through tumor microenvironment (TME) interactions or tissue-specific genetic alterations.

While the therapeutic targeting of PTPRK direct translation into therapeutic strategies remains challenging due to its shallow catalytic pocket and conserved active-site architecture [152], insights from druggable PTPs family members might give us actionable frameworks. For example, the development of allosteric inhibitors (e.g., SHP099 for SHP2 [153]) and compounds disrupting oligomerization interfaces (e.g., Cmpd-43 for PRL phosphatases [154]) demonstrates that bypassing catalytic domains can circumvent selectivity barriers. These strategies highlight the potential to exploit unique structural features of individual PTPs [155, 156], such as autoinhibitory conformations or non-catalytic regulatory regions, rather than competing with endogenous substrates at conserved active sites.

For PTPRK, analogous approaches could focus on its extracellular domains or disease-associated dimerization interfaces, which may offer context-specific vulnerabilities. Structural studies of PTPRK in complex with binding partners or pathogenic mutants could reveal druggable pockets analogous to those exploited in SHP2 or PTP1B inhibition. Furthermore, covalent inhibitors targeting redox-sensitive cysteines near catalytic sites, as explored in PTP1B [157], might overcome kinetic challenges posed by PTPRK's high enzymatic activity.

PTPRK's functional duality provokes critical inquiry: Does its tissue-specific tumor-suppressive versus oncogenic switching arise from microenvironmental matrix or cancer-type-dependent substrate selectivity? Specifically, could divergent phosphorylation landscapes across

malignancies – shaped by post-translational modifications or isoform expression – redirect PTPRK's enzymatic activity toward distinct signaling nodes, thereby generating phenotypically opposed outcomes? Perhaps soon, more attention will decrypt the signal mechanism and therapeutic potential of PTPRK. Targeting PTPRK, either by enhancing its activity as a tumor suppressor in tumors or by inhibiting its function to promote tumorigenesis, may provide new avenues for cancer therapy.

Supplementary Information

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Supplementary Material 1

Author contributions

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Data availability

The data sets supporting the conclusions of this article are included within this article and all drawings are from FIGDRAW.com. Manuscript is available on the main electronic data storage system the School of Basic Medical Sciences of Wenzhou Medical University and access can be provided upon request to the authors.

Declarations

Consent for publication

None.

Abbreviations

Supplementary S1 for details.

Competing interests

The authors state that they have no competing interests.

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