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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 al[5] 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-1204[7] (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 ($PVT1^{\Delta E4}$) 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 $PVT1^{\Delta E4}$ 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]

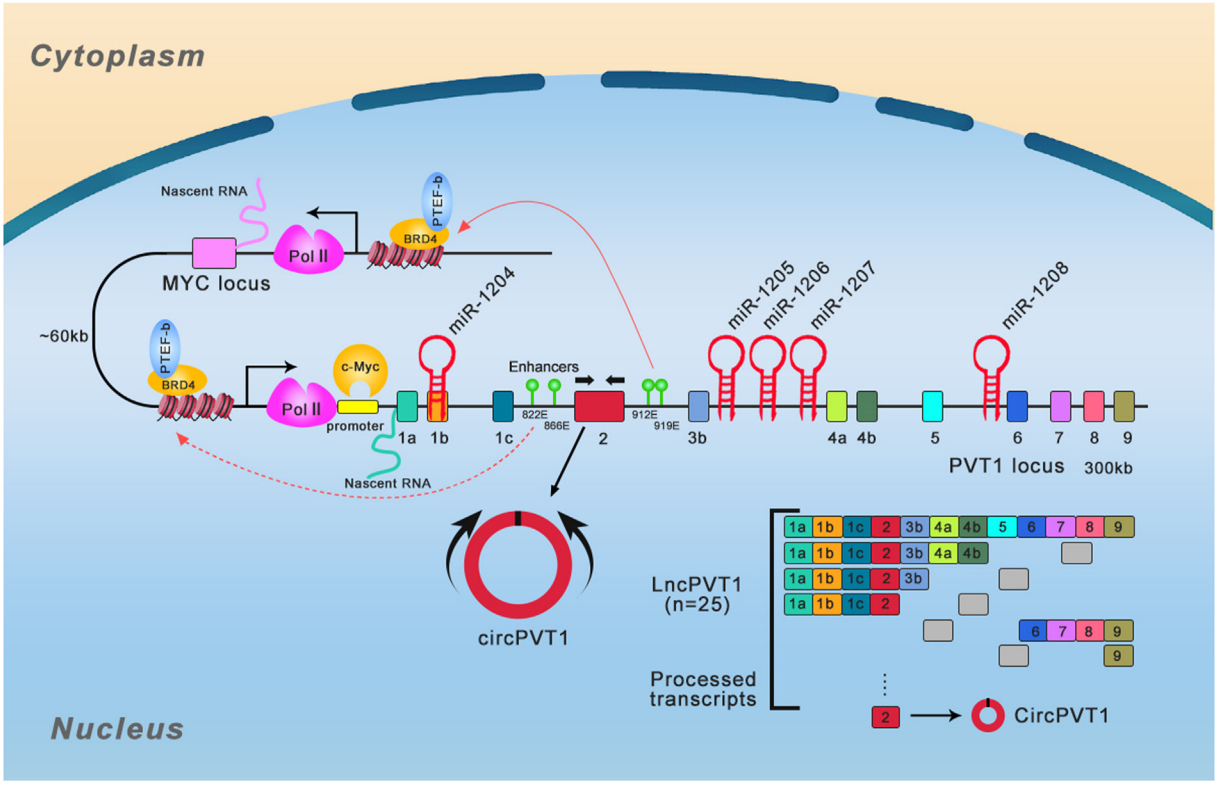

Figure 1 Schematic view of human *PVT1* gene locus and alternative splicing. *PVT1* located in the region of 8q24.21 harboring *MYC*/*PVT1* loci and *PVT1*-encoded five miRNAs and probable mode of biogenesis of circPVT1. The positive feedback and promoter-enhancer competition between *PVT1* and *MYC* 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 cancer[25] 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

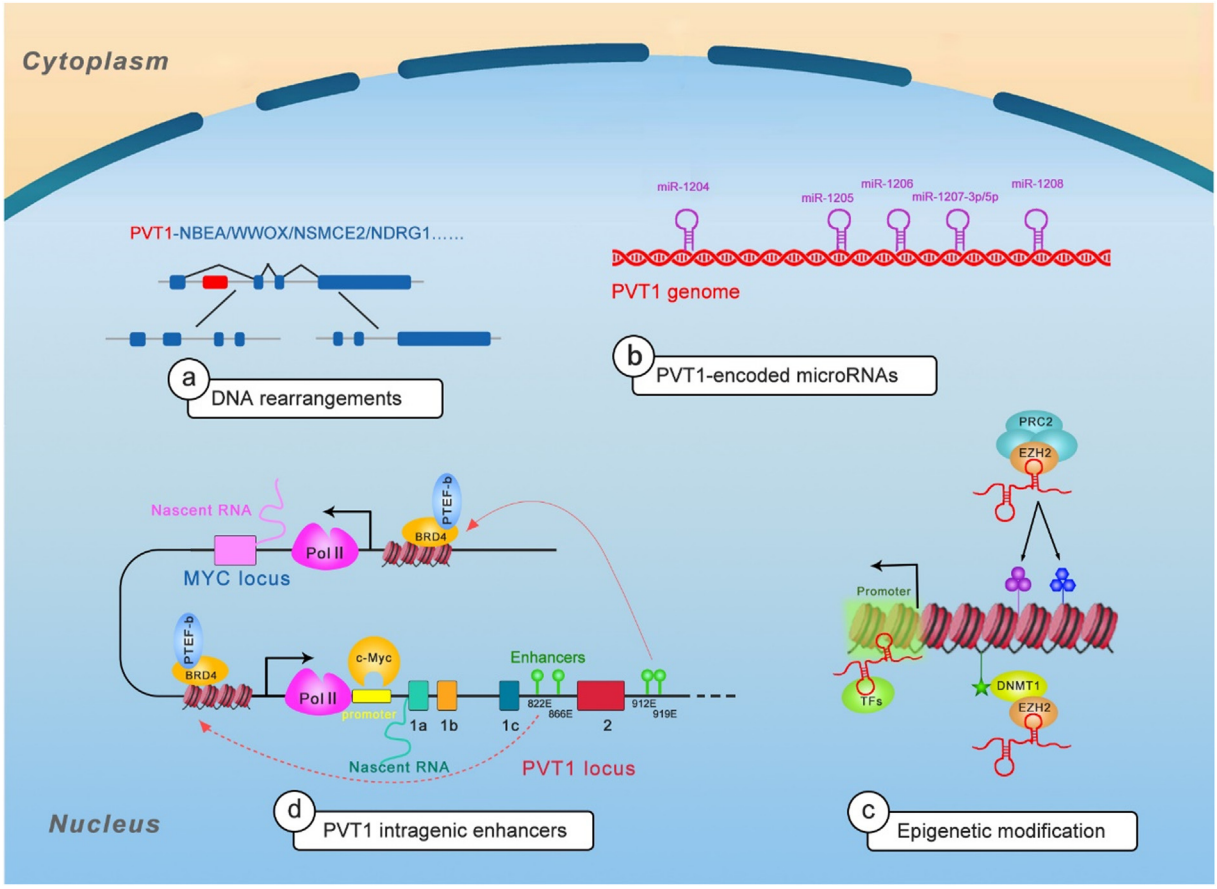

Figure 2 The mechanisms of *PVT1* in pretranscription regulation. **a** Listed are a few examples of *PVT1* gene rearrangements and fusion transcripts. **b** Listed are five *PVT1*-encoded miRNAs. **c** showed the mechanisms of *PVT1* in epigenetic modification. **d** showed schematic representing the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

(3;8) (q26;q24) are located at *EV1/MDS1* on chromosome 3 and distal to *PVT1* on chromosome 8, and this rearrangement can induce aberrant expression of *EVI1*, 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 cancer[28]; 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 Drosha 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 TGFβ1 and glucose is independent of *PVT1*. Similar with *PVT1*, miR-1207-5p upregulates FN1, PAI-1, and TGF-β1 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, circPVT1 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

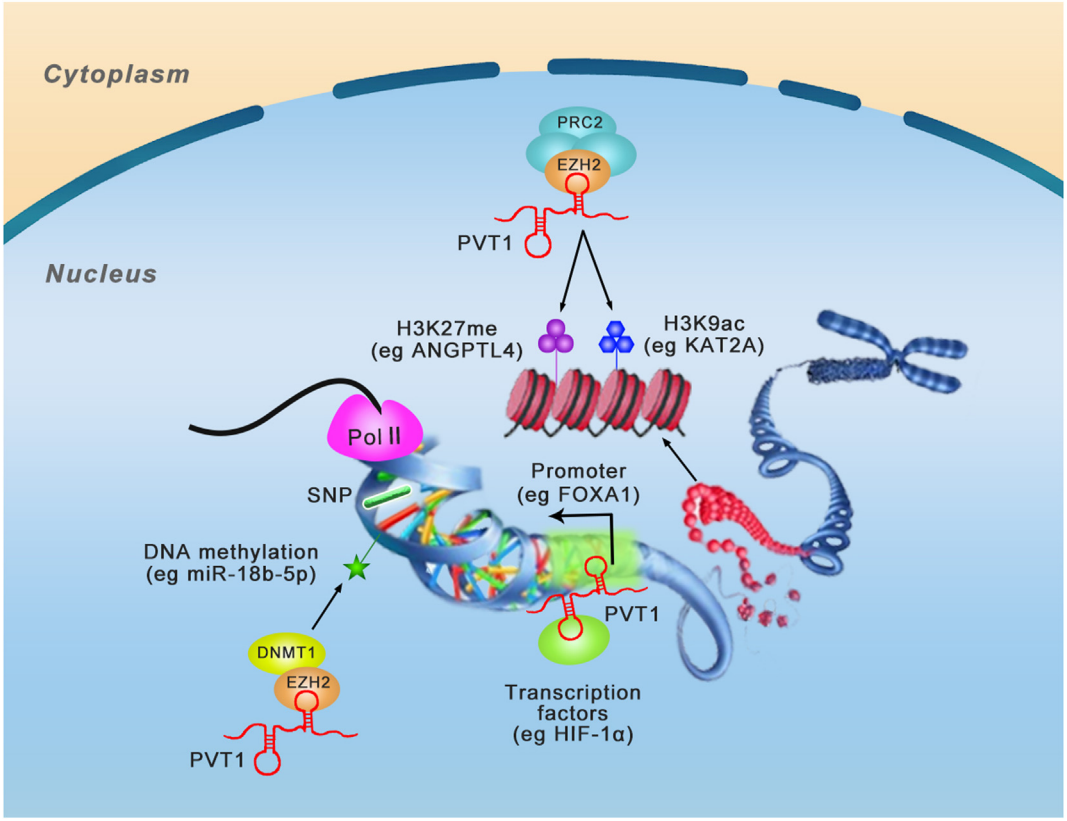

Figure 3 The mechanisms of *PVT1* in epigenetic modification. *PVT1* can act as scaffold binds to chromatin and epigenetic modifier, guide the epigenetic modifier to gene promotor. *PVT1* can facilitate enhancer and promoter element interactions, critical for gene activation. Listed are a few examples 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 al[51] found that *PVT1* can act as a scaffold for KAT2A, a chromatin modification factor, induce acetylation of H3K9, recruiting TIF1β to activate the transcription of *NF90*, thereby activating the *KAT2A* acetyltransferase, stabilizing HIF-1α, 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-1α.[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 promotor. 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-1α* 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, m^6A modification of *PVT1* transcripts enhances its interaction with *MYC* and stabilizes the MYC protein in epidermal progenitor

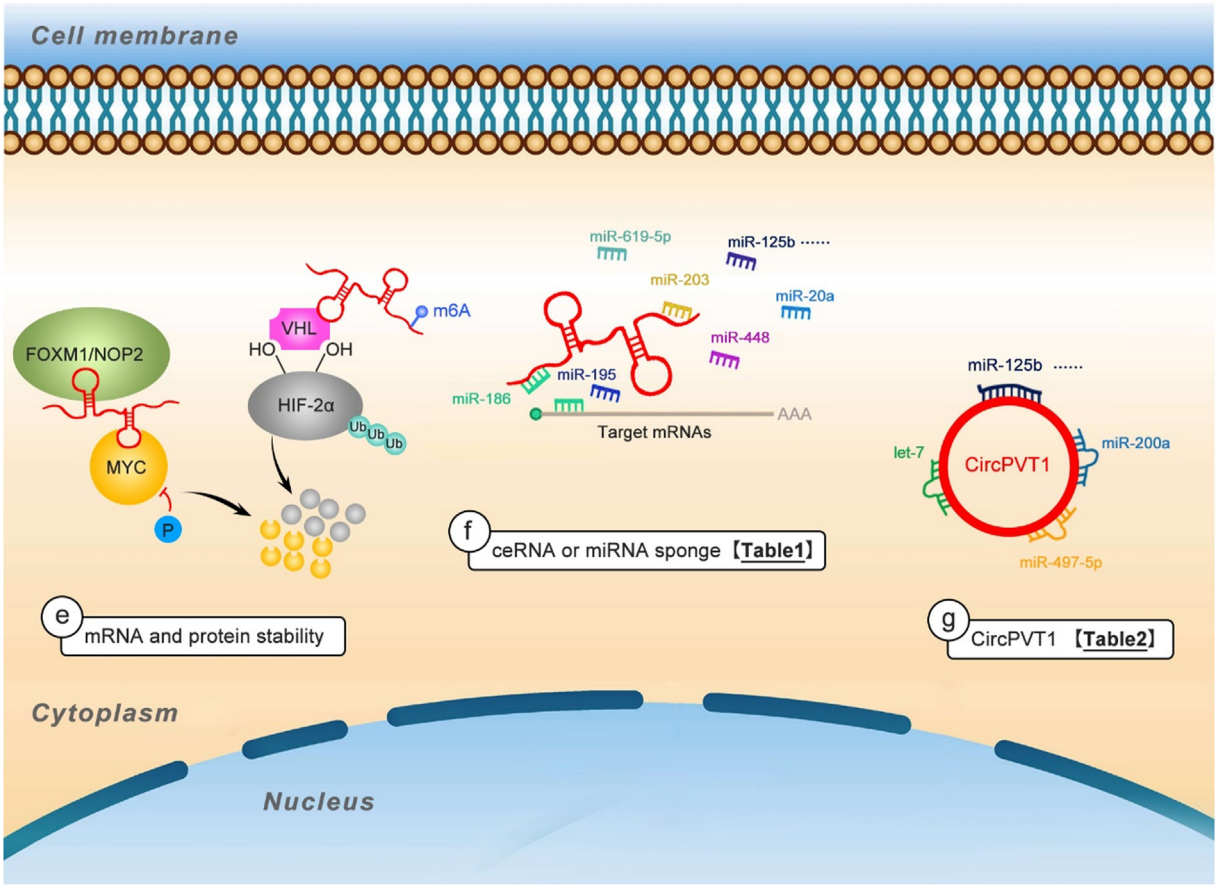

Figure 4 The mechanisms of *PVT1* in posttranscription regulation. **e** listed *PVT1* can interact with proteins and/or mRNAs to form RNP complexes, or act as scaffold for two or more proteins, thus stabilizing and protecting mRNAs from degradation, which regulate posttranscriptional gene regulation. **f** listed *PVT1* acting as miRNA sponges attenuates the miRNA′ effect on down-regulating mRNA expression (Table 1). **g** listed CircPVT1 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-1α[60] and HIF-2α[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 upregulated 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	*NLRP3*	Modulate NLRP3-mediated pyroptosis	66
Atrial fibrillation	miR-145-5p	*IL-16*	Boost the extracellular matrix remodeling of atrial fibroblasts	67
Bladder cancer	miR-194-5p	*BCLAF1*	Increase malignant phenotypes	68
Cardiac hypertrophy	miR-196b	*OSMR*	Knockdown attenuates the myocardial hypertrophy	69
Cardiotoxicity	miR-187-3p	*AGO1*	Aggravate doxorubicin-induced cardiomyocyte apoptosis	70
Cervical cancer	miR-140-5p	*SMAD3*	Promote the proliferation and metastasis	71
Clear cell renal cell carcinoma (ccRcc)	miR-328-3p	*FAM193B*	Promote the proliferation of ccRCC cells	72
Diabetic cataract (DC)	miR-214-3p	*MMP2*, regulated by SP1	Modulate the proliferation and apoptosis of lens epithelial cells	73
Diabetic nephropathy (DN)	miR-23b-3p	*WT1*	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	*LASP1*	Promote ESCC progression	76
Gallbladder cancer (GBC)	miR-143	*HK2*	Knockdown inhibits cell proliferation, migration, and invasion	77
Gastric cancer	miR-186	*HIF-1α*	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	*STAT3*, regulated by SOX2	Depleting improves ischemic stroke	80
Myocardial ischemia/ reperfusion (I/R) injury	miR-186	*Beclin-1*	Knockdown protects cardiomyocytes apoptosis and autophagy	81
Neuropathic pain	miR-186-5p	*CXCL13/CXCR5*	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	*MMP9*	Promote the invasive ability of NSCLC cells	83
Osteoarthritis (OA)	miR-27b-3p	*TRAF3*	Inhibit IL-1β-induced injury in chondrocytes	84
Osteosarcoma (OS)	miR-497	*HK2*	Contribute to OS cell glucose metabolism, cell proliferation, and motility	85
Papillary thyroid carcinoma (PTC)	miR-30a	*IGF1R*	Enhance the viability and invasion	86
PM2.5-exposed lung cancer	miR-199a-5p	*Caveolin 1*	Affect the role of lentinan in PM2.5-exposed lung cancer cells	87
Pulpitis	miR-455-5p	*SOCS3* and *PLXNC1*	Involve in the pathogenesis of pulpitis	88
Retinoblastoma (RB)	miR-488-3p	*NOTCH2*	Silencing inhibits cell proliferation, migration, invasion, and cell cycle progression and induces cell apoptosis	89
Rheumatoid arthritis (RA)	miR-543	*SCUBE2*	Regulate apoptosis of fibroblast-like synoviocytes	90
RSV-infected asthma	miR-203a	*E2F3*	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
			asthma	
Temporomandibular joint osteoarthritis (TMJ OA)	miR-211-3p	*TNF-α*	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 transcripted 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 al[118] 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	*TALIN1*	Promote eutopic endometrial cell proliferation and invasion	[99]
Breast cancer (BCa)	MiR-29a-3p	AGR2-HIF-1α Pathway	Promote the progression of breast cancer	[100]
Clear cell renal cell carcinoma (ccRcc)	miR-145-5p	*TBX15*	Promote ccRCC growth and metastasis	[101]
Colorectal cancer (CRC)	let-7	*NRAS*	Drive cancer cells towards oncogenicity	[102]
Epithelial ovarian cancer (EOC)	miR-149	*NR*	Enhance cell proliferation but inhibits apoptosis	[103]
Esophageal carcinoma (EC)	miR-4663	*PAXs and PPARs*	Promote cell invasive ability	[104]
Gastric cancer (GC)	miR-124-3p	*ZEB1*	Contribute to paclitaxel resistance of gastric cancer cells	[105]
Hepatocellular carcinoma (HCC)	miR-3666	*SIRT7*	Promote HCC cell growth	[106]
Lung adenocarcinoma (LADC)	miR-429	*FOXK1*	Interference inhibits the progression of lung ADC and enhances its sensitivity to DDP	[107]
Lung squamous cell carcinoma (LUSC)	miR-30d and miR-30e	*CCNF*, regulated by HuR	Promote the proliferation of LUSC cells	[108]
Myocardial infarction (MI)	miR-125b, miR-200a	*p53/Traf6, Sirt7, Keap 1/Nrf 2, and PDCD4*	Apoptotic signaling	[109]
Neck squamous cell carcinoma (HNSCC)	miR-497-5p	*P53/YAP/TEAD*	Increase the malignant phenotype	[110]
Non-small cell lung cancer (NSCLC)	miR-125b	*E2F2*	Promote NSCLC cell growth and invasion	[111]
Oral squamous cell carcinoma (OSCC)	miR-125b	*STAT3*	Regulate cell proliferation	[112]
Osteosarcoma (OS)	miR-137	*TRIAP1*	Boosted doxorubicin (DXR) resistance	[113]
Senescence	let-7	*IGF2BP1, KRAS and HMGA2*	Silencing promotes cell senescence and reverses the proliferative phenotype	[98]
Steroid-induced osteonecrosis of the femoral head (SIONFH)	miR-21-5p	SMAD7/TGFβ signaling pathway	Attenuate the apoptosis and cell viability inhibition	[114]
T cell acute lymphoblastic leukemia (T-ALL)	miR-30e	DLL4-NOTCH signaling	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.

References

1. Chen H, Shan G. The physiological function of long-noncoding RNAs. *Noncoding RNA Res*. 2020;5(4):178—184.
2. Fu L, Ding Z, Tan D, et al. Genome-wide discovery and functional prediction of salt-responsive lncRNAs in duckweed. *BMC Genom*. 2020;21(1):212.
3. Ye M, Zhang J, Wei M, et al. Emerging role of long noncoding RNA-encoded micropeptides in cancer. *Cancer Cell Int*. 2020; 20:506.
4. Fang Y, Fullwood MJ. Roles, functions, and mechanisms of long non-coding RNAs in cancer. *Dev Reprod Biol*. 2016;14(1): 42—54.
5. Huppi K, Volfovsky N, Runfola T, et al. The identification of microRNAs in a genomically unstable region of human chromosome 8q24. *Mol Cancer Res*. 2008;6(2):212—221.
6. Huppi K, Siwarski D, Goodnight J, et al. Alternative splicing of pvt-1 transcripts in murine lymphocytic-B neoplasms accompanies amplification and chromosomal translocation. *Int J Oncol*. 1992;1(5):525—532.
7. Ghetti M, Vannini I, Storlazzi CT, et al. Linear and circular PVT1 in hematological malignancies and immune response: two faces of the same coin. *Mol Cancer*. 2020;19(1):69.
8. Cho SW, Xu J, Sun R, et al. Promoter of lncRNA gene PVT1 is a tumor-suppressor DNA boundary element. *Cell*. 2018;173(6): 1398—1412.
9. Tseng YY, Moriarity BS, Gong W, et al. PVT1 dependence in cancer with MYC copy-number increase. *Nature*. 2014; 512(7512):82—86.
10. Jin K, Wang S, Zhang Y, et al. Long non-coding RNA PVT1 interacts with MYC and its downstream molecules to synergistically promote tumorigenesis. *Cell Mol Life Sci*. 2019;76(21): 4275—4289.
11. Ule J, Blencowe BJ. Alternative splicing regulatory networks: functions, mechanisms, and evolution. *Mol Cell*. 2019;76(2): 329—345.
12. Alvarez ML, Khosroheidari M, Eddy E, et al. Role of microRNA 1207-5P and its host gene, the long non-coding RNA Pvt1, as mediators of extracellular matrix accumulation in the kidney: implications for diabetic nephropathy. *PLoS One*. 2013;8(10): e77468.
13. Ilboudo A, Chouhan J, McNeil BK, et al. PVT1 exon 9: a potential biomarker of aggressive prostate cancer? *Int J Environ Res Publ Health*. 2015;13(1):ijerph13010012.
14. Pal G, Huaman J, Levine F, et al. Long noncoding RNA from PVT1 exon 9 is overexpressed in prostate cancer and induces malignant transformation and castration resistance in prostate epithelial cells. *Genes*. 2019;10(12):964.
15. Pal G, Di L, Orunmuyi A, et al. Population differentiation at the PVT1 gene locus: implications for prostate cancer. *G3 (Bethesda)*. 2020;10(7):2257—2264.
16. Yang T, Zhou H, Liu P, et al. lncRNA PVT1 and its splicing variant function as competing endogenous RNA to regulate clear cell renal cell carcinoma progression. *Oncotarget*. 2017; 8(49):85353—85367.
17. Mfossa ACM, Thekkekara Puthenparampil H, Inalegwu A, et al. Exposure to ionizing radiation triggers prolonged changes in circular RNA abundance in the embryonic mouse brain and primary neurons. *Cells*. 2019;8(8):778.
18. Tolomeo D, Agostini A, Visci G, et al. PVT1: a long non-coding RNA recurrently involved in neoplasia-associated fusion transcripts. *Gene*. 2021;779:145497.
19. Croft D, O'Kelly G, Wu G, et al. Reactome: a database of reactions, pathways and biological processes. *Nucleic Acids Res*. 2011;39(Database issue):D691—D697.
20. Shtivelman E, Bishop JM. The PVT gene frequently amplifies with MYC in tumor cells. *Mol Cell Biol*. 1989;9(3): 1148—1154.
21. Northcott PA, Shih DJ, Peacock J, et al. Subgroup-specific structural variation across 1,000 medulloblastoma genomes. *Nature*. 2012;488(7409):49—56.
22. AACR Project GENIE Consortium. AACR project GENIE: powering precision medicine through an international consortium. *Cancer Discov*. 2017;7(8):818—831.
23. Nagoshi H, Taki T, Hanamura I, et al. Frequent PVT1 rearrangement and novel chimeric genes PVT1-NBEA and PVT1-WWOX occur in multiple myeloma with 8q24 abnormality. *Cancer Res*. 2012;72(19):4954—4962.
24. Chinen Y, Sakamoto N, Nagoshi H, et al. 8q24 amplified segments involve novel fusion genes between NSMCE2 and long noncoding RNAs in acute myelogenous leukemia. *J Hematol Oncol*. 2014;7:68.
25. Mishra A, Bonello M, Byron A, et al. Evaluation of gene expression data from cybrids and tumours highlights elevated *NDRG1*-driven proliferation in triple-negative breast cancer. *Breast Cancer*. 2020;14:1178223420934447.
26. Zhao K, Zhao Y, Zhu JY, et al. A panel of genes identified as targets for 8q24.13-24.3 gain contributing to unfavorable overall survival in patients with hepatocellular carcinoma. *Curr Med Sci*. 2018;38(4):590—596.
27. Lennon PA, Abruzzo LV, Medeiros LJ, et al. Aberrant EVI1 expression in acute myeloid leukemias associated with the t(3;8)(q26;q24). *Cancer Genet Cytogenet*. 2007;177(1): 37—42.
28. Kim HP, Cho GA, Han SW, et al. Novel fusion transcripts in human gastric cancer revealed by transcriptome analysis. *Oncogene*. 2014;33(47):5434—5441.
29. Beck-Engeser GB, Lum AM, Huppi K, et al. Pvt 1-encoded microRNAs in oncogenesis. *Retrovirology*. 2008;5:4.
30. Barsotti AM, Beckerman R, Laptenko O, et al. p53-Dependent induction of PVT1 and miR-1204. *J Biol Chem*. 2012;287(4): 2509—2519.
31. Bisio A, De Sanctis V, Del Vescovo V, et al. Identification of new p53 target microRNAs by bioinformatics and functional analysis. *BMC Cancer*. 2013;13:552.
32. Wang Y, Li X, Liu W, et al. MicroRNA-1205, encoded on chromosome 8q24, targets EGLN3 to induce cell growth and contributes to risk of castration-resistant prostate cancer. *Oncogene*. 2019;38(24):4820—4834.

33. Naidoo M, Levine F, Gillot T, et al. MicroRNA-1205 regulation of FRYL in prostate cancer. *Front Cell Dev Biol*. 2021;9:647485.
34. Takahashi Y, Sawada G, Kurashige J, et al. Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers. *Br J Cancer*. 2014;110(1):164—171.
35. Cui M, Chang Y, Fang QG, et al. Non-coding RNA Pvt 1 promotes cancer stem cell-like traits in nasopharyngeal cancer via inhibiting miR-1207. *Pathol Oncol Res*. 2019;25(4):1411—1422.
36. Das DK, Ogunwobi OO. A novel microRNA-1207-3p/FNDC1/FN1/AR regulatory pathway in prostate cancer. *RNA Dis*. 2017;4(1):e1503.
37. Yan C, Chen Y, Kong W, et al. PVT1-derived miR-1207-5p promotes breast cancer cell growth by targeting STAT6. *Cancer Sci*. 2017;108(5):868—876.
38. You L, Wang H, Yang G, et al. Gemcitabine exhibits a suppressive effect on pancreatic cancer cell growth by regulating processing of PVT1 to miR 1207. *Mol Oncol*. 2018;12(12):2147—2164.
39. Huang M, Li T, Wang Q, et al. Silencing circPVT1 enhances radiosensitivity in non-small cell lung cancer by sponging microRNA-1208. *Cancer Biomarkers*. 2021;31(3):263—279.
40. Tan JZ, Yan Y, Wang XX, et al. EZH2: biology, disease, and structure-based drug discovery. *Acta Pharmacol Sin*. 2014;35(2):161—174.
41. Kong R, Zhang EB, Yin DD, et al. Long noncoding RNA PVT1 indicates a poor prognosis of gastric cancer and promotes cell proliferation through epigenetically regulating p15 and p16. *Mol Cancer*. 2015;14:82.
42. Li T, Yang J, Yang B, et al. Ketamine inhibits ovarian cancer cell growth by regulating the lncRNA-PVT1/EZH2/p57 axis. *Front Genet*. 2021;11:597467.
43. Yu Y, Zhang M, Liu J, et al. Long non-coding RNA PVT1 promotes cell proliferation and migration by silencing ANGPTL4 expression in cholangiocarcinoma. *Mol Ther Nucleic Acids*. 2018;13:503—513.
44. Xu Y, Lian Y, Zhang Y, et al. The long non-coding RNA PVT1 represses ANGPTL4 transcription through binding with EZH2 in trophoblast cell. *J Cell Mol Med*. 2018;22(2):1272—1282.
45. Wan L, Sun M, Liu GJ, et al. Long noncoding RNA PVT1 promotes non-small cell lung cancer cell proliferation through epigenetically regulating LATS2 expression. *Mol Cancer Therapeut*. 2016;15(5):1082—1094.
46. Guo J, Hao C, Wang C, et al. Long noncoding RNA PVT1 modulates hepatocellular carcinoma cell proliferation and apoptosis by recruiting EZH2. *Cancer Cell Int*. 2018;18:98.
47. Zhou Q, Chen J, Feng J, et al. Long noncoding RNA PVT1 modulates thyroid cancer cell proliferation by recruiting EZH2 and regulating thyroid-stimulating hormone receptor (TSHR). *Tumour Biol*. 2016;37(3):3105—3113.
48. Zhang S, Zhang G, Liu J. Long noncoding RNA PVT1 promotes cervical cancer progression through epigenetically silencing miR-200b. *APMIS*. 2016;124(8):649—658.
49. Shen CJ, Cheng YM, Wang CL. LncRNA PVT1 epigenetically silences miR-195 and modulates EMT and chemoresistance in cervical cancer cells. *J Drug Target*. 2017;25(7):637—644.
50. Liu DW, Zhang JH, Liu FX, et al. Silencing of long noncoding RNA PVT1 inhibits podocyte damage and apoptosis in diabetic nephropathy by upregulating FOXA1. *Exp Mol Med*. 2019;51(8):1—15.
51. Wang Y, Chen W, Lian J, et al. The lncRNA PVT1 regulates nasopharyngeal carcinoma cell proliferation via activating the KAT2A acetyltransferase and stabilizing HIF-1α. *Cell Death Differ*. 2020;27(2):695—710.
52. Jiang B, Yang B, Wang Q, et al. lncRNA PVT1 promotes hepatitis B virus-positive liver cancer progression by disturbing histone methylation on the c-Myc promoter. *Oncol Rep*. 2020;43(2):718—726.
53. Jin L, Cai Q, Wang S, et al. Long noncoding RNA PVT1 promoted gallbladder cancer proliferation by epigenetically suppressing miR-18b-5p via DNA methylation. *Cell Death Dis*. 2020;11(10):871.
54. Liu HT, Fang L, Cheng YX, et al. LncRNA PVT1 regulates prostate cancer cell growth by inducing the methylation of miR-146a. *Cancer Med*. 2016;5(12):3512—3519.
55. Li Z, Tan H, Yu H, et al. DNA methylation and gene expression profiles characterize epigenetic regulation of lncRNAs in colon adenocarcinoma. *J Cell Biochem*. 2020;121(3):2406—2415.
56. Ahmed M, Soares F, Xia JH, et al. CRISPRi screens reveal a DNA methylation-mediated 3D genome dependent causal mechanism in prostate cancer. *Nat Commun*. 2021;12(1):1781.
57. Liu SJ, Horlbeck MA, Cho SW, et al. CRISPRi-based genome-scale identification of functional long noncoding RNA loci in human cells. *Science*. 2017;355(6320):aah7111.
58. Pyfrom SC, Luo H, Payton JE. PLAIDOH: a novel method for functional prediction of long non-coding RNAs identifies cancer-specific LncRNA activities. *BMC Genom*. 2019;20(1):137.
59. Guo L, Li J, Zeng H, et al. A combination strategy targeting enhancer plasticity exerts synergistic lethality against BETi-resistant leukemia cells. *Nat Commun*. 2020;11(1):740.
60. Zhu Y, Wu F, Gui W, et al. A positive feedback regulatory loop involving the lncRNA PVT1 and HIF-1α in pancreatic cancer. *J Mol Cell Biol*. 2021;13(9):676—689.
61. Alessio E, Buson L, Chemello F, et al. Single cell analysis reveals the involvement of the long non-coding RNA Pvt 1 in the modulation of muscle atrophy and mitochondrial network. *Nucleic Acids Res*. 2019;47(4):1653—1670.
62. Lee J, Wu Y, Harada BT, et al. N6 -methyladenosine modification of lncRNA Pvt 1 governs epidermal stemness. *EMBO J*. 2021;40(8):e106276.
63. Xu MD, Wang Y, Weng W, et al. A positive feedback loop of lncRNA- *PVT1* and FOXM1 facilitates gastric cancer growth and invasion. *Clin Cancer Res*. 2017;23(8):2071—2080.
64. Zhang MX, Zhang LZ, Fu LM, et al. Positive feedback regulation of lncRNA PVT1 and HIF2α contributes to clear cell renal cell carcinoma tumorigenesis and metastasis. *Oncogene*. 2021;40(37):5639—5650.
65. Wang F, Yuan JH, Wang SB, et al. Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. *Hepatology*. 2014;60(4):1278—1290.
66. Deng LT, Wang QL, Yu C, et al. lncRNA PVT1 modulates NLRP3-mediated pyroptosis in septic acute kidney injury by targeting miR-20a-5p. *Mol Med Rep*. 2021;23(4):271.
67. Cao F, Li Z, Ding W, et al. Angiotensin II-treated cardiac myocytes regulate M1 macrophage polarization via transferring exosomal PVT1. *J Immunol Res*. 2021;2021:1994328.
68. Chen M, Zhang R, Lu L, et al. LncRNA PVT1 accelerates malignant phenotypes of bladder cancer cells by modulating miR-194-5p/BCLAF1 axis as a ceRNA. *Aging (Albany NY)*. 2020;12(21):22291—22312.
69. Wu Q, Chen Q, Wang J, et al. Long non-coding RNA Pvt 1 modulates the pathological cardiac hypertrophy via miR-196b-mediated OSMR regulation. *Cell Signal*. 2021;86:110077.
70. Zhan J, Hu P, Wang Y. lncRNA PVT1 aggravates doxorubicin-induced cardiomyocyte apoptosis by targeting the miR-187-3p/AGO1 axis. *Mol Cell Probes*. 2020;49:101490.
71. Chang QQ, Chen CY, Chen Z, et al. LncRNA PVT1 promotes proliferation and invasion through enhancing Smad 3 expression by sponging miR-140-5p in cervical cancer. *Radiol Oncol*. 2019;53(4):443—452.
72. Xie G, Zheng X, Zheng Z, et al. The ceRNA PVT1 inhibits proliferation of ccRCC cells by sponging miR-328-3p to elevate

FAM193B expression. *Aging (Albany NY)*. 2021;13(17):21712—21728.
73. Yang J, Zhao S, Tian F. SP1-mediated lncRNA PVT1 modulates the proliferation and apoptosis of lens epithelial cells in diabetic cataract via miR-214-3p/MMP2 axis. *J Cell Mol Med*. 2020;24(1):554—561.
74. Zhong W, Zeng J, Xue J, et al. Knockdown of lncRNA PVT1 alleviates high glucose-induced proliferation and fibrosis in human mesangial cells by miR-23b-3p/WT1 axis. *Diabetol Metab Syndrome*. 2020;12:33.
75. Wang YZ, Yao-Li, Liang SK, et al. LncPVT1 promotes cartilage degradation in diabetic OA mice by downregulating miR-146a and activating TGF-β/SMAD4 signaling. *J Bone Miner Metabol*. 2021;39(4):534—546.
76. Li PD, Hu JL, Ma C, et al. Upregulation of the long non-coding RNA PVT1 promotes esophageal squamous cell carcinoma progression by acting as a molecular sponge of miR-203 and LASP1. *Oncotarget*. 2017;8(21):34164—34176.
77. Chen J, Yu Y, Li H, et al. Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. *Mol Cancer*. 2019;18(1):33.
78. Huang T, Liu HW, Chen JQ, et al. The long noncoding RNA PVT1 functions as a competing endogenous RNA by sponging miR-186 in gastric cancer. *Biomed Pharmacother*. 2017;88:302—308.
79. Fu C, Li D, Zhang X, et al. LncRNA PVT1 facilitates tumorigenesis and progression of glioma via regulation of miR-128-3p/GREM1 axis and BMP signaling pathway. *Neurotherapeutics*. 2018;15(4):1139—1157.
80. Chen Z, Fan T, Zhao X, et al. Depleting SOX2 improves ischemic stroke via lncRNA PVT1/microRNA-24-3p/STAT3 axis. *Mol Med*. 2021;27(1):107.
81. Ouyang M, Lu J, Ding Q, et al. Knockdown of long non-coding RNA PVT1 protects human AC16 cardiomyocytes from hypoxia/reoxygenation-induced apoptosis and autophagy by regulating miR-186/Beclin-1 axis. *Gene*. 2020;754:144775.
82. Zhang P, Sun H, Ji Z. Downregulating lncRNA PVT1 relieves astrocyte overactivation induced neuropathic pain through targeting miR-186-5p/CXCL13/CXCR5 axis. *Neurochem Res*. 2021;46(6):1457—1469.
83. Chen W, Zhu H, Yin L, et al. lncRNA-PVT1 facilitates invasion through upregulation of MMP9 in nonsmall cell lung cancer cell. *DNA Cell Biol*. 2017;36(9):787—793.
84. Lu X, Yu Y, Yin F, et al. Knockdown of PVT1 inhibits IL-1β-induced injury in chondrocytes by regulating miR-27b-3p/TRAF3 axis. *Int Immunopharm*. 2020;79:106052.
85. Song J, Wu X, Liu F, et al. Long non-coding RNA PVT1 promotes glycolysis and tumor progression by regulating miR-497/HK2 axis in osteosarcoma. *Biochem Biophys Res Commun*. 2017;490(2):217—224.
86. Feng K, Liu Y, Xu LJ, et al. Long noncoding RNA PVT1 enhances the viability and invasion of papillary thyroid carcinoma cells by functioning as ceRNA of microRNA-30a through mediating expression of insulin like growth factor 1 receptor. *Biomed Pharmacother*. 2018;104:686—698.
87. Qi H, Liu Y, Wang N, et al. Lentinan attenuated the PM2.5 exposure-induced inflammatory response, epithelial-mesenchymal transition and migration by inhibiting the PVT1/miR-199a-5p/caveolin 1 pathway in lung cancer. *DNA Cell Biol*. 2021;40(5):683—693.
88. Lei F, Zhang H, Xie X. Comprehensive analysis of an lncRNA-miRNA-mRNA competing endogenous RNA network in pulpitis. *PeerJ*. 2019;7:e7135.
89. Wu XZ, Cui HP, Lv HJ, et al. Knockdown of lncRNA PVT1 inhibits retinoblastoma progression by sponging miR-488-3p. *Biomed Pharmacother*. 2019;112:108627.
90. Wang J, Kong X, Hu H, et al. Knockdown of long non-coding RNA PVT1 induces apoptosis of fibroblast-like synoviocytes through modulating miR-543-dependent SCUBE2 in rheumatoid arthritis. *J Orthop Surg Res*. 2020;15(1):142.
91. Yu X, Zhe Z, Tang B, et al. α-Asarone suppresses the proliferation and migration of ASMCs through targeting the lncRNA-PVT1/miR-203a/E2F3 signal pathway in RSV-infected rats. *Acta Biochim Biophys Sin*. 2017;49(7):598—608.
92. Xu K, Meng Z, Xian XM, et al. LncRNA PVT1 induces chondrocyte apoptosis through upregulation of TNF-α in synoviocytes by sponging miR-211-3p. *Mol Cell Probes*. 2020;52:101560.
93. Shaker F, Nikravesh A, Arezumand R, et al. Web-based tools for miRNA studies analysis. *Comput Biol Med*. 2020;127:104060.
94. Mortazavi SS, Bahmanpour Z, Daneshmandpour Y, et al. An updated overview and classification of bioinformatics tools for MicroRNA analysis, which one to choose? *Comput Biol Med*. 2021;134:104544.
95. Ogunwobi OO, Kumar A. Chemoresistance mediated by ceRNA networks associated with the PVT1 locus. *Front Oncol*. 2019;9:834.
96. Panda AC, De S, Grammatikakis I, et al. High-purity circular RNA isolation method (RPAD) reveals vast collection of intronic circRNAs. *Nucleic Acids Res*. 2017;45(12):e116.
97. Adhikary J, Chakraborty S, Dalal S, et al. Circular PVT1: an oncogenic non-coding RNA with emerging clinical importance. *J Clin Pathol*. 2019;72(8):513—519.
98. Panda AC, Grammatikakis I, Kim KM, et al. Identification of senescence-associated circular RNAs (SAC-RNAs) reveals senescence suppressor CircPVT1. *Nucleic Acids Res*. 2017;45(7):4021—4035.
99. Wang YY, Duan H, Wang S, et al. Elevated circular RNA PVT1 promotes eutopic endometrial cell proliferation and invasion of adenomyosis via miR-145/Talin 1 axis. *BioMed Res Int*. 2021;2021:8868700.
100. Wang J, Huang K, Shi L, et al. CircPVT1 promoted the progression of breast cancer by regulating miR-29a-3p-mediated AGR2-HIF-1α pathway. *Cancer Manag Res*. 2020;12:11477—11490.
101. Zheng Z, Chen Z, Zhong Q, et al. CircPVT1 promotes progression in clear cell renal cell carcinoma by sponging miR-145-5p and regulating TBX15 expression. *Cancer Sci*. 2021;112(4):1443—1456.
102. Danac JMC, Garcia RL. CircPVT1 attenuates negative regulation of NRAS by let-7 and drives cancer cells towards oncogenicity. *Sci Rep*. 2021;11(1):9021.
103. Sun X, Luo L, Gao Y. Circular RNA PVT1 enhances cell proliferation but inhibits apoptosis through sponging microRNA-149 in epithelial ovarian cancer. *J Obstet Gynaecol Res*. 2020;46(4):625—635.
104. Zhong R, Chen Z, Mo T, et al. Potential Role of circPVT1 as a proliferative factor and treatment target in esophageal carcinoma. *Cancer Cell Int*. 2019;19:267.
105. Liu YY, Zhang LY, Du WZ. Circular RNA circ-PVT1 contributes to paclitaxel resistance of gastric cancer cells through the regulation of ZEB1 expression by sponging miR-124-3p. *Biosci Rep*. 2019;39(12):BSR20193045.
106. Li Y, Shi H, Yuan J, et al. Downregulation of circular RNA circPVT1 restricts cell growth of hepatocellular carcinoma through downregulation of Sirtuin 7 via microRNA-3666. *Clin Exp Pharmacol Physiol*. 2020;47(7):1291—1300.
107. Cao L, Zhou X, Ding X, et al. Knockdown of circ-PVT1 inhibits the progression of lung adenocarcinoma and enhances the sensitivity to cisplatin via the miR-429/FOXK1 signaling axis. *Mol Med Rep*. 2021;24(4):684.
108. Shi J, Lv X, Zeng L, et al. CircPVT1 promotes proliferation of lung squamous cell carcinoma by binding to miR-30d/e. *J Exp Clin Cancer Res*. 2021;40(1):193.
109. Luo C, Ling GX, Lei BF, et al. Circular RNA PVT1 silencing prevents ischemia-reperfusion injury in rat by targeting

microRNA-125b and microRNA-200a. *J Mol Cell Cardiol*. 2021;159:80—90.
110. Verduci L, Ferraiuolo M, Sacconi A, et al. The oncogenic role of circPVT1 in head and neck squamous cell carcinoma is mediated through the mutant p53/YAP/TEAD transcription-competent complex. *Genome Biol*. 2017;18(1):237.
111. Li X, Zhang Z, Jiang H, et al. Circular RNA circPVT1 promotes proliferation and invasion through sponging miR-125b and activating E2F2 signaling in non-small cell lung cancer. *Cell Physiol Biochem*. 2018;51(5):2324—2340.
112. He T, Li X, Xie D, et al. Overexpressed circPVT1 in oral squamous cell carcinoma promotes proliferation by serving as a miRNA sponge. *Mol Med Rep*. 2019;20(4):3509—3518.
113. Li D, Huang Y, Wang G. Circular RNA circPVT1 contributes to doxorubicin (DXR) resistance of osteosarcoma cells by regulating TRIAP1 via miR-137. *BioMed Res Int*. 2021;2021:7463867.
114. Hao Y, Lu C, Zhang B, et al. CircPVT1 up-regulation attenuates steroid-induced osteonecrosis of the femoral head through regulating miR-21-5p-mediated Smad 7/TGFβ signalling pathway. *J Cell Mol Med*. 2021;25(10):4608—4622.
115. Jia Y, Gu W. Up-regulation of circPVT1 in T cell acute lymphoblastic leukemia promoted cell proliferation via miR-30e/DLL4 induced activating NOTCH signaling. *Pathol Res Pract*. 2021;224:153536.
116. Hanson RL, Craig DW, Millis MP, et al. Identification of PVT1 as a candidate gene for end-stage renal disease in type 2 diabetes using a pooling-based genome-wide single nucleotide polymorphism association study. *Diabetes*. 2007;56(4):975—983.
117. Alwohhaib M, Alwaheeb S, Alyatama N, et al. Single nucleotide polymorphisms at erythropoietin, superoxide dismutase 1, splicing factor, arginine/serin-rich 15 and plasmacytoma variant translocation genes association with diabetic nephropathy. *Saudi J Kidney Dis Transpl*. 2014;25(3):577—581.
118. Zhou S, Liu Y, Li M, et al. Combined effects of PVT1 and miR-146a single nucleotide polymorphism on the lung function of smokers with chronic obstructive pulmonary disease. *Int J Biol Sci*. 2018;14(10):1153—1162.
119. Dryden NH, Broome LR, Dudbridge F, et al. Unbiased analysis of potential targets of breast cancer susceptibility loci by Capture Hi-C. *Genome Res*. 2014;24(11):1854—1868.
120. Opstal-van Winden AWJ, de Haan HG, Hauptmann M, et al. Genetic susceptibility to radiation-induced breast cancer after Hodgkin lymphoma. *Blood*. 2019;133(10):1130—1139.
121. Zhang Z, Zhu Z, Zhang B, et al. Frequent mutation of rs13281615 and its association with PVT1 expression and cell proliferation in breast cancer. *J Genet Genomics*. 2014;41(4):187—195.
122. Meyer KB, Maia AT, O'Reilly M, et al. A functional variant at a prostate cancer predisposition locus at 8q24 is associated with PVT1 expression. *PLoS Genet*. 2011;7(7):e1002165.
123. Haverty PM, Hon LS, Kaminker JS, et al. High-resolution analysis of copy number alterations and associated expression changes in ovarian tumors. *BMC Med Genom*. 2009;2:21.
124. Kulakova O, Bashinskaya V, Kiselev I, et al. Pharmacogenetics of glatiramer acetate therapy for multiple sclerosis: the impact of genome-wide association studies identified disease risk loci. *Pharmacogenomics*. 2017;18(17):1563—1574.
125. Divers J, Ma L, Brown WM, et al. Genome-wide association study for time to failure of kidney transplants from African American deceased donors. *Clin Transplant*. 2020;34(6):e13827.
126. Lin HY, Callan CY, Fang Z, et al. Interactions of *PVT1* and *CASC11* on prostate cancer risk in African Americans. *Cancer Epidemiol Biomarkers Prev*. 2019;28(6):1067—1075.
127. He RQ, Qin MJ, Lin P, et al. Prognostic significance of LncRNA PVT1 and its potential target gene network in human cancers: a comprehensive inquiry based upon 21 cancer types and 9972 cases. *Cell Physiol Biochem*. 2018;46(2):591—608.