



REVIEW ARTICLE

Regulation mechanism and pathogenic role of lncRNA plasmacytoma variant translocation 1 (*PVT1*) in human diseases

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Abstract Plasmacytoma variant translocation 1 (*PVT1*) is a long non-coding RNA (lncRNA) gene identified as a recurrent breakpoint of Burkitt's lymphomas. Human *PVT1* gene is located on region 8q24.21, a well-known cancer risk region, and encodes at least 26 linear ncRNA isoforms and 26 circular RNA isoforms, as well as 6 microRNAs. Several *PVT1* functioning models have been reported recently such as competing endogenous RNA (ceRNA) activity and regulating protein stability of oncogenes, especially MYC oncogene. The promoter of *PVT1* gene is a boundary element of tumor-suppressor DNA. CircPVT1 derived from *PVT1* gene is also a critical non-coding oncogenic RNA. Although substantial advancements have been made in understanding the roles of *PVT1* in cancer recently, the detailed mechanisms underlying its functions remain unclear. Herein, we summarize the recent progressions on the mechanisms underlying *PVT1* regulated gene expression at different levels. We also discuss the interaction between lncRNA and protein, RNA and DNA, as well as the potential cancer therapy strategy by targeting these networks.

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Introduction

Long non-coding RNAs (lncRNAs), the RNAs containing more than 200 nucleotides while lacking extended open reading frames, are involved in the regulation of cell survival, proliferation, metabolism, differentiation, as well as other functions.¹ With the development of genome-wide sequencing technology, hundreds of types of functional lncRNAs have been identified, and their biological functions have been elucidated. A variety of lncRNAs exist throughout the genome.² lncRNAs exhibit a significant temporal and spatial specificity during histological development and differentiation. During the differentiation process, different splicing manners and/or dynamic expression may happen. Numerous lncRNAs have been demonstrated to function in tumorigenesis and organ development,³ and many of them can regulate carcinogenesis through impacting the oncogenes and/or tumor suppressing genes.⁴

Accumulating evidence highlights that *PVT1* is a critical gene expression regulator in differentiation, development, heart diseases and cancers. Previous studies have revealed that *PVT1* plays critical roles in the generation, growth, and metastasis of human cancers, and it is frequently upregulated in various cancers including lung, pancreas, colorectal, breast, gastric, and cervical cancer.⁵ Therefore, *PVT1* is a potential diagnostic and therapeutic biomarker for some cancers. Studies have identified specific regulatory functions and mechanisms of *PVT1* in a series of crucial biological processes, including cell survival, differentiation, proliferation, and chromatin. Via crosstalk with other RNA species and/or through different chromatin-based mechanisms, *PVT1* participates in remodeling of chromatin, and regulation of transcriptional and/or post-transcriptional events. *PVT1* can function as scaffolds, decoys, guides, or enhancer RNA.⁶

As supported by increasing evidence, *PVT1* may have competing endogenous RNA (ceRNA) activity.⁷ Moreover, *PVT1* gene promoter may compete with protein coding gene promoter. Cho et al reported that the promoter of *PVT1* gene can inhibit the *MYC* gene expression by competing with the *MYC* promoter.⁸ More and more studies have demonstrated that *PVT1* can bind to DNAs, mRNAs, microRNAs (miRNAs), and/or proteins, thereby regulating a variety of cellular processes. This review summarizes the characteristics of *PVT1*, including their biological functions and the related mechanisms, which was the most comprehensive to date.

lncRNA *PVT1*

PVT1 is encoded by a gene that resides in a cancer-associated region: a long arm of mouse chromosome 15 (qD1) and human chromosome 8 (8q24). In 1992, for the first time, Huppi K et al⁵ found *PVT1* transcripts accompanies chromosomal translocation and amplification in murine lymphocytic-B neoplasms. The *PVT1* gene locus was determined as a cluster of T(8;22) and T(2;8) variant *MYC*-activating chromosomal translocation breakpoints, localized 400 kb downstream of *MYC*.⁵ Human *PVT1* genomic locus is localized

54 kb downstream of proto-oncogene *MYC*⁶ (Fig. 1). These two genes have some interactions, including feedback regulation, and they synergistically drive tumorigenesis as the oncogenic function of *MYC* relies on the expression of *PVT1*.^{9,10} The *PVT1* locus contains at least 12 exons, which gives rise to multiple alternatively spliced non-protein coding transcripts, and encodes at least 52 ncRNA variants with oncogenic functions, including 26 circular and 26 linear RNA isoforms and 6 miRNAs: miR-1208, miR-1207-5p, miR-1207-3p, miR-1205, and miR-1204⁷ (Fig. 1). Recent studies have identified several functioning models of *PVT1*, such as protein stability regulation for important oncogenes especially *MYC* oncogene and competing endogenous RNA activity.

Alternative splicing from one primary transcript to generate multiple protein isoforms represents a major proteomic diversity driver in human cells.¹¹ *PVT1* is a lncRNA with multiple alternatively spliced transcripts polyadenylated at 3' end and capped at 5' end.^{7,12} *PVT1* isoforms exhibit significantly different expression manners across different human tissues: heart and adrenal gland have the highest expression levels, while white blood cells and lymph nodes have the lowest expression levels.⁷ *PVT1* has been shown to play crucial roles in cancers as well as other diseases. Different *PVT1* exons could be expressed differentially and might have different functions. Ilboudo A et al found that the expression manners of most *PVT1* exons are consistent in prostate cancer (PCa). More specifically, *PVT1* exon 9 was consistently overexpressed in the aggressive PCa cell lines compared to their non-tumorigenic mother cell lines. Among all the 12 *PVT1* exons, *PVT1* exon 9 was the only one exhibiting a very consistent expression, suggesting that the overexpression of *PVT1* exon 9 is closely correlated with the aggressiveness in this PCa model.^{13,14} Pal G et al utilized data from 1000 genomes to analyze the *PVT1* locus and found there was a significant difference in chromosomal region spanning *PVT1* exons 4A and 4B between African and non-African populations, and the gene expression of *PVT1* exons 4A and 4B was dramatically enhanced in PCa tissues compared to benign prostatic hyperplasia and normal prostate tissues. These results suggest that *PVT1* exons 4A and 4B might have clinical implications in PCa.¹⁵ A novel splicing variant transcript of *PVT1* lacking exon 4 (*PVT1*^{ΔE4}) has also been reported in clear cell renal cell carcinoma (ccRcc), which has a higher endogenous expression level than full-length transcript but can similarly enhance cell invasion and proliferation as full-length transcript does. In addition, study showed that *SRSF1* decreased the inclusion of full-length transcript exon 4 while enhanced the expression of *PVT1*^{ΔE4} in ccRcc.¹⁶ Mfossa A et al investigated the expression patterns of possible circRNA variants for numerous genes including *PVT1* in mouse utero and primary cortical neurons and found three (circ-0005724, circ-0005721 and circ-0000604) among five circular transcripts were significantly amplified. Two circular variants (circ-0005724 and circ-0000604) were more stable than the linear cognates in primary cortical neurons. Moreover, the circular and linear transcripts were highly enriched in brain and liver, respectively, and the expression of *PVT1* transcripts elevated during the development of embryonic brain.¹⁷

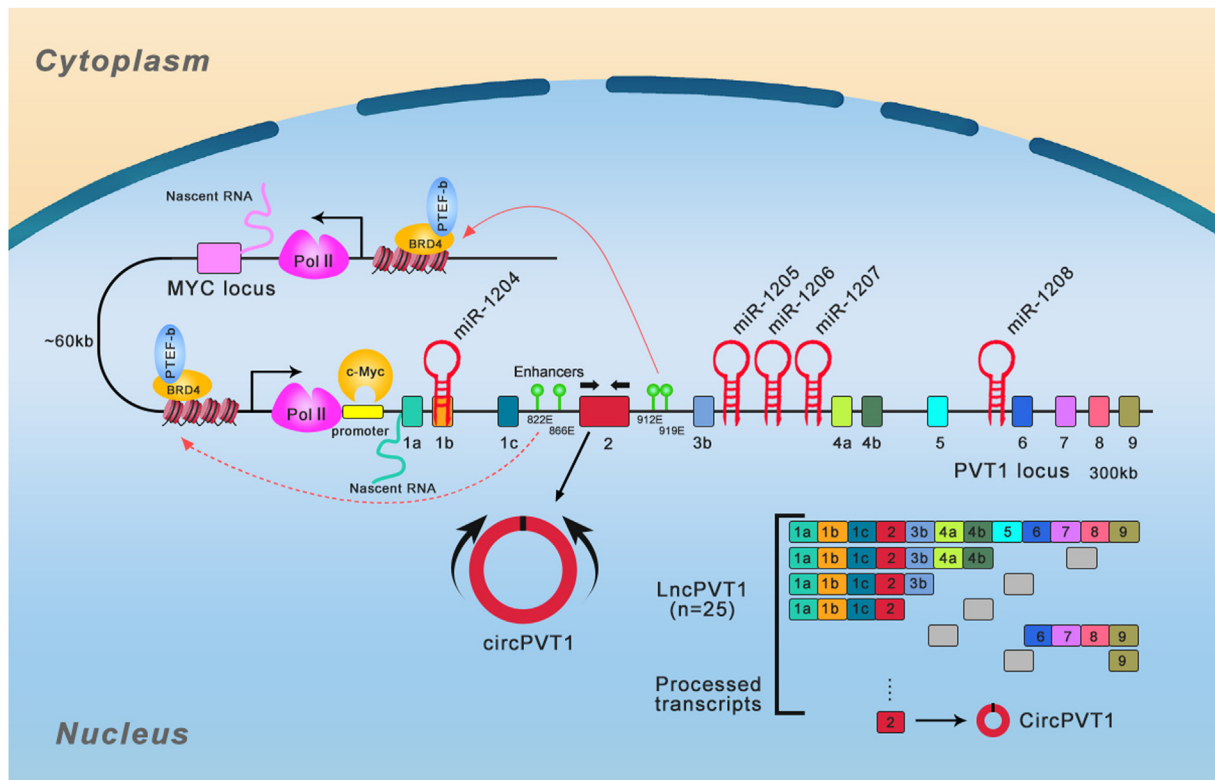


Figure 1 Schematic view of human *PVT1* gene locus and alternative splicing. *PVT1* located in the region of 8q24.21 harboring *MYC/PVT1* loci and *PVT1*-encoded five miRNAs and probable mode of biogenesis of circPVT1. The positive feedback and promoter-enhancer competition between *PVT1* and *MYC* were shown. The rectangles represent the exons.

The role of *PVT1* in pretranscription regulation

PVT1 influences all the stages of gene life cycle—from chromatin remodeling and epigenetic regulation to transcriptional and posttranscriptional control to protein metabolism (Fig. 2).

PVT1 can act as a fusion partner

With the development of sequencing technologies, a total of 98 different *PVT1* fusion transcripts have been identified in both solid tumors and hematological malignancies, which arise from rearrangements of the 8q24 chromosomal region and induce abnormalities of this region.¹⁸ The roles of lncRNA gene fusions in joining two protein-coding genes have not been sufficiently investigated. *PVT1* is a well-known fusion partner, and *PVT1* fusion transcripts are powerful driver in cancers. Most *PVT1* fusions are characterized by amplification of genomic locus (8q24.21).¹⁸ Analysis of Reactome pathways reveals that some *PVT1* fusion partners converge in carcinogenic events, like NOTCH1 signaling, TP53 regulation, AP transcription factor family activity, and UB-specific processing proteases.¹⁹

The *PVT1-MYC/MYC-PVT1* fusion was fully studied in cancers. *PVT1* fusion genes were first described when *PVT1* displaced intron 1 and exon 1 in colorectal adenocarcinoma, which resulted in rearrangement of DNA.²⁰ Later, two different *PVT1-MYC* fusions were identified, both of which involved *PVT1* the 5' end (with exon 1 or exon 1 and 3) fused to *MYC* (exons 2 and 3).²¹ *PVT1-MYC* fusion is

present in 0.18% of Genomics Evidence Neoplasia Information Exchange (GENIE) cases in American Association for Cancer Research (AACR) projects with breast invasive ductal carcinoma, endometrial endometrioid adenocarcinoma, Burkitt lymphoma, diffuse large B-cell lymphoma, and colon adenocarcinoma, not otherwise specified having the greatest prevalence.²² In a multiple myeloma study, two highly expressed chimeric genes, *PVT1-WWOX* harboring der(16)t(16;22)ins(16;8) (q23;q24) and *PVT1-NBEA* harboring t(8;13) (q24;q13), were identified. The *PVT1-WWOX* in which *PVT1* exon 1 was fused to *WWOX* exon 9 and *PVT1-NBEA* chimera in which *PVT1* exon 1 was fused to *NBEA* exon 2 were correlated with the high expression of abnormal *WWOX* and *NBEA*, respectively. Both *WWOX* and *NBEA* are tumor suppressors in multiple myeloma.²³ In a study on acute myelogenous leukemia, the genomic junctions of *PVT1-NSMCE2* were found to be located within intron 1 of *PVT1* and in a region upstream of exon 1 of *NSMCE2*, and *PVT1-NSMCE2* was also accompanied by amplification of 8q24. *NSMCE2* rearrangement can induce chromosomal breakage and loss.²⁴ *PVT1-NDRG1*, a highly recurrent fusion gene in which *PVT1* exon 1 is fused to the 3' end of *NDRG1*, has been identified in medulloblastoma,²¹ breast cancer²⁵ and hepatocellular carcinoma.²⁶ However, the functions of *PVT1-NDRG1* need to be further elucidated. *EVI1* is a proto-oncogene associated with human myeloid leukemia. The aberrant expression of *EVI1* in acute myeloid leukemia (AML) is correlated with the t (3;8) (q26;q24). Further study showed that the breakpoints in t

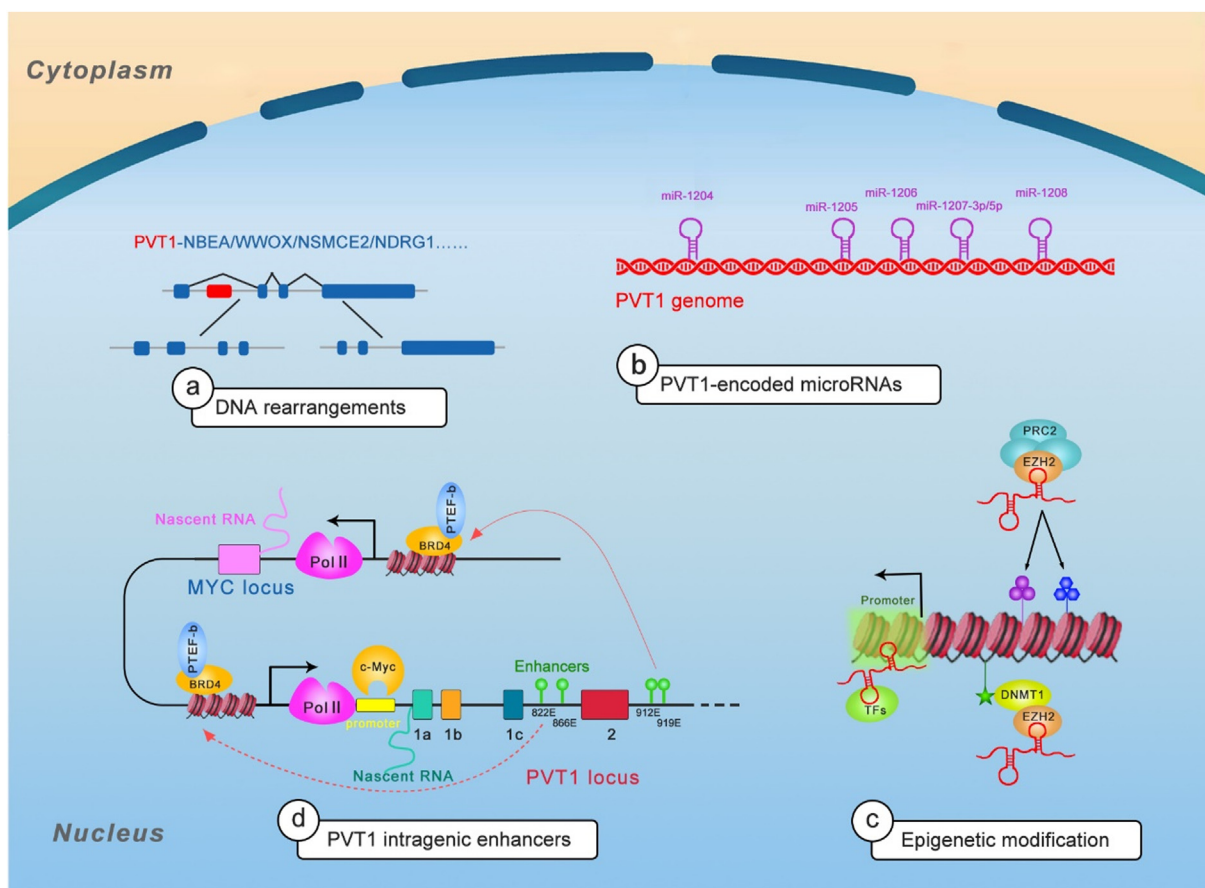


Figure 2 The mechanisms of *PVT1* in pretranscription regulation. **a** Listed are a few examples of *PVT1* gene rearrangements and fusion transcripts. **b** Listed are five *PVT1*-encoded miRNAs. **c** showed the mechanisms of *PVT1* in epigenetic modification. **d** showed schematic representing the model of promoter-enhancer competition between *PVT1* and *MYC*. *PVT1* promoter regulates *MYC* expression in *cis* manner.

(3;8) (q26;q24) are located at *EV11/MDS1* on chromosome 3 and distal to *PVT1* on chromosome 8, and this rearrangement can induce aberrant expression of *EV11*, thus increasing tumorigenesis.²⁷ Notably, all of these fusion genes contain *PVT1* exon 1. Using whole transcriptome analysis, Kim et al identified six different inter-chromosomal fusion genes (*PVT1-PPAPDC1A*, *PVT1-ATE1*, *PVT1-APIP*, *PDHX-PVT1*, and *PVT1-PDHX*) in human gastric cancer²⁸; two variants were identified for *PVT1/PDHX*, with *PVT1* exon 1 being fused to *PDHX* exon 9 or 2, and two *PVT1/APIP* variants were identified with *PVT1* exon 1 being fused to *APIP* exon 2 or 6. All the identified fusions involved *PVT1* exon 1 except *PDHX/PVT1*, where *PDHX* exon 3 is fused to *PVT1* exon 4. The *PVT1* fusion partners *APIP* and *ATE1* were found to be amplified, indicative of important role for *PVT1* in DNA rearrangement.

These studies suggest that *PVT1* exon 1 is frequently involved in DNA rearrangement, and *PVT1* can thereby act as a fusion partner in cancers, impact regulation of oncogenes and tumor suppressors, and promote tumorigenesis.

***PVT1* can encode miRNAs**

Increasing evidence has shown that the miRNAs residing in *PVT1* locus are the key driver for the oncogenic roles of *PVT1*. Reports have shown that miRNAs can act as tumor

suppressors or oncogenes due to their frequent deregulation in cancers. Critically, miRNAs can be applied as cancer therapeutic targets or for cancer phenotype evaluation. As mentioned above, *PVT1* encodes a series of non-coding RNAs, including a group of six annotated miRNAs: miR-1208, miR-1207-3p, miR-1207-5p, miR-1206, miR-1205, and miR-1204.^{5,29}

Residing in *PVT1* exon (1b), *mir-1204* is fused to the light chain of immunoglobulin in a subset of Burkitt's lymphoma and highly present in tumors with amplified *PVT1-MYC* fusion.⁵ The miR-1204 expression level is higher in *PVT1-MYC* fusion-positive than in -negative medulloblastomas, which has a correlation with malignant phenotypes.²¹ Studies showed that P53 can induce the expression of the *PVT1* locus, thereby activating miR-1204 transcription. Reversely, ectopic expression of miR-1204 can enhance P53 level and induce cell death, indicative of a positive feedback loop between them.^{30,31} *Mir-1205*, which is encoded on the *PVT1* intron 3 locus, can increase growth of castration-resistant PCa by targeting Egl-9 family hypoxia inducible factor 3 (EGLN3)³² and fry-like (FRYL).³³

PVT1 has been demonstrated to have a positively correlated expression pattern with its encoded miRNAs. However, paradoxical conclusions were reported between *mir-1207* pair and *PVT1*. Takahashi Y et al showed that

different from other *PVT1* encoded miRNAs, miR-1207-5p is the only miRNA inhibited by *PVT1*. MiR-1207-5p can decrease CASP9 and suppress apoptosis in colorectal cancer.³⁴ Cui M et al demonstrated that *PVT1* could strengthen cancer stem cell-like properties in nasopharyngeal carcinoma (NPC) through activating PI3K/AKT signal pathway and inhibiting miR-1207.³⁵ Das DK et al found that miR-1207-3p, but not miR-1207-5p, is remarkably down-regulated in PCa and promotes tumorigenesis by targeting fibronectin type III domain containing 1 (FNDC1).³⁶ Moreover, Yan C et al demonstrated that miR-1207-5p and *PVT1* were consistently induced by estrogen and promote breast cancer tumorigenesis by targeting *STAT6*.³⁷ You L et al showed that gemcitabine increased the miR-1207 pair (miR-1207-3p and miR-1207-5p) and decreased *PVT1* levels through upregulating microprocessor complex subunit DGCR8 and ribonuclease III Droscha and targeting *RhoA* (by miR-1207-3p) and *SRC* (by miR-1207-5p).³⁸ Alvarez ML et al showed that miR-1207-5p up-regulation induced by TGF β 1 and glucose is independent of *PVT1*. Similar with *PVT1*, miR-1207-5p upregulates FN1, PAI-1, and TGF- β 1 independent of host gene in diabetic nephropathy.¹² The functions of miR-1206 and miR-1208 associated with *PVT1* have not been reported yet. However, circ*PVT1* knockdown enhances radiosensitivity in NSCLC by sponging miR-1208.³⁹ The functions of *PVT1*-encoded miRNAs have not been elucidated sufficiently, and further studies are required

and may provide novel insights into the *PVT1* functions (Fig. 2B).

PVT1 can act as an epigenetic modulator

A hallmark function of *PVT1* is its ability to interact with histone-modifying complexes, mediating epigenetic regulation (Fig. 3). Studies showed that *PVT1* can act at chromatin level as signal, guide, or scaffold to modulate gene expression. Enhancer of zeste homolog 2 (EZH2) is an enzymatic subunit and histone methyltransferase of polycomb repressive complex 2 (PRC2), which is an epigenetic multiprotein complex and plays critical roles in the progression of cancers and other diseases. Histone methyltransferase enhancer of EZH2 is responsible to catalyze mono-, di-, and tri-methylate lysine 27 of histone H3 (H3K27me1/2/3) and induces silencing of the involved genes.⁴⁰

Epigenetic modification complex PRC2 was found to communicate with *PVT1*. *PVT1* combines with EZH2 and recruits EZH2 to anti-tumor gene promoter regions, then enhances histone H3K27 trimethylation and decreases gene transcription levels.⁴¹ *PVT1* increases proliferation of gastric cancer cells through silencing *p15^{INK4a}* and *p16^{INK4b}* by the occupancy of EZH2, which is recruited by *PVT1*.⁴¹ Similarly, *PVT1* binds EZH2, and down-regulates *P57* expression, and changes the biology of ovarian cancer cells.⁴² *PVT1* can regulate histone methylation of angiopoietin-like 4

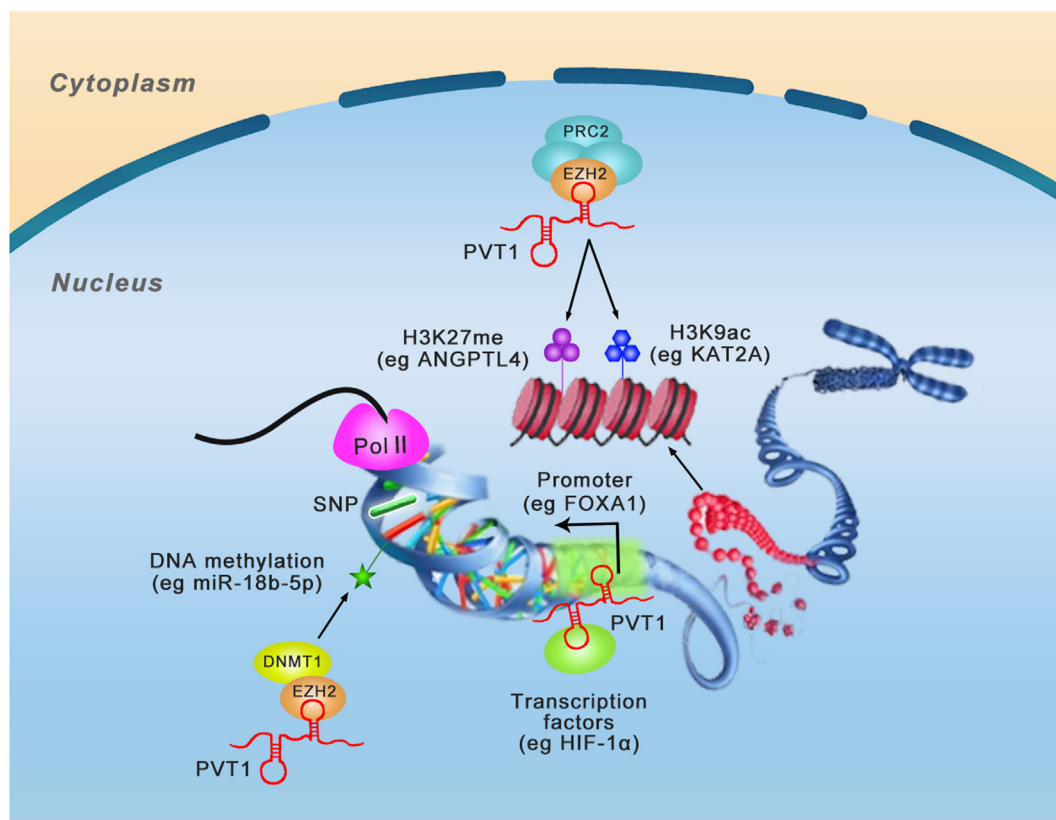


Figure 3 The mechanisms of *PVT1* in epigenetic modification. *PVT1* can act as scaffold binds to chromatin and epigenetic modifier, guide the epigenetic modifier to gene promoter. *PVT1* can facilitate enhancer and promoter element interactions, critical for gene activation. Listed are a few examples of *PVT1* regulation from epigenetic regulation and chromatin remodeling to transcriptional control.

(ANGPTL4), thereby promoting cholangiocarcinoma (CCA) oncogenesis and development by binding to PRC2.⁴³ Similar mechanism targeting protein ANGPTL4 was also reported in preeclampsia patients.⁴⁴ Similarly, *PVT1* can also down-regulate large tumor suppressor kinase 2 (LATS2) in non-small cell lung cancer (NSCLC) through methylation of the *LATS2* promoter and recruitment of EZH2.⁴⁵

PVT1 suppresses cell apoptosis and enhances cell proliferation by stabilizing expression of murine double minute 2 (MDM2), suppressing expression of *P53* and recruiting EZH2 in hepatocellular carcinoma (HCC).⁴⁶ *PVT1* regulates proliferation of thyroid cancer cells by modulating thyroid-stimulating hormone receptor (TSHR) and recruiting EZH2.⁴⁷ *PVT1* can also recruit EZH2 to the *mir-200b* promoter and inhibit its expression via increasing the trimethylation level of its histone H3K27. The cell proliferation and migration promoting effects of *PVT1* in cervical cancer relies on the silencing of miR-200b.⁴⁸ *PVT1* can also regulate miR-195 through promoting the methylation of H3K27me3 in the promoter region via recruiting EZH2.⁴⁹ A study on diabetic nephropathy (DN) patients revealed that substantial C-phosphate-G (CpG) island sites are localized at the promoter region of forkhead box A1 (FOXA1), where *PVT1* recruits EZH2 to accumulate H3K27me3, thereby suppressing the level of *FOXA1*. Reversely, the silencing of *PVT1* attenuated the damage and suppressed apoptosis of podocytes in DN through increasing *FOXA1*.⁵⁰ Apart from regulating the methylation of H3K27, Wang et al⁵¹ found that *PVT1* can act as a scaffold for KAT2A, a chromatin modification factor, induce acetylation of H3K9, recruiting TIF1 β to activate the transcription of *NF90*, thereby activating the *KAT2A* acetyltransferase, stabilizing HIF-1 α , and enhancing malignant phenotype in NPC. Notably, different from inhibiting target genes, *PVT1* can also bind to EZH2 and inhibit its recruitment to *MYC* promoter, thereby enhancing the expression of *MYC* by altering the status of H3K37me3 in hepatitis B virus-positive liver cancer.⁵²

DNA methylation as an epigenetic mechanism is also involved in the function of *PVT1*. *PVT1* can recruit DNA methyltransferase 1 (DNMT1) to the *mir-18b-5p* promoter through EZH2 and suppress miR-18b-5p transcription via DNA methylation. Moreover, *PVT1* can regulate proliferation of gallbladder cancer (GBC) cells via HIF-1 α .⁵³ *PVT1* also induces expression of miR-146a in prostate cancer by promoting DNA methylation of CpG island in its promoter. The functions of *PVT1* in prostate cancer tumorigenesis relies on miR-146a, and overexpression of miR-146a can eliminate the effects of *PVT1* knockdown.⁵⁴ In addition, it is worth mentioning that *PVT1* itself is regulated by DNA methylation.^{55,56}

The role of *PVT1* in transcription regulation

The transcription stages include initiation, elongation, and termination. Transcription initiates from binding of RNA polymerase II (RNA Pol II) to a gene's promoter region supported by general transcription factors (TFs), and other TFs accelerate transcription by binding to enhancer region. When the polymerase meets the terminator, the transcription is terminated. *PVT1* can affect gene expression through direct binding to TFs and impacting binding of

polymerase to promoter. Liu SJ et al conducted a CRISPR interference (CRISPRi)-based genome-scale identification with an sgRNA library along the *PVT1* locus in ENCODE (ENCyclopedia of DNA Elements Project) cancer cell lines. The sgRNAs outside of 1 kb window around the TSSs had no effect on the transcription of major *PVT1* isoform, suggesting the observed pro-growth phenotype is mediated by transcriptional interference.⁵⁷ Pyfrom SC et al performed a novel computational method PLAIDOH to calculate the transcript *cis*-regulatory predictive scores of cancer-specific lncRNAs and found that *PVT1* has a dramatical high enhancer *cis*-regulatory score,⁵⁸ which was validated to suppress *MYC* in *cis* via promoter competing for common intragenic enhancer elements.⁸ These results suggest that *PVT1* promoter has a *PVT1* gene independent tumor suppressing function. The regulation of *MYC* in *cis* by *PVT1* locus might be attributed to the *MYC* gene body that functions independently of the transcribed RNA, or DNA within *PVT1* promoter or sequence-specific functions of mature *PVT1* transcript. Guo L et al found a strong enrichment of RNA Pol II at the place where the *MYC* promoter interacts with the BET inhibitor (BETi) resistance-specific *PVT1* enhancer in leukemia cells, raising the possibility that combination therapy may block the loading of RNA Pol II at this place. CDK7 inhibitor can block loading of RNA Pol II at *PVT1* enhancer, thereby inhibiting *MYC* transcription, thereby exerting a synergistic effect on BETi-resistant leukemia.⁵⁹ Moreover, our previous work demonstrated that *PVT1* can bind to the *HIF-1 α* promoter and induce the transcription, thereby driving progression of pancreatic cancer (PC), indicating that *PVT1* can regulate unlinked gene expression through with enhancers and/or promoters.⁶⁰ However, the mechanisms underlying the functions of *PVT1* in elongation and termination processes require further research.

The role of *PVT1* in posttranscription regulation

Following transcription, a variety of RNA-binding proteins (RBPs) regulate the pre-mRNAs, including capping, polyadenylating, splicing, editing, and transferring them from nucleus to cytoplasm. The mRNA stability is very important for translation. *PVT1* plays critical roles in mRNA splicing, stability, and translation, and it can also indirectly regulate mRNA expression by competing endogenous RNA or acting as a miRNA sponge (Fig. 4).

PVT1 can enhance the mRNA and protein stability

Modulation of mRNA degradation is a control step in gene expression for regulation of protein synthesis, and the combination between *PVT1* and *MYC* has been well studied. As a tumorigenesis driver, *MYC* regulates a large number of genes involved in multiple oncogenic processes. *PVT1* promotes *MYC* stability via protecting it against proteasome-dependent degradation and decreasing its phosphorylation at threonine 58 (Thr58).^{9,20} Not only in cancers, in skeletal muscle cells, during muscle atrophy, *PVT1* also interacts with *MYC*, and the up-regulated *PVT1* blocks the phosphorylation and degradation of *MYC*.⁶¹ Notably, m⁶A modification of *PVT1* transcripts enhances its interaction with *MYC* and stabilizes the *MYC* protein in epidermal progenitor

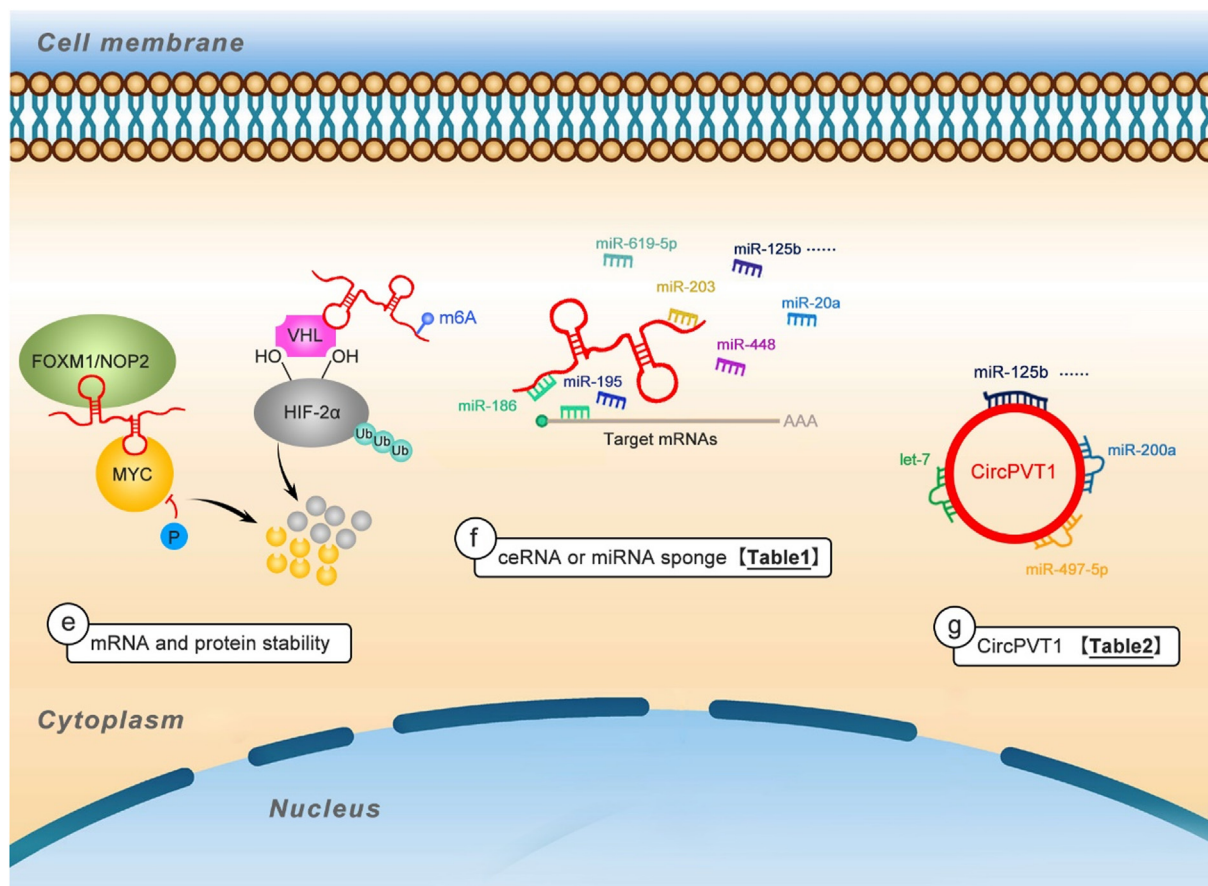


Figure 4 The mechanisms of *PVT1* in posttranscription regulation. **e** listed *PVT1* can interact with proteins and/or mRNAs to form RNP complexes, or act as scaffold for two or more proteins, thus stabilizing and protecting mRNAs from degradation, which regulate posttranscriptional gene regulation. **f** listed *PVT1* acting as miRNA sponges attenuates the miRNA' effect on down-regulating mRNA expression (Table 1). **g** listed Circ*PVT1* acting as molecular sponges for miRNAs (Table 2).

cells.⁶² Besides *PVT1*-MYC pair, the positive feedback loop between *PVT1* and other TFs has also been reported in a variety of tumors. *PVT1* can block protein degeneration and ubiquitination via direct binding to proteins. For example, *PVT1* directly binds to FOXM1 and stabilizes FOXM1, thereby enhancing gastric cancer cell proliferation and invasion.⁶³ *PVT1* binds to the VHL region of HIF-1 α ⁶⁰ and HIF-2 α ⁶⁴ proteins and enhances their stability by blocking ubiquitination-dependent degradation in PC and ccRcc, respectively. In turn, these TFs can also bind to the enhancer of *PVT1* to transactivate its expression.^{60,63,64} Wang F et al found that *PVT1* can bind to NOP2 and enhance the stability of NOP2; moreover, *PVT1* functions depending on the presence of NOP2 in hepatocellular carcinoma.⁶⁵

PVT1 can act as miRNA sponges

Competing endogenous RNAs (ceRNAs), also called miRNA decoys or miRNA sponges, have been identified as drivers in many diseases, especially cancers. The ceRNAs encompass different RNAs (lncRNAs, circRNAs, or pseudogenes) competing with each other to attract miRNAs. *PVT1* can act as a miRNA sponge to suppress miRNAs binding to their mRNA targets, thereby promoting the stability of the target mRNAs, and regulating protein expression. Table 1 and

Table S1 list the related diseases and miRNAs sponged by *PVT1*.

First, the researchers analyzed their concerned disease-related lncRNAs by microarray analysis or in the public databases TCGA or GEO and determined the research target *PVT1*. Then, the structure and function of *PVT1* were analyzed, and the expression pattern of *PVT1* in cells as well as the correlation between *PVT1* levels and clinical prognosis was investigated. The results showed that *PVT1* was closely related to the concerned disease (often up-regulated in cancers or other diseases). *PVT1* was identified as an oncogenic lncRNA that could act as a prognostic or prognostic biomarker in cancers. Furthermore, gain- and loss-of-function assays revealed that *PVT1* could enhance proliferation, migration, and invasion of cancer cells, inhibit apoptosis, promote tumor growth and angiogenesis of tumor tissues in mice, and impair sensitivity to antineoplastic drugs *in vitro* and *in vivo*, suggesting that *PVT1* affects the progression of cancer. Finally, subcellular localization was conducted for subsequent analysis from the perspective of ceRNA.

After the target lncRNA-*PVT1* was identified, the miRNA docking site of *PVT1* was predicted with RegRNA, miRDB, miRWalk, miRBase, miRPathDB, miRanda, TargetScan, or

Table 1 Related diseases and miRNAs sponged by *PVT1*.

Related diseases	miRNAs	Target genes or signaling pathways	Function	References
Acute kidney injury (AKI)	miR-20a-5p	<i>NLRP3</i>	Modulate NLRP3-mediated pyroptosis	66
Atrial fibrillation	miR-145-5p	<i>IL-16</i>	Boost the extracellular matrix remodeling of atrial fibroblasts	67
Bladder cancer	miR-194-5p	<i>BCLAF1</i>	Increase malignant phenotypes	68
Cardiac hypertrophy	miR-196b	<i>OSMR</i>	Knockdown attenuates the myocardial hypertrophy	69
Cardiotoxicity	miR-187-3p	<i>AGO1</i>	Aggravate doxorubicin-induced cardiomyocyte apoptosis	70
Cervical cancer	miR-140-5p	<i>SMAD3</i>	Promote the proliferation and metastasis	71
Clear cell renal cell carcinoma (ccRcc)	miR-328-3p	<i>FAM193B</i>	Promote the proliferation of ccRCC cells	72
Diabetic cataract (DC)	miR-214-3p	<i>MMP2</i> , regulated by SP1	Modulate the proliferation and apoptosis of lens epithelial cells	73
Diabetic nephropathy (DN)	miR-23b-3p	<i>WT1</i>	Knockdown alleviates high glucose-induced proliferation and fibrosis in human mesangial cells	74
Diabetic osteoarthritis (DOA)	miR-146a	TGF- β /SMAD4 pathway	Promote cartilage degradation	75
Esophageal squamous cell carcinoma (ESCC)	miR-203	<i>LASP1</i>	Promote ESCC progression	76
Gallbladder cancer (GBC)	miR-143	<i>HK2</i>	Knockdown inhibits cell proliferation, migration, and invasion	77
Gastric cancer	miR-186	<i>HIF-1α</i>	promoted the GC cell proliferation and invasion	78
Glioma	miR-128-3p	GREM1 and BMP Signaling Pathway	Promote tumorigenesis and progression	79
Ischemic stroke	miR-24-3p	<i>STAT3</i> , regulated by SOX2	Depleting improves ischemic stroke	80
Myocardial ischemia/reperfusion (I/R) injury	miR-186	<i>Beclin-1</i>	Knockdown protects cardiomyocytes apoptosis and autophagy	81
Neuropathic pain	miR-186-5p	<i>CXCL13/CXCR5</i>	Depletion alleviates neuropathic pain, astrocytic activation and reduced the expression of neuroinflammatory factors and proteins	82
Non-small cell lung cancer (NSCLC)	miR-200a and miR-200b	<i>MMP9</i>	Promote the invasive ability of NSCLC cells	83
Osteoarthritis (OA)	miR-27b-3p	<i>TRAF3</i>	Inhibit IL-1 β -induced injury in chondrocytes	84
Osteosarcoma (OS)	miR-497	<i>HK2</i>	Contribute to OS cell glucose metabolism, cell proliferation, and motility	85
Papillary thyroid carcinoma (PTC)	miR-30a	<i>IGF1R</i>	Enhance the viability and invasion	86
PM2.5-exposed lung cancer	miR-199a-5p	<i>Caveolin 1</i>	Affect the role of lentinan in PM2.5-exposed lung cancer cells	87
Pulpitis	miR-455-5p	<i>SOCS3</i> and <i>PLXNC1</i>	Involve in the pathogenesis of pulpitis	88
Retinoblastoma (RB)	miR-488-3p	<i>NOTCH2</i>	Silencing inhibits cell proliferation, migration, invasion, and cell cycle progression and induces cell apoptosis	89
Rheumatoid arthritis (RA)	miR-543	<i>SCUBE2</i>	Regulate apoptosis of fibroblast-like synoviocytes	90
RSV-infected asthma	miR-203a	<i>E2F3</i>	Involve in the mechanism of α -asarone in treating RSV-induced	91

Table 1 (continued)

Related diseases	miRNAs	Target genes or signaling pathways	Function	References
Temporomandibular joint osteoarthritis (TMJ OA)	miR-211-3p	<i>TNF-α</i>	asthma Induce chondrocyte apoptosis	92

starBase bioinformatics data resources.^{93,94} Then, the sequence and function of target miRNA were analyzed, and the expression pattern of miRNA in cells as well as the correlation between *PVT1* levels and clinical prognosis was investigated. To confirm the ceRNA relationship between *PVT1* and the targeted miRNA, *PVT1* was silenced/overexpressed *in vitro* and *in vivo*, followed by analysis using luciferase assay and RNA immunoprecipitation (RIP) assay. Furthermore, the biological functions of miRNA were also analyzed using gain- and loss-of-function assays. Functional experiments showed that miRNA could inhibit cell proliferation, migration, and invasion, while promote cell apoptosis. In addition, functional rescue experiments further demonstrated that there was an antagonistic effect between *PVT1* and the target miRNA.

After *PVT1* and miRNA were identified, the final mRNA needs to be determined. The above bioinformatics data resources were used to predict the target genes of miRNA. TCGA and GEO data or RT-PCR, Western blot and/or immunohistochemical assay were used again to analyze the expression level of target mRNA, and the clinical prognosis, binding relationship, and the correlation between *PVT1* and miRNA were analyzed. The target mRNA was proved to function in carcinogenesis. After finding the target mRNA of miRNA, the lncRNA-miRNA-mRNA were correlated, and it was accurately demonstrated that this ceRNA network did affect the occurrence and development of cancers or other diseases. Thus, a relatively complete ceRNA regulatory network was basically formed. This ceRNA network involving *PVT1* and miRNA in cancers characterizes the signaling pathways mediating tumorigenesis, tumor metastasis and chemoresistance in a variety of cancers.⁹⁵ More importantly, though identified as an oncogenic lncRNA at the very beginning, *PVT1* was demonstrated to play critical roles in non-cancer diseases, such as diabetes and its complications, osteoarthritis, and myocardial infarction, among others (Table 1 and Table S1).

The role of *PVT1* in relation with circPVT1

CircPVT1, located on chromosome 8q24, is generated by circularization from exon 2 of the *PVT1* gene, the same genetic locus encoding for *PVT1* (Fig. 1). However, current reports showed that *PVT1* and circPVT1 are independently transcribed by different promoters. *PVT1* primarily localizes in the nucleus, while circPVT1 generally localizes in the cytoplasm, indicative of different post-transcriptional regulation for circPVT1 and *PVT1*.⁹⁶ Both circRNAs and circPVT1 have significant importance in pathological processes like cancer. Circular RNA profile allows circPVT1 to

act as a prognostic marker and proliferative factor in many cancers. Studies focusing on circPVT1 showed that circPVT1 can enhance proliferation migration, and invasion of cancer cells, as well as drug resistance.⁹⁷ CircPVT1 was also identified as a senescence-associated circRNA (SAC-RNA). Several proliferative proteins such as IGF2BP1, KRAS and HMGA2, encoded by let-7 target mRNAs, can prevent senescence, and the levels of these proteins can be decreased by circPVT1 silencing.⁹⁸

The interaction between circPVT1 and *PVT1* has been highlighted in a few studied malignancies. Current reports indicated their cooperation with an undifferentiated and/or more aggressive cell phenotype, thereby promoting cancer progression. Martina Ghetti et al found that upregulation of circPVT1 and *PVT1* through genomic rearrangements or amplification and/or promoted transcription can enhance proliferation of malignant cells in acute lymphoblastic leukemia (circular *PVT1*), Burkitt lymphoma, acute promyelocytic leukemia, acute myeloid leukemia, and multiple myeloma (linear *PVT1*).⁷

Numerous studies showed that circRNAs function as miRNA sponges or ceRNAs. The role of circPVT1 in oncogenesis has also been correlated with their function as ceRNA. CircPVT1 and miRNAs could act as sponges for RNA-binding proteins through binding to tumor suppressors. Table 2 and Table S2 list the related diseases and miRNAs sponged by circPVT1.

The role of SNPs at *PVT1*

The role of single nucleotide polymorphisms (SNP) at *PVT1* associated with diseases was also explored. A pooling-based genome-wide SNP association study identified *PVT1* as a candidate gene for end-stage renal disease (ESRD) in type 2 diabetes and found rs2720709 at *PVT1* might contribute to ESRD susceptibility in diabetes.¹¹⁶ Similarly, SNP was also found to be associated with diabetic nephropathy.¹¹⁷ Zhou S et al¹¹⁸ found that the combined SNP actions in *mir-146a* rs2910164 and *PVT1* rs13281615 impacted the function of lung in chronic obstructive pulmonary disease (COPD) smokers. An analysis of breast cancer susceptibility loci potential targets by capture Hi-C identified more than 70 variants correlated with risk of breast cancer, including the risk loci targeting *PVT1*.¹¹⁹ An intronic variant in *PVT1* rs10505506 was associated with chest radiotherapy-induced breast cancer risk after Hodgkin lymphoma (HL) in female.¹²⁰ In addition, the risk allele (G) of SNP rs13281615 was observed to function in breast cancer via affecting the expression of *PVT1*.¹²¹ Moreover, the GG genotype of rs378854 was identified as a new risk variant for prostate

Table 2 Related diseases and miRNAs sponged by circPVT1.

Related diseases	miRNAs	Target genes or signaling pathways	Function	References
Adenomyosis (ADS)	miR-145	<i>TALIN1</i>	Promote eutopic endometrial cell proliferation and invasion	99
Breast cancer (BCa)	MiR-29a-3p	AGR2-HIF-1 α Pathway	Promote the progression of breast cancer	100
Clear cell renal cell carcinoma (ccRcc)	miR-145-5p	<i>TBX15</i>	Promote ccRCC growth and metastasis	101
Colorectal cancer (CRC)	let-7	<i>NRAS</i>	Drive cancer cells towards oncogenicity	102
Epithelial ovarian cancer (EOC)	miR-149	<i>NR</i>	Enhance cell proliferation but inhibits apoptosis	103
Esophageal carcinoma (EC)	miR-4663	<i>PAXs and PPARs</i>	Promote cell invasive ability	104
Gastric cancer (GC)	miR-124-3p	<i>ZEB1</i>	Contribute to paclitaxel resistance of gastric cancer cells	105
Hepatocellular carcinoma (HCC)	miR-3666	<i>SIRT7</i>	Promote HCC cell growth	106
Lung adenocarcinoma (LADC)	miR-429	<i>FOXK1</i>	Interference inhibits the progression of lung ADC and enhances its sensitivity to DDP	107
Lung squamous cell carcinoma (LUSC)	miR-30d and miR-30e	<i>CCNF</i> , regulated by HuR	Promote the proliferation of LUSC cells	108
Myocardial infarction (MI)	miR-125b, miR-200a	<i>p53/Traf6, Sirt7, Keap1/Nrf 2, and PDCD4</i>	Apoptotic signaling	109
Neck squamous cell carcinoma (HNSCC)	miR-497-5p	<i>P53/YAP/TEAD</i>	Increase the malignant phenotype	110
Non-small cell lung cancer (NSCLC)	miR-125b	<i>E2F2</i>	Promote NSCLC cell growth and invasion	111
Oral squamous cell carcinoma (OSCC)	miR-125b	<i>STAT3</i>	Regulate cell proliferation	112
Osteosarcoma (OS)	miR-137	<i>TRIAP1</i>	Boosted doxorubicin (DXR) resistance	113
Senescence	let-7	<i>IGF2BP1, KRAS and HMGA2</i>	Silencing promotes cell senescence and reverses the proliferative phenotype	98
Steroid-induced osteonecrosis of the femoral head (SIONFH)	miR-21-5p	<i>SMAD7/TGFβ signaling pathway</i>	Attenuate the apoptosis and cell viability inhibition	114
T cell acute lymphoblastic leukemia (T-ALL)	miR-30e	<i>DLL4-NOTCH signaling</i>	Knockdown inhibits the cell proliferation and increase the cell apoptosis	115

cancer by increasing the expression of *PVT1*, but not *MYC*.¹²² SNP array data obtained from 52 ovarian tumors showed that *PVT1*, but not *MYC*, was significantly upregulated when compared with normal ovary, as well as tumors lacking copy number alterations.¹²³ A genome-wide association study (GWAS) showed that *PVT1* rs2114358*A was associated with event-free phenotype during an at least two-year GA treatment.¹²⁴ A GWAS on kidney transplants in 532 African American (AA) deceased donors (DDs) found that several SNPs in *PVT1* affected renal allograft survival following transplantation independently or via interaction with apolipoprotein L1 gene (*APOL1*).¹²⁵ Moreover, the SNP-SNP interactions in region of *CASC11-MYC-PVT1* have a more significant influence than individual effects of SNP on risk of prostate cancer in AA men.¹²⁶ These studies consistently point to an important role of *PVT1* in diseases.

Conclusions and perspectives

PVT1 has been demonstrated as the most potent long noncoding RNA with oncogenic functions. Recent studies have been performed on all aspects of *PVT1*, including its potential oncogenic roles, molecular alteration, biogenesis, as well as its bioactivities including regulating protein interactions, modulating miRNA expression, forming fusion genes, targeting regulatory genes, interacting with *MYC* and its circular transcripts—circPVT1, functioning as a ceRNA, among others. In this review, we summarized recent progress in *PVT1* functions and metabolism. We speculate that the modes of action of *PVT1* may also be applied to many other lncRNAs such as *HOTAIR*, *H19*, *NEAT*, *MALAT1*, *HOTTIP*, among others; thus, our summary of *PVT1* may provide hints for studies of other lncRNAs.

Another research hotspot is the therapeutic potential of lncRNAs. A comprehensive inquiry on 9972 cancer cases of 21 types has demonstrated that *PVT1* may act as a potential human cancer biomarker correlated with cancer prognosis and progression.¹²⁷ Besides its critical roles in diagnostic and prognostic process, *PVT1* also has potential therapeutic roles. *PVT1* can act either as a biomarker to make the existing cancer therapeutics more effective or as a potential target for designing novel therapeutic candidates. However, there will be a long way to go to be able to fully exploit *PVT1* for cancer therapy and prognostication, which will be the next focus and research direction.

Conflict of interests

The authors declare that they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gendis.2022.05.037>.

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