IncRNA PVT1: a novel oncogene in multiple cancers

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Abstract
Long noncoding RNAs are involved in epigenetic gene modification, including binding to the chromatin rearrangement complex in pre-transcriptional regulation and to gene promoters in gene expression regulation, as well as acting as microRNA sponges to control messenger RNA levels in post-transcriptional regulation. An increasing number of studies have found that long noncoding RNA plasmacytoma variant translocation 1 (PVT1) plays an important role in cancer development. In this review of a large number of studies on PVT1, we found that PVT1 is closely related to tumor onset, proliferation, invasion, epithelial–mesenchymal transformation, and apoptosis, as well as poor prognosis and radiotherapy and chemotherapy resistance in some cancers. This review comprehensively describes PVT1 expression in various cancers and presents novel approaches to the diagnosis and treatment of cancer.

Keywords: Long noncoding RNA, PVT1, Oncogene, Cancer

Introduction
Cancer death rate has continuously declined in the past 2 years, although it remains the second leading cause of death worldwide according to the latest cancer statistics from the USA [1]. Changes at the gene level include gene mutations, amplification, deletion, DNA methylation, and insertion mutations. Abnormal oncogene activation and tumor suppressor gene inactivation are important factors that lead to the occurrence of cancer. Advances in genetic research have revealed the pathogenesis of many cancers, which has led to the development of effective treatments. For example, leukemia caused by breakpoint cluster region–Abelson mutations can be effectively cured using imatinib [2]. Protein-coding genes account for < 2% of the total genome. The remaining genome consists of noncoding genes that are responsible for the vast majority of tumorigenesis.

Long noncoding RNAs (lncRNAs) are RNAs that are longer than 200 nucleotides. lncRNAs are located in the nucleus or cytoplasm of eukaryotic cells and have a variety of functions, including regulating gene expression in both a cis and a trans manner, acting as a sponge for microRNA (miRNA), and directly affecting proteins and other RNAs [3]. In the early twentieth century, the lncRNA X-inactive specific transcript was first discovered, wrapping the X chromosome in a cis-like manner, resulting in silencing of
the entire chromosome. IncRNAs have been discovered and have been proven to play important roles in many diseases and cell development and as biomarkers. For example, abnormal MALAT1 expression promotes the development of bladder cancer [4]. IncRNAs in kinase activation are associated with poor prognosis in patients with breast or lung cancer [5]. However, the mechanism by which IncRNAs regulate tumor development remains unclear, and further studies are needed to explore and summarize the potential mechanisms of action of IncRNAs.

The IncRNA plasmacytoma variant translocation 1 (PVT1), which is located on the telomeres of chromosome 8 in the c-Myc gene, was first reported by Guan et al. [5]. Recently, abnormal PVT1 expression was found in a variety of human malignancies, including non-small cell lung cancer (NSCLC) [6], nasopharyngeal carcinoma (NPC) [7], gastric cancer (GC) [8], oral squamous cell carcinoma (OSCC) [9], esophageal cancer (EC) [10], colorectal cancer (CRC) [11], hepatocellular carcinoma (HCC) [12], gallbladder cancer (GBC) [13], cholangiocarcinoma (CCA) [14], pancreatic cancer (PC) [15], breast cancer (BC) [16], cervical cancer (CC) [17], endometrial cancer [18], ovarian cancer (OC) [19], renal cell carcinoma (RCC) [20], bladder cancer [21], prostate cancer (PCa) [22], glioma [23], osteosarcoma (OS) [24], multiple myeloma (MM) [25], thyroid cancer (TC) [26], lymphoma [27], and leukemia [28]. Identifying the mechanisms of action of various cancers has helped researchers discover new biomarkers and therapeutic targets. Here, we aimed to identify new biomarkers and therapeutic targets by summarizing the mechanisms of PVT1 in various cancers.

Functions of IncRNA

Many studies have shown that IncRNAs play vital roles as biomarkers in cancer diagnosis, therapeutic targets, prognosis, drug sensitizers, stratification, and other aspects [6–11].

IncRNAs can regulate chromatin topology by binding to H3K4me3 and H3K36me3 and through histone acetylation and other activated histone modifications to promote gene transcription [29]. Conversely, IncRNAs induce chromatin closure by binding to H3K9me3, H3K27me3, and H4K20me3 and through DNA methylation and other suppressive histone modification factors [30]. IncRNAs can serve as a central platform for assembling relevant molecular components, binding to nucleic acids through sequence complementation, and binding to proteins through RNA structural elements [31–33]. A variety of signaling pathways rely on scaffolds to deliver precise signals. IncRNAs can bind to multiple effector elements in the same space at the same time and integrate the information of the depression effector elements or activity effector elements. IncRNAs act as decoys and can directly bind to proteins, messenger RNAs (mRNAs), and miRNAs [34–36]. Accumulating evidence suggests that the decoy function of IncRNAs plays an irreplaceable role in tumor initiation, progression, and metastasis.

Role of PVT1 in various human tumors

PVT1 is abnormally overexpressed in a variety of cancers and often promotes the occurrence, progression, invasion, metastasis, and chemoradiotherapy resistance in tumors by interacting with c-Myc [37–40]. The most common mechanism of PVT1 in various cancers is regulation of the relevant signaling pathways by competitive endogenous
RNA (ceRNA), which promotes the occurrence and development of cancer. PVT1 can also directly regulate RNA, DNA, and protein expression. For example, in NPC, PVT1 stabilizes the structure of c-Myc by preventing its phosphorylation, promoting DNA repair in NPC cells, and increasing radiotherapy resistance [7]. In addition, PVT1 acts as a scaffold to regulate downstream genes and pathways. For example, in NPC, PVT1 promotes H3K9 acetylation by recruiting KAT2A [41]. PVT1 can recruit EZH2 to the promoter region of LAST2 and inhibit LAST2 expression in patients with NSCLC [42]. Similarly, PVT1 regulates P15/P16 and vascular endothelial growth factor (VEGF) A expression by recruiting EZH2 and signal transducer and activator of transcription (STAT)3 in GC cells [43]. In addition, PVT1 recruits EZH2 to downregulate miR-214 and P53 expression in HCC cells [44]. PVT1 regulates EZH2 binding to ANGPTL4 in CCA cells to inactivate its promoter region and reduce its expression [45]. In CC cells, PVT1 reduces the miR-200b expression by recruiting EZH2 to the promoter region of miR-200b [46]. In androgen-independent castration-resistant PCa, the promoter region of NOV is bound by EZH2 recruited by PVT1, which ultimately inhibits NOV expression [47]. In TC, PVT1 also promotes the proliferation of TC cells by recruiting EZH2, thereby affecting its expression of TSHR [26]. In general, PVT1 overexpression is associated with poor prognosis [48–51]. However, in the early stages of some cancers, such as OC, it predicts a good prognosis [52]. Recently, several studies have shown that PVT1 is involved in the clinical and pathological development of various cancers. The functions and mechanisms of action of PVT1 in human tumors are listed in Tables 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12.

Role of PVT1 in the respiratory system

**PVT1 in nasopharyngeal carcinoma**

NPC originates from nasopharyngeal epithelial cells and is particularly common in Southeast Asia, North Africa, and southern China. New cases accounted for only 0.7% of the total cancer incidence, and the mortality rate has decreased significantly with advancements in medical treatments. However, the treatment of NPC is difficult owing to radiotherapy and chemotherapy resistance, postoperative recurrence, diffusion, and metastasis, which require further exploration to better diagnose and treat patients with NPC [53].

In a study by Cui et al. [54] on the formation, metastasis, and recurrence of NPC, the authors reported that PVT1 promoted tumor stem cell growth by inhibiting miR-1207 and activating the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway (Fig. 1A). In addition, He et al. [7] demonstrated that PVT1 acted as a radioresistant factor, thereby promoting DNA repair and inhibiting apoptosis in NPC cells by activating ATM/Chk2/p53 phosphorylation. Han et al. [55] revealed that PVT1 controls NPC cell radioresistance and proliferation through the miR-515-5p/PIK3CA axis (Fig. 1B). Wang et al. [41] discovered another mechanism by which PVT1 reduces radiotherapy sensitivity in NPC cells. They validated that PVT1 acts as a scaffold to promote H3K9 acetylation by the chromatin modifier KAT2A, thereby activating the downstream expression of nuclear factor 90 through H3K9ac binding to TIF1β. Furthermore, the stability of hypoxia-inducible factor (HIF)-1α mRNA was further strengthened to achieve tumor resistance to radiotherapy.
In conclusion, PVT1 plays an important role in the tumorigenesis and radioresistance of NPC.

**PVT1 in non-small cell lung cancer**

As of 2022, lung cancer accounted for 12% and 13% of all cancers in men and women, respectively [1]. Advanced NSCLC remains the leading cause of cancer-related deaths. However, little progress has been made in understanding its molecular mechanisms. Therefore, a study elucidating the underlying mechanisms of NSCLC is urgently needed.

A previous study showed that PVT1 promotes NSCLC cell proliferation by inhibiting P15 and P21 expression [6]. Another study reported that PVT1 regulates miR-497 to promote tumor formation in patients with NPC (Fig. 1C) [56]. Wan et al. [42] demonstrated that PVT1 repressed the expression of LAST2 by recruiting EZH2 to the

| Tumor type            | Expression | Role                      | Function role                           | miRNAs             | Related genes | References |
|-----------------------|------------|---------------------------|----------------------------------------|--------------------|---------------|------------|
| Nasopharyngeal carcinoma | Upregulation | Oncogene                | Proliferation                          | miR-1207           | P13K/AKT      | [54]       |
| Nasopharyngeal carcinoma | Upregulation | Oncogene                | Proliferation and radioresistance      | miR-515-5p         | PIK3CA        | [55]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation                          | /                  | F15/P21       | [6]        |
| Lung cancer           | Upregulation | Oncogene                | Invasion and proliferation             | miR-497            | /             | [56]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation                          | /                  | LAT52         | [42]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation, migration, invasion, and EMT | miR-497            | YAP1          | [57]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation and migration            | miR-526b           | EZH2          | [58]       |
| Lung cancer           | Upregulation | Oncogene                | Invasion                               | miR-200a/200b      | MMP9          | [59]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation                          | miR-199a-5p        | HIF-1α         | [60]       |
| Lung cancer           | Upregulation | Oncogene                | Angiogenesis                           | miR-29c            | VEGF          | [61]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation and metastasis           | miR-128            | VEGFC         | [62]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation, migration, invasion     | miR-361-3p         | SOX9          | [63]       |
| Lung cancer           | Upregulation | Oncogene                | Migration and invasion                 | miR-760            | IL-6          | [64]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation                          | miR-17-5p          | Bambi         | [65]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation and migration            | miR-148            | RAB34         | [66]       |
| Lung cancer           | Upregulation | Oncogene                | Proliferation, migration, invasion     | miR-551b           | FGFR1         | [67]       |
| Lung cancer           | Upregulation | Oncogene                | Invasion and growth                    | miR-378c           | SLC2A1        | [68]       |
| Lung cancer           | Upregulation | Oncogene                | Radioresistance                        | miR-195            | /             | [69]       |
| Lung cancer           | Upregulation | Oncogene                | Radioresistance                        | miR-424-5p         | CARM1         | [70]       |
| Lung cancer           | Upregulation | Oncogene                | Cisplatin-resistance                   | miR-181a-5p        | SPI           | [71]       |
| Lung cancer           | Upregulation | Oncogene                | Cisplatin-resistance                   | miR-216b           | Beclin-1      | [72]       |
| Study | Tumor type          | Sample size (normal: tumor) | Detection method | \( P \) value | TNM (\( P \) value) | LNM (\( P \) value) | DM (\( P \) value) | OS (\( P \) value) | DFS (\( P \) value) | References |
|-------|---------------------|-----------------------------|------------------|---------------|----------------------|----------------------|------------------|----------------|------------------|------------|
| Cui   | Nasopharyngeal carcinoma | 15:15                      | qRT-PCR         | <0.001        | /                    | /                    | /                | 0.0385         | 0.0261          | [54]       |
| Cui   | Lung cancer          | 108:108                     | qRT-PCR         | <0.05         | 0.003                | <0.001               | 0.571            | 0.014           | 0.036            | [6]        |
| Wan   | Lung cancer          | 105:105                     | qRT-PCR         | <0.05         | 0.001                | 0.011                | /                | /               | /                | [42]       |
| Chen  | Lung cancer          | 80:80                       | qRT-PCR         | <0.0001       | /                    | /                    | /                | /               | /                | [59]       |
| Qi    | Lung cancer          | 30:30                       | qRT-PCR         | <0.05         | /                    | /                    | /                | /               | /                | [63]       |
| Wu    | Lung cancer          | 31:31                       | qRT-PCR         | <0.05         | 0.017                | 0.018                | /                | /               | /                | [69]       |
| Chen  | Lung cancer          | 40:40                       | qRT-PCR         | <0.05         | 0.001                | 0.0146               | /                | /               | /                | [72]       |
Table 3  Functional characterization of PVT1 in digestive system tumors

| Tumor type                  | Expression | Role        | Function role                          | miRNAs   | Related genes | References |
|-----------------------------|------------|-------------|----------------------------------------|----------|---------------|------------|
| Oral squamous cell carcinoma| Upregulation | Oncogene    | Proliferation, invasion, and migration | miR-150-5p | GLUT-1        | [9]        |
| Oral squamous cell carcinoma| Upregulation | Oncogene    | Proliferation and chemoresistance      | miR-194-5p | HIF1α         | [75]       |
| Esophageal cancer           | Upregulation | Oncogene    | Proliferation, migration, and invasion | miR-186-5p | PTTG1         | [10]       |
| Esophageal cancer           | Upregulation | Oncogene    | Growth and invasion                    | miR-203  | LASP1         | [78]       |
| Esophageal cancer           | Upregulation | Oncogene    | Migration and invasion                 | miR-145  | FSCN1         | [79]       |
| Gastric cancer              | Upregulation | Oncogene    | Growth and invasion                    |          | FOXM1         | [84]       |
| Gastric cancer              | Upregulation | Oncogene    | Angiogenesis                           |          | Slug/VEGFA    | [43]       |
| Gastric cancer              | Upregulation | Oncogene    | Growth and invasion                    | miR-186  | HIF-1α        | [85]       |
| Gastric cancer              | Upregulation | Oncogene    | EMT                                     | miR-30a  | Snail         | [87]       |
| Gastric cancer              | Upregulation | Oncogene    | Proliferation                          |          | NOP2          | [92]       |
| Gastric cancer              | Upregulation | Oncogene    | Growth and invasion                    | miR-214  | /             | [44]       |
| Gastric cancer              | Upregulation | Oncogene    | Proliferation                          |          | P53           | [95]       |
| Gastric cancer              | Upregulation | Oncogene    | Migration and invasion                 | miR-3619-5p | MKL1         | [97]       |
| Gastric cancer              | Upregulation | Oncogene    | Invasion and migration                 | miR-186-5p | YAP1         | [98]       |
| Gastric cancer              | Upregulation | Oncogene    | Growth and invasion                    | miR-150  | HIG2          | [99]       |
| Gastric cancer              | Upregulation | Oncogene    | Proliferation                          | miR-424-5p | INCENP       | [100]      |
| Gastric cancer              | Upregulation | Oncogene    | Autophagy                              | miR-365  | ATG3          | [101]      |
| Gastric cancer              | Upregulation | Oncogene    | Proliferation, migration, and invasion | miR-186  | SEMA4D        | [14]       |
| Cholangiocarcinoma          | Upregulation | Oncogene    | Migration and invasion                 |          | ANGPTL4       | [45]       |
| Gallbladder cancer          | Upregulation | Oncogene    | Proliferation                          | miR-18b-5p | HIF1α        | [13]       |
| Gallbladder cancer          | Upregulation | Oncogene    | Proliferation                          | miR-143  | HK2           | [105]      |
| Gallbladder cancer          | Upregulation | Oncogene    | Growth and invasion                    | miR-30d-5p | /             | [106]      |
| Pancreatic cancer           | Upregulation | Oncogene    | EMT                                    |          | TGF-β/Smad    | [108]      |
| Pancreatic cancer           | Upregulation | Oncogene    | EMT                                    |          | P21           | [109]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Proliferation and migration            | miR-448  | SERBP1        | [110]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Progression and glycolysis             | miR-519d-3p | HIF-1A       | [111]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Autophagy                              | miR-20a-5p | ULK1          | [113]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Chemoresistance                        |          | EZH2          | [115]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Chemoresistance                        | miR-1207 | /             | [116]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Chemoresistance                        | miR-409  | SHH/GLI/MGMT  | [117]      |
| Pancreatic cancer           | Upregulation | Oncogene    | Chemoresistance                        | miR-619-5p | Pygo2        | [118]      |
promoter region of LAST2. LAST2 is an upstream phosphokinase of the Hippo signaling pathway that can phosphorylate YAP1 to reduce its expression and activate the Hippo signaling pathway. Subsequently, Zeng et al. [57] further confirmed that PVT1 promoted YAP1 expression by downregulating miR-497 by mediating EZH2, leading to the inhibition of the Hippo signaling pathway. Ultimately, the neurogenic locus notch homolog protein 1 (NOTCH1) signaling pathway was activated to promote NSCLC cell proliferation, migration, and epithelial–mesenchymal transition (EMT) (Fig. 1D). Another study emphasized that PVT1 upregulated EZH2 by acting as a sponge for miR-526b (Fig. 1E) [58].

PVT1 can also promote NSCLC progression as a ceRNA. Chen et al. [59] showed that PVT1 overexpression promoted NSCLC invasion by competitively binding miR-200a/200b to upregulate MMP9 expression (Fig. 1F). Additionally, Wang et al. [60] indicated that PVT1 was overexpressed in patients with hypoxic NSCLC and upregulated HIF-1α expression by acting as a sponge for miR-199a-5p. These findings suggest that PVT1 may serve as a potential therapeutic target for the treatment of hypoxic NSCLC (Fig. 1G). Several studies have indicated an important role of the lncRNA–miRNA–mRNA axis in patients with NSCLC. Specifically, PVT1 reportedly contributed to the proliferation, migration, invasion, and apoptosis of NSCLC cells by upregulating VEGF, VEGFC, SOX9, interleukin-6, BAMBI, RAB34, fibroblast growth factor receptor 1 (FGFR1), and SLC2A1 via miR-29c, miR-128, miR-361-3p, miR-760, miR-17-5p, miR-148, miR-551b, and miR-378c regulation (Fig. 1H–O) [61–68], respectively.

PVT1 also plays an important role in radiotherapy and chemotherapy in patients with advanced NSCLC. Wu et al. [69] found that miR-195 release after PVT1 knockdown increased NSCLC cell apoptosis during radiotherapy (Fig. 1P). Subsequently, Wang et al. [70] revealed that PVT1 and CARM1 downregulation led to miR-424-5p overexpression, which may improve radiosensitivity in patients with NSCLC (Fig. 1Q). Interestingly,
| Study | Tumor type                  | Sample size (normal: tumor) | Detection method | $P$ value | TNM ($P$ value) | LNM ($P$ value) | DM ($P$ value) | OS ($P$ value) | DFS ($P$ value) | References |
|-------|----------------------------|----------------------------|------------------|----------|----------------|----------------|--------------|--------------|---------------|------------|
| Li    | Oral squamous cell carcinoma | 70:70                      | qRT-PCR          | < 0.01   | < 0.05         | /              | < 0.01       | /            | /             | [9]        |
| Zheng | Esophageal cancer           | 77:77                      | qRT-PCR          | 0.002    | 0.009          | /              | /            | /            | /            | [77]       |
| Li    | Esophageal cancer           | 104:104                    | qRT-PCR          | 0.024    | 0.001          | 0.597          | /            | 0.005        | 0.011       | [78]       |
| Xu    | Gastric cancer              | 190:190                    | qRT-PCR          | < 0.001  | /              | /              | /            | /            | /            | [84]       |
| Huang | Gastric cancer              | 68.68                      | qRT-PCR          | < 0.05   | 0.022          | 0.005          | /            | /            | /            | [85]       |
| Li    | Gastric cancer              | 20:20                      | qRT-PCR          | 0.0004   | /              | /              | /            | /            | /            | [86]       |
| Wang  | Gastric cancer              | 42.42                      | qRT-PCR          | < 0.01   | < 0.05         | < 0.01         | /            | /            | /            | [87]       |
| Ding  | Liver cancer                | 58.58                      | qRT-PCR          | 0.042    | 0.005          | /              | /            | /            | 0.021       | [12]       |
| Wang  | Liver cancer                | 89.89                      | qRT-PCR          | < 0.05   | 0.007          | /              | /            | 0.0104       | 0.0043      | [92]       |
| Gou   | Liver cancer                | 92.92                      | qRT-PCR          | < 0.05   | 0.005          | /              | /            | /            | /            | [44]       |
| Guo   | Liver cancer                | 121:121                    | qRT-PCR          | < 0.05   | 0.010          | /              | /            | /            | /            | [95]       |
| Lan   | Liver cancer                | 48.48                      | qRT-PCR          | < 0.001  | < 0.05         | /              | /            | 0.035        | /            | [98]       |
| Yang  | Liver cancer                | 80.80                      | qRT-PCR          | 0.005    | 0.041          | /              | /            | /            | /            | [101]      |
| Jin   | Gallbladder cancer          | 55.55                      | qRT-PCR          | < 0.001  | < 0.011        | < 0.032        | /            | < 0.001      | /            | [13]       |
| Chen  | Gallbladder cancer          | 20.20                      | qRT-PCR          | < 0.05   | < 0.001        | /              | 0.047        | < 0.05       | /            | [105]      |
| Wu    | Pancreatic cancer           | 30.20                      | qRT-PCR          | < 0.01   | < 0.05         | < 0.05         | /            | /            | /            | [109]      |
| Zhao  | Pancreatic cancer           | 34.34                      | qRT-PCR          | < 0.05   | 0.038          | /              | 0.000        | /            | /            | [110]      |
| Sun   | Pancreatic cancer           | 30.30                      | qRT-PCR          | < 0.001  | 0.05           | 0.004          | /            | /            | < 0.05       | [111]      |
| Huang | Pancreatic cancer           | 68.68                      | qRT-PCR          | < 0.001  | < 0.05         | /              | /            | < 0.05       | /            | [113]      |
| Zeng  | Colorectal cancer           | 70.70                      | qRT-PCR          | < 0.001  | 0.029          | 0.014          | /            | /            | /            | [126]      |
| Wu    | Colorectal cancer           | 72.72                      | qRT-PCR          | < 0.05   | < 0.01         | < 0.05         | /            | /            | /            | [127]      |
| Chai  | Colorectal cancer           | 20.20                      | qRT-PCR          | < 0.001  | /              | /              | /            | /            | /            | [129]      |
| Yu    | Colorectal cancer           | 60.60                      | qRT-PCR          | < 0.05   | 0.040          | 0.006          | /            | /            | < 0.05       | [130]      |
| Liu   | Colorectal cancer           | 62.62                      | qRT-PCR          | < 0.05   | 0.0001         | 0.005          | 0.002        | /            | /            | [133]      |
| Ping  | Colorectal cancer           | 112.112                    | qRT-PCR          | < 0.05   | 0.001          | 0.015          | 0.007        | /            | /            | [136]      |
the Chinese herbal prescription Xiaoji decoction enhanced the efficacy of cisplatin in patients with NSCLC by decreasing the expression of the PVT1/miR-181a-5p/SP1 axis (Fig. 1R) [71]. Similarly, Chen et al. [72] reported that PVT1 enhances cisplatin resistance in patients with NSCLC by regulating the miR-216b/Beclin-1 axis (Fig. 1S).

Table 5 Functional characterization of PVT1 in endocrine reproductive system tumors

| Tumor type             | Expression | Role                      | Function role                  | miRNAs                  | Related genes     | References |
|------------------------|------------|---------------------------|--------------------------------|-------------------------|-------------------|------------|
| Breast cancer          | Upregulation | Oncogene                  | Proliferation                  | /                       | P21               | [140]      |
| Breast cancer          | Upregulation | Oncogene                  | EMT                             | /                       | SOX2              | [142]      |
| Breast cancer          | Upregulation | Oncogene                  | Migration                       | /                       | Claudin 4         | [145]      |
| Breast cancer          | Upregulation | Oncogene                  | Proliferation                   | miR-1207-5p             | STAT6             | [146]      |
| Breast cancer          | Upregulation | Oncogene                  | EMT and proliferation           | miR-1204                | VDR               | [147]      |
| Breast cancer          | Upregulation | Oncogene                  | Proliferation                   | miR-543                 | TRPS1             | [148]      |
| Breast cancer          | Upregulation | Oncogene                  | Chemoresistance                 | /                       | Nrf2              | [149]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Growth and invasion             | miR-133a                | /                 | [151]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation                   | miR-140                 | /                 | [152]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-214          | /                 | [153]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Growth                          | /                       | PS7               | [154]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-543          | SERPIN1           | [155]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Chemoresistance                 | /                       | TGF-β, p-Smad4, Caspase-3 | [19]       |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation, migration, invasion, viability, and EMT | miR-148a-3p | AGO1 | [156]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-370          | FOXM1             | [158]      |
| Ovarian cancer         | Upregulation | Oncogene                  | Proliferation and invasion      | /                       | JAK2/STAT3/PD-L1 | [159]      |
| Cervical cancer        | Upregulation | Oncogene                  | Proliferation and migration     | miR-200b               | /                 | [46]       |
| Cervical cancer        | Upregulation | Oncogene                  | EMT and chemoresistance         | miR-195               | /                 | [163]      |
| Cervical cancer        | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-424          | /                 | [164]      |
| Cervical cancer        | Upregulation | Oncogene                  | Growth                          | /                       | TGF-β1            | [165]      |
| Cervical cancer        | Upregulation | Oncogene                  | Growth and apoptosis            | miR-16                | NF-κB             | [166]      |
| Cervical cancer        | Upregulation | Oncogene                  | Growth and invasion             | miR-486-3p            | ECM1              | [167]      |
| Cervical cancer        | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-503          | ARL2              | [168]      |
| Cervical cancer        | Upregulation | Oncogene                  | Growth and invasion             | miR-140-5p            | Smad3             | [169]      |
| Endometrial carcinoma  | Upregulation | Oncogene                  | Proliferation, migration, and invasion | miR-195-5p | FGFR1/FGF2 | [18]       |
Table 6  Main characteristics of the studies included in the review of endocrine reproductive system tumors

| Study  | Tumor type    | Sample size (normal:tumor) | Detection method | $P$ value | TNM ($P$ value) | LNM ($P$ value) | DM ($P$ value) | OS ($P$ value) | DFS ($P$ value) | References |
|--------|---------------|-----------------------------|------------------|-----------|----------------|----------------|-------------|--------------|---------------|------------|
| Li     | Breast cancer | 84:84                       | qRT-PCR          | < 0.01    | 0.061          | 0.117          | /           | 0.034        | 0.045         | [140]      |
| Wang   | Breast cancer | 38:38                       | qRT-PCR          | < 0.0001  | 0.002          | 0.023          | 0.009       | 0.003        | /             | [142]      |
| Wang   | Breast cancer | 30:30                       | qRT-PCR          | < 0.05    | /              | /             | /           | /            | /             | [148]      |
| Yang   | Ovarian cancer| 42:42                       | qRT-PCR          | < 0.01    | /              | /             | /           | <0.05        | /             | [141]      |
| Ding   | Ovarian cancer| /                           | qRT-PCR          | < 0.05    | < 0.05         | /             | /           | 0.0230       | /             | [152]      |
| Chen   | Ovarian cancer| 58:231                      | qRT-PCR          | < 0.05    | < 0.05         | 0.436          | /           | 0.020        | 0.016        | [153]      |
| Qu     | Ovarian cancer| 42:42                       | qRT-PCR          | < 0.01    | /              | /             | /           | 0.012        | /             | [155]      |
| El-Khazragy | Ovarian cancer | 30:100                      | qRT-PCR          | < 0.001   | 0.001          | /             | 0.001       | 0.001        | 0.01          | [157]      |
| Chen   | Ovarian cancer| 38:91                       | qRT-PCR          | < 0.001   | < 0.05         | < 0.05        | /           | < 0.001      | 0.002        | [159]      |
| Iden   | Cervical cancer| 30:127                      | qRT-PCR          | < 0.001   | /              | /             | /           | 0.03         | /             | [17]       |
| Zhang  | Cervical cancer| 90:90                       | qRT-PCR          | < 0.001   | /              | /             | /           | 0.015        | /             | [46]       |
| Wang   | Cervical cancer| 39:156                      | qRT-PCR          | < 0.05    | /              | /             | /           | < 0.05       | /             | [165]      |
These results suggest that lncRNA PVT1 plays a vital role in the invasion, proliferation, migration, drug resistance, and radiosensitivity of NSCLC cells.

**Role of PVT1 in the digestive system**

*PVT1 in oral squamous cell carcinoma*

OSCC is a malignant tumor derived from oral epithelial cells with a high incidence in Southeast Asia and southern China that may be related to dietary habits, such as betel nut consumption. In 2021, there were 377,713 new cases, accounting for 2% of all cancers, and 177,757 new deaths accounting for 1.8% of all cancers [73]. The number of patients with OSCC is expected to increase by 30% within the next 10 years, with a 5-year survival rate of only 50% [53]. Therefore, further studies on the pathogenesis of OSCC are required to improve its diagnosis, treatment, and prognosis.

Li et al. [9] verified that PVT1 downregulation inhibits glucose transporter protein type 1 through miR-150-5p, regulates glucose metabolism in tumor cells, promotes invasion and migration of OSCC cells, and inhibits cell apoptosis (Fig. 2A). Wang et al. [74] found that PVT1 accelerated the development of EMT and led to tumor progression in patients with OSCC.

Cisplatin is a chemotherapeutic agent commonly used for the treatment of OSCC. Most patients with OSCC with poor prognosis have multiple drug resistance; however, the underlying mechanism remains unclear. Wang et al. [75] reported that PVT1

### Table 7 Functional characterization of PVT1 in urinary system tumors

| Tumor type       | Expression | Role         | Function role                                                                 | miRNAs                  | Related genes                          | References |
|------------------|------------|--------------|-------------------------------------------------------------------------------|-------------------------|----------------------------------------|------------|
| Renal cell carcinoma | Upregulation | Oncogene     | Apoptosis                                                                     | /                       | EGFR/AKT/MYC                           | [173]      |
| Renal cell carcinoma | Upregulation | Oncogene     | Apoptosis                                                                     | /                       | Mcl-1                                  | [174]      |
| Renal cell carcinoma | Upregulation | Oncogene     | Proliferation, migration, invasion, and angiogenesis                          | miR-200s                | BMI1, ZEB1 and ZEB2                    | [179]      |
| Renal cell carcinoma | Upregulation | Oncogene     | Proliferation, invasion, and EMT                                             | miR-16-5p               | /                                      | [180]      |
| Bladder cancer    | Upregulation | Oncogene     | Proliferation, migration, invasion and metastasis                             | miR-31                  | CDK1                                   | [184]      |
| Bladder cancer    | Upregulation | Oncogene     | Proliferation, migration, and apoptosis                                       | miR-128                 | VEGF/C                                 | [185]      |
| Bladder cancer    | Upregulation | Oncogene     | Proliferation, invasion, apoptosis, and chemoresistance                      | miR-194-5p              | BCLAF1                                 | [186]      |
| Bladder cancer    | Upregulation | Oncogene     | Growth                                                                        | /                       | Wnt/β-catenin                          | [187]      |
| Prostate cancer   | Upregulation | Oncogene     | Growth                                                                        | /                       | c-Myc                                  | [189]      |
| Prostate cancer   | Upregulation | Oncogene     | EMT                                                                            | miR-186                 | Twist1                                 | [190]      |
| Prostate cancer   | Upregulation | Oncogene     | Proliferation and migration                                                   | /                       | P38                                    | [191]      |
| Prostate cancer   | Upregulation | Oncogene     | Metastasis                                                                     | /                       | NOP2                                   | [192]      |
| Prostate cancer   | Upregulation | Oncogene     | Migration and invasion                                                        | miR-15a-5p              | KIF23                                  | [193]      |
| Prostate cancer   | Upregulation | Oncogene     | Growth                                                                         | miR-146a                | /                                      | [194]      |
Table 8  Main characteristics of the studies included in the review of urinary system tumors

| Study | Tumor type   | Sample size (normal: tumor) | Detection method | $P$ value | TNM ($P$ value) | LNM ($P$ value) | DM ($P$ value) | OS ($P$ value) | DFS ($P$ value) | References |
|-------|--------------|------------------------------|------------------|-----------|----------------|----------------|----------------|---------------|----------------|------------|
| Li    | Renal cancer | 40:40                        | qRT-PCR          | $< 0.001$ | $< 0.05$       | /              | /              | $< 0.01$      | /              | [173]      |
| Zhuang| Bladder cancer | 32:32                      | qRT-PCR          | $< 0.01$  | 0.002          | /              | /              | /             | /              | [21]       |
| Li    | Bladder cancer | 98:98                      | qRT-PCR          | $< 0.001$ | 0.02           | $< 0.001$      | /              | 0.004         | /              | [183]      |
| Tian  | Bladder cancer | 35:35                      | qRT-PCR          | $< 0.01$  | /              | /              | /              | /             | /              | [184]      |
| Chen  | Bladder cancer | 27:43                      | qRT-PCR          | $< 0.01$  | $< 0.001$      | 0.394          | /              | /             | /              | [186]      |
| Yang  | Prostate cancer | 30:152                    | qRT-PCR          | $< 0.0001$| $< 0.01$      | > 0.05         | /              | 0.0127        | 0.0097        | [189]      |
| Chang | Prostate cancer | 52:499                    | qRT-PCR          | $0.05$    | /              | /              | /              | 0.046         | /              | [190]      |
| Wu    | Prostate cancer | 25:25                      | qRT-PCR          | $< 0.01$  | /              | /              | /              | /             | /              | [193]      |
regulates cisplatin resistance in patients with OSCC through the miR-194-5p/HIF-1α signaling pathway (Fig. 2B).

These studies confirm that PVT1 is responsible for the occurrence, invasion, and drug resistance of OSCC cells.

**PVT1 in esophageal cancer**

EC causes 500,000 deaths annually, accounting for 5.5% of all cancer-related deaths worldwide. Esophageal squamous cell carcinoma (ESCC) is the most common type [76]. The latest data show that the incidence of EC is only 3.1% among all cancers, although its mortality rate is 5.5% [53]. ESCC is mainly associated with a poor prognosis because early detection is difficult. Most patients present with extensive metastases at the time of diagnosis [76]. Therefore, its pathogenesis should be further explored to improve the diagnosis and treatment of EC.

Yang et al. [10] reported that PVT1 might function as a ceRNA by targeting miR-186-5p to upregulate the oncogene PTTG1 (Fig. 2C). Zheng et al. [77] revealed that lncRNA PVT1 induces EMT by regulating the expression of EMT markers (E-cadherin, N-cadherin, and vimentin) (Fig. 2D). Li et al. [78] found that PVT1 upregulates LASP1 expression by targeting miR-203, thereby promoting ESCC progression (Fig. 2E). Shen et al. [79] demonstrated upregulated miR-145 and downregulated FSCN1 expression after PVT1 knockout, which inhibited ESCC cell invasion, migration, and survival (Fig. 2F). Xu et al. [80] discovered that silencing PVT1 might lead to decreased YAP1 expression through phosphorylated LATS1, thereby inhibiting tumor growth (Fig. 2G).

In summary, these studies indicate that PVT1 is involved in ESCC progression and acts as a diagnostic biomarker and therapeutic target.

**PVT1 in gastric cancer**

GC is the fourth most common cancer and the second most lethal malignant tumor worldwide. With the development of gastrointestinal endoscopy technology and GC drugs, GC death rates have decreased in recent years. However, advanced GC remains

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**Table 9 Functional characterization of PVT1 in immune system**

| Disease type                  | Expression | Role         | Function role                          | miRNAs | Related genes | References |
|------------------------------|------------|--------------|----------------------------------------|---------|---------------|------------|
| Sjogren’s syndrome           | Upregulation | Pathogenic factor | Activate CD4⁺ T cells | /       | /             | [196]      |
| Heart transplant rejection   | Downregulation | Protection factor | Regulation of autophagy in regulatory T cells | miR-146a | /             | [197]      |
| Infectious myocardial injury | Upregulation | Pathogenic factor | Promote macrophage polarization | miR-29a | HMGB1         | [198]      |
| Immune thrombocytopenia      | Downregulation | Protection factor | Downregulation of Th17 cell differentiation | /       | NOTCH1        | [199]      |
| Tumor immune suppression     | Upregulation | Pathogenic factor | Enhancing the function of MDSCs | /       | /             | [200]      |
Table 10  Main characteristics of the studies included on the immune system

| Study | Disease type               | Sample size (normal: tumor) | Detection method | $P$ value | TNM ($P$ value) | LNM ($P$ value) | DM ($P$ value) | OS ($P$ value) | DFS ($P$ value) | References |
|-------|---------------------------|-----------------------------|------------------|-----------|----------------|----------------|----------------|----------------|----------------|------------|
| Fu    | Sjogren’s syndrome        | 4:4                         | qRT-PCR          | < 0.05    | /              | /              | /              | /              | /              | [196]      |
| Lu    | Transplant rejection      | 6:6                         | qRT-PCR          | < 0.01    | /              | /              | /              | /              | /              | [197]      |
| Yu    | Immune thrombocytopenia   | 12:12                       | qRT-PCR          | < 0.01    | /              | /              | /              | /              | /              | [199]      |
difficult to cure [1]. Identifying new biomarkers and therapeutic methods is an effective method for determining the pathogenesis of GC.

Recent studies have shown that PVT1 promotes GC migration, invasion, and lymph node metastasis (LNM) [81–83]. Kong et al. [8] reported that PVT1 negatively regulates P15/P16 through the epigenetic recruitment of EZH2, thereby promoting GC proliferation (Fig. 2H). Subsequently, Xu et al. [84] revealed that PVT1 promotes GC growth and invasion through a positive feedback loop with FOXM1 (Fig. 2I). In addition, Zhao et al. [43] found that PVT1 binds to STAT3, resulting in

| Tumor type        | Expression | Role                  | Function role                  | miRNAs                      | Related genes | References |
|-------------------|------------|-----------------------|--------------------------------|-----------------------------|---------------|------------|
| Glioma            | Upregulation | Oncogene              | Growth                         | miR-190a-5p/               | MEF2C         | [202]      |
|                   |            |                       |                                | miR-488-3p                 |               |            |
|                   |            |                       |                                | miR-424                    | /             | [203]      |
| Glioma            | Upregulation | Oncogene              | Cell activity, migration, and invasion | miR-200a                  | /             | [204]      |
| Glioma            | Upregulation | Oncogene              | Growth and invasion            | miR-128-3p                 | GREM1         | [23]       |
| Glioma            | Upregulation | Oncogene              | Proliferation and migration    | miR-128-1-5p               | PTBP1         | [206]      |
| Glioma            | Upregulation | Oncogene              | Proliferation, invasion, and apoptosis | miR-1301-3p               | TMBIM6        | [207]      |
| Glioma            | Upregulation | Oncogene              | EMT                             | miR-1207-3p                | HNF1B         | [208]      |
| Glioma            | Upregulation | Oncogene              | Proliferation and migration    | miR-186                    | Atg7/Bclin1   | [209]      |
| Glioma            | Upregulation | Oncogene              | Proliferation, migration, invasion, stemness, and chemoresistance | miR-365                   | ELF4/SOX2     | [210]      |
| Osteosarcoma      | Upregulation | Oncogene              | Proliferation, migration, and invasion | miR-195                   | BCL2          | [24]       |
| Thyroid cancer    | Upregulation | Oncogene              | Proliferation                   | /                          | TSHR          | [26]       |
| Thyroid cancer    | Upregulation | Oncogene              | Viability and invasion          | miR-30a                    | IGF1R         | [212]      |
| Thyroid cancer    | Upregulation | Oncogene              | Proliferating, invasion, and apoptosis | miR-423-5p               | PAK3          | [213]      |
| Osteosarcoma      | Upregulation | Oncogene              | Growth and invasion             | miR-497                    | HK2           | [217]      |
| Osteosarcoma      | Upregulation | Oncogene              | Growth and metastasis           | miR-183-5p                 | ERG           | [218]      |
| Osteosarcoma      | Upregulation | Oncogene              | Metastasis                      | miR-484                    | /             | [219]      |
| Osteosarcoma      | Upregulation | Oncogene              | Chemoresistance                 | miR-152                    | c-MET/PI3K/AKT | [222]      |
| Multiple myeloma  | Upregulation | Oncogene              | Proliferation                   | miR-203a                   | /             | [25]       |
| Leukemia          | Upregulation | Oncogene              | Growth, migration, invasion, and apoptosis | miR-29 family             | WAVE1         | [231]      |
Table 12  Main characteristics of the studies included in the review of other system tumors

| Study | Tumor type       | Sample size (normal:tumor) | Detection method | P value | TNM (P value) | LNM (P value) | DM (P value) | OS (P value) | DFS (P value) | References |
|-------|------------------|----------------------------|------------------|---------|---------------|---------------|--------------|--------------|---------------|------------|
| Gong  | Glioma           | 28:30                      | qRT-PCR          | <0.01   | <0.01         | /             | /            | 0.0240       | /             | [210]      |
| Zhou  | Osteosarcoma     | 26:26                      | qRT-PCR          | <0.05   | /             | /             | /            | <0.05        | /             | [24]       |
| Song  | Osteosarcoma     | 46:46                      | qRT-PCR          | 0.0009  | <0.001        | /             | /            | 0.011        | /             | [217]      |
| Yan   | Osteosarcoma     | 48:48                      | qRT-PCR          | <0.0001 | 0.008         | /             | 0.001        | 0.0001       | /             | [219]      |
| Xun   | Osteosarcoma     | 78:78                      | qRT-PCR          | <0.001  | 0.000         | 0.017         | 0.017        | /             | /             | [220]      |
| Zhou  | Thyroid cancer   | 84:84                      | qRT-PCR          | <0.0001 | /             | /             | /            | /             | /             | [26]       |
| Feng  | Thyroid cancer   | 72:72                      | qRT-PCR          | <0.005  | <0.01         | <0.01         | /            | /             | /             | [212]      |
| Lin   | Thyroid cancer   | 47:47                      | qRT-PCR          | <0.001  | /             | /             | /            | /             | /             | [213]      |
| Yang  | Multiple myeloma | 33:14                      | qRT-PCR          | <0.005  | /             | /             | /            | /             | /             | [25]       |
| Yang  | Leukemia         | 62:286                     | qRT-PCR          | <0.001  | /             | /             | /            | <0.001       | /             | [27]       |
| Izadifard | AML             | 40:22                      | qRT-PCR          | 0.017   | /             | /             | /            | /             | /             | [227]      |
| El-Khazragy | AML           | 70:20                      | qRT-PCR          | <0.01   | /             | /             | /            | /             | /             | [228]      |
| Cheng | AML              | 30:30                      | qRT-PCR          | <0.01   | /             | /             | /            | /             | /             | [231]      |
the recruitment of STAT3 to VEGFA and Slug promoters, whereas increased VEGFA led to angiogenesis and increased Slug-mediated GC vasculogenic mimicry network formation (Fig. 2 J).

PVT1 can also regulate tumor progression through the lncRNA–miRNA–mRNA axis in patients with GC. Huang et al. [85] reported that PVT1 plays a key role in GC pathogenesis and may be a potential therapeutic target via miR-186/HIF-1α signaling (Fig. 2K). Similarly, Li et al. [86] indicated that PVT1 promotes GC growth and invasion by competitively binding to miR-152 to regulate CD151 and FGF2 (Fig. 2L). Furthermore, Wang et al. [87] demonstrated that PVT1 controls the EMT of GC via the miR-30a/Snail axis (Fig. 2 M).

PVT1 is also involved in multidrug resistance in patients with GC. Zhang et al. [88] reported that PVT1 promotes the expression of adenosine triphosphate-dependent efflux pump P-glycoprotein protein by upregulating multidrug resistance 1 (MDR1) and multidrug resistance-related protein 1 (MRP1) expression, thereby leading to the occurrence of multidrug resistance (Fig. 2 N).

Thus, PVT1 can be used as a biomarker for the diagnosis and prognosis of GC. High expression often represents deep infiltration; advanced tumor, node, metastasis (TNM) stages; and poor prognosis.
Although the incidence of HCC has gradually stabilized after rapid growth in recent decades, the HCC survival rate is only 20% [1]. Approximately one-quarter of patients with HCC have genetic mutations [89]. Therefore, the pathogenesis of HCC should be studied to identify novel targets and treatments.

Ding et al. [12] found that increased PVT1 often indicated poor prognosis and a high recurrence rate, which was closely related to alpha-fetoprotein levels. Yu et al. [90, 91] suggested that PVT1 can be combined with several other lncRNAs as a complementary diagnostic tool for HCC. Wang et al. [92] revealed that hepatitis B virus (HBV) infection promotes proliferation, development, and stem cell characteristics in HCC cells by enhancing the transforming growth factor beta (TGF-β)1/lncRNA-hPVT1/NOP2 signaling pathway, thereby accelerating the cell cycle. Similarly, Yan et al. [93] found that PVT1 upregulation was more common in early-onset than late-onset HCC after HBV infection. Subsequently, Jiang et al. [94] confirmed that PVT1 expression in HCC cells caused by HBV infection was significantly higher than that in HCC cells without HBV infection. Gou et al. [44] found that PVT1 interacts with EZH2 to downregulate miR-214 and promote the proliferation and invasion of HCC cells. Another research group revealed that PVT1 increases the stability of the MDM2 protein by enhancing EZH2 and inhibiting P53 protein expression to promote HCC cell proliferation.
cell proliferation [95]. Furthermore, Zhang et al. [96] speculated that PVT1 may play an important role in the occurrence and development of HCC by affecting the DLC1 and Hippo signaling pathways.

Increasing evidence shows that PVT1 functions as a ceRNA through IncRNA–miRNA–mRNA signaling. A previous study demonstrated that PVT1 upregulates the MKL1 expression by binding to miR-3619-5p in a positive feedback pathway. MKL1 in turn promotes PVT1 expression by binding to the CArG box, which is located in the PVT1 promoter region (Fig. 3A) [97]. Subsequently, several studies have shown that PVT1 promotes the invasion, migration, and proliferation of HCC cells by upregulating YAP1, HIG2, INCENP, and ATG3 by modulating miR-186-5p, miR-150, miR-424-5p, and miR-365 (Fig. 3B–E) [98–101], respectively.

Interferon alpha (IFN-α) has a significant effect on prolonging the postoperative disease-free survival and prognosis of patients with HCC, although patients' tolerance to IFN-α remains an unsolved problem. A recent study suggests that IFN-α decreases PVT1 methylation by regulating H3K4me3 in the PVT1 promoter region, thereby increasing PVT1 expression. PVT1 subsequently reduces STAT1 phosphorylation, thereby blocking the IFN-α signaling pathway (Fig. 3F) [102].
The above evidence suggests that PVT1 plays an important role in the invasion, migration, proliferation, and drug resistance of HCC.

**PVT1 in gallbladder cancer and cholangiocarcinoma**

GBC is a rare disease that is caused by long-term gallstones and cholecystitis. The prognosis of GBC is usually poor because of early metastasis [103]. CCA is mainly derived from bile duct epithelial cells and peribiliary glands or hepatocytes. CCA is a fatal epithelial malignancy, and most patients have no identifiable risk factors [104]. Therefore, early detection of the related biomarkers can facilitate the early diagnosis of GBC and CCA, which is crucial for improving patient prognosis.

Yu et al. [14] showed that SRY-box transcription factor 2 (SOX2) activates the PVT1/miR-186/SEMA4D axis by promoting PVT1 expression, thereby enhancing CCA cell viability (Fig. 3G). Another study showed that PVT1 inactivated the ANGPTL4 promoter region by binding to EZH2, thereby regulating CCA vascular endothelial cell apoptosis (Fig. 3H) [45]. Similarly, Jin et al. [13] demonstrated that PVT1 recruits DNA methyltransferase through EZH2 and inhibits miR-18b-5p, thereby upregulating HIF-1α and promoting GBC cell proliferation (Fig. 3I). Moreover, Chen et al. [105] found that PVT1 controls aerobic glucose metabolism in GBC cells through the PVT1/miR-143/HK2 axis, thereby promoting tumor proliferation and metastasis (Fig. 3J). Liu et al. [106] reported that PVT1 promotes GBC progression by acting as a ceRNA of miR-30d-5p (Fig. 3K).

In conclusion, PVT1 shows strong carcinogenicity and can be used as a potential biomarker and therapeutic target in CBC and CCA.

**PVT1 in pancreatic cancer**

PC is the leading cause of cancer-related deaths worldwide, and is one of the top five causes of cancer-related deaths in the USA. According to the latest cancer statistics, PC has a 5-year survival rate of only 11%. Therefore, further exploration of the molecular markers is crucial for the early diagnosis and treatment of PC [1, 107].

Xie et al. [15] found that PVT1 and HOTAIR may serve as biomarkers for predicting early-stage PC. Two years later, Zhang et al. [108] demonstrated that PVT1 regulates PC cell survival, metastasis, and EMT by affecting the TGF-β/Smad signaling pathway. Similarly, Wu et al. [109] reported that silencing PVT1 increased tumor suppressor P21 and downregulated the EMT transcription factors Snail and ZEB1, suggesting that PVT1 affects EMT through P21 in PC cells. Moreover, Zhao et al. [110] showed that PVT1 promotes PC cell proliferation and migration by functioning as a ceRNA to regulate SERBP1 by sequestering miR-448 (Fig. 3L). Another study reported that PVT1 acts as a sponge for miR-519d-3p to modulate HIF-1α, which in turn activates angiogenesis, glucose metabolism, cell proliferation, migration, and metastasis (Fig. 3M) [111]. Subsequently, Zhu et al. [112] reported a positive feedback regulatory loop between PVT1 and HIF-1α, indicating that HIF-1α promotes PVT1 expression in hypoxia, whereas PVT1 promotes HIF-1α expression in normoxic environments. In addition, Huang et al. [113] revealed that PVT1 promotes the development of PC by regulating miR-20a-5p/ULK1 to increase cellular protective autophagy (Fig. 3N).
Chemotherapeutic drugs, such as gemcitabine (GEM), are important in the treatment of patients with advanced PC. Therefore, predicting the efficacy of chemotherapy and exploring the causes of chemotherapy resistance are important for improving patient prognosis and making correct treatment decisions. Wang et al. [114] pointed out that the combination of PVT1, HOTTIP, and MALAT1 may be a new noninvasive biomarker for predicting GEM efficacy in patients with PC. Another study showed that PVT1 and EZH2 combine to form a complex that promotes c-Myc expression and enhances PC resistance to GEM (Fig. 3O) [40]. Another study by Sun et al. [115] showed that HAT1 improves the resistance of PC to chemotherapy by promoting PVT1 expression and inhibiting EZH2 degradation. Moreover, You et al. [116] confirmed that the chemotherapy resistance of PC can be inhibited by silencing PVT1 or overexpressing miR-1207 (Fig. 3P). Furthermore, Shi et al. [117] showed that PVT1 can directly target miR-409 to promote the SHH/GLI/MBT signaling pathway and enhance chemoresistance to GEM (Fig. 3Q). Similarly, Zhou et al. [118] found that PVT1 activates the Wnt/β-catenin signaling pathway via the miR-619-5p/Pyg02 axis to influence the chemotherapeutic sensitivity of GEM (Fig. 3R). A year later, Liu et al. [119] revealed that PVT1 knockdown inhibited autophagy by regulating the miR-143/HIF-1α/VMP1 axis, thereby improving PC cell sensitivity to chemotherapy (Fig. 3S).

Overall, PVT1 is strongly correlated with drug resistance in patients with PC and can be used as a new biomarker for PC.

**PVT1 in colorectal cancer**

CRC is the third most common cancer worldwide, with 151,030 new cases estimated to occur by 2022 [1]. CRC occurs at a younger age and is expected to become one of the leading causes of cancer-related deaths among people aged 20–49 years by 2030 [120, 121]. Developing more sensitive screening methods, enriching treatment options, and further exploring the role of PVT1 in CRC is urgently needed.

PVT1 upregulation promotes the proliferation, invasion, and metastasis of CRC and suggests poor prognosis [48–51]. PVT1 is a highly effective biomarker for early CRC screening and has greater diagnostic and prognostic value than that of carcinoembryonic antigen [122, 123]. Zhang et al. [11] confirmed that PVT1 promotes CRC cell proliferation and metastasis by inhibiting miR-26b as an endogenous sponge (Fig. 4A). In addition, Guo et al. [124] reported that PVT1 in extracellular vesicles promotes CRC cell progression. Four years later, Lai et al. [125] demonstrated that PVT1 in exosomes upregulates VEGFA and EGFR by regulating miR-152-3p expression, thereby promoting the distant metastasis of CRC cells (Fig. 4B). In addition, Ansari and Shigeyasu et al. [37, 38] found that PVT1 extensively affects CRC signaling pathways, including the TGFβ/Smad and Wnt/β-catenin signaling pathways, and promotes CRC cell metastasis by regulating MYC, which may lead to a poor prognosis by promoting the ability of CRC stem cells.

Transformation of the cell phenotype from epithelial cells to mesenchymal cells is an important factor leading to tumor invasion and metastasis. YBX1 is a multifunctional tumor protein that promotes EMT by increasing the expression of angiogenesis factors. Zeng et al. [126] found that PVT1 promotes YBX1 expression by downregulating miR-216a-5p, thereby promoting EMT, invasion, and CRC cell metastasis.
Recently, Wu et al. [127] found that PVT1 promotes angiogenesis and EMT through the miR-16-5p/VEGFA/VEGFR1/AKT signaling pathway (Fig. 4D). Radwan et al. [128] discovered a new signaling pathway that induces EMT. PVT1 increased the expression of the related transcription factor TWIST1 during EMT by downregulating miR-186 (Fig. 4E).

Chai et al. [129] reported that PVT1, as a key component of the RUNX2/PVT1/miR-455/RAF-1 axis, affects the growth and invasion of CRC (Fig. 4F). Subsequently, Yu et al. [130] confirmed that PVT1 promotes CRC cell proliferation through the miR-30d-5p/RUNX2 axis (Fig. 4G). Moreover, Shang et al. [131] reported that PVT1 upregulates IRS1 by targeting miR-214-3p and ultimately activates PI3K/AKT signaling pathway to promote CRC proliferation and invasion (Fig. 4H). Several studies have reported on the lncRNA–miRNA–mRNA signaling in CRC and demonstrated that PVT1 promotes CRC cell proliferation, migration, and invasion by upregulating COX2, FJX1, and MAPK1 via the modulation of miR-146a, miR-106b-5p, and miR-761 (Fig. 4I–K) [132–134], respectively.

Chemotherapy is crucial in the treatment of CRC; however, the emergence of drug resistance often indicates a low survival rate and poor prognosis. Fan et al. [135] showed that PVT1 enhances cisplatin resistance in patients with CRC by inhibiting the endogenous apoptosis signaling pathway. Another research group discovered that PVT1 downregulated pro-apoptotic proteins [B-cell lymphoma 2 (Bcl-2) associated X protein and cleaved caspase-3] and upregulated the expression of anti-apoptotic protein BCL-2 (Fig. 4L) [136].

These findings indicate that PVT1 can be used as a new biomarker for the diagnosis and treatment of CRC, providing a novel target for future treatments.
Role of PVT1 in the endocrine reproductive system

**PVT1 in breast cancer**

According to the 2022 Cancer Statistics, BC is the most common cancer among women, accounting for approximately 30% of all cancers. BC accounts for 15% of all cancer-related deaths and ranks second among the top ten causes of cancer-related deaths. Advances in BC diagnosis and treatment have greatly improved 5-year survival rates. However, recurrence, metastasis, and chemotherapy resistance remain urgent and unsolved problems [1]. Therefore, in-depth exploration of the molecular mechanisms can improve BC diagnosis in the future.

Guan et al. [16] showed that inhibition of PVT1 may inhibit BC proliferation. Zhang et al. [137] suggested that the GG genotype of the single nucleotide polymorphism rs13281615 may influence the development of BC through PVT1 and is associated with estrogen receptor positivity, higher tumor grades, and higher proliferative indices. Another study showed that activated PVT1-KLF5-CTNNB1 (β-catenin) promotes the proliferation of triple-negative BC [138]. RSPO1 is a key regulator of the β-catenin signaling pathway required for female development. A study showed that MYC-PVT1 overexpression causes RSPO1 upregulation, which ultimately leads to the development of cancer [139]. Another study showed that PVT1 promoted BC cell proliferation through the negative regulation of P21 [140]. A year later, Wang et al. [141] also demonstrated that PVT1 influenced EMT through P21, resulting in the proliferation and migration of triple-negative BC. The transcription factor SOX2 plays an important role in various cancers by controlling stem cell activity. Wang et al. [142] showed that PVT1 promotes EMT through SOX2 upregulation, thereby regulating BC invasion and growth. Zhu et al. [143] conducted a bioinformatics analysis and reported that a prediction model composed of four lncRNAs, PVT1, MAPT-AS1, LINC00667, and LINC00938, had good sensitivity and specificity for predicting BC prognosis. Subsequently, El-Fattah et al. [144] revealed the efficacy of PVT1, HOTAIR, NEAT1, PAI-1, and OPN as diagnostic biomarkers in BC. A year later, Levine et al. [145] suggested that PVT1 exon 9 may regulate BC cell migration by reducing claudin 4 expression.

Moreover, Yan et al. [146] showed that PVT1 promotes BC cell proliferation and colony formation by downregulating STAT6 cell cycle regulators through miR-1207-5p (Fig. 5A). Similarly, Liu et al. [147] found that PVT1 promoted BC cell EMT and proliferation by increasing VDR by antagonizing miR-1204 (Fig. 5B). In addition, Wang et al. [148] reported that PVT1 affects cell proliferation by promoting TRPS1 expression by sponging miR-543 in BC cells (Fig. 5C).

In addition, PVT1 promoted chemotherapy resistance to adriamycin in triple-negative BC cells by competitively binding Keap1 to degrade the nuclear factor erythroid 2-related factor 2 protein (Fig. 5D) [149].

Taken together, these studies suggest that PVT1 plays an important role in the proliferation, invasion, and metastasis of BC, and is related to the drug resistance mechanism of triple-negative BC.
OC originates from the germinal epithelium of the ovary and can be divided into serous, endometrioid, clear cell, and mucous types. OC is the seventh most common cancer among women worldwide, with a survival rate of 46%. Therefore, the development of new detection methods and treatments is urgently needed [150].

Several studies have demonstrated that PVT1 regulates OC cell proliferation and invasion by acting as a ceRNA of miR-133a, miR-140, and miR-214 (Fig. 5E–G) [151–153]. Li et al. [154] demonstrated that PVT1 can inactivate EZH2 by recruiting it to the promoter region of tumor suppressor gene P57. Ketamine can reduce this recruitment, which in turn increases P57 expression. Another study showed that PVT1 knockdown may induce apoptosis through the miR-543/SERPINS1 axis in OC cells (Fig. 5H) [155].

PVT1 can regulate the resistance of OC to cisplatin by regulating the expression of apoptosis-related proteins such as TGF-β1, p-Smad4, and caspase-3 [19]. Wu et al. [156] demonstrated that PVT1 upregulates AGO1 by sponging miR-148a-3p, thereby down-regulating TGF-β and promoting OC progression (Fig. 5I). Subsequent studies have also demonstrated that PVT1, TUG1, and MEG3 can lead to cisplatin resistance by inhibiting OC cell apoptosis [157]. Yi et al. [158] reported that PVT1 could directly bind to FOXM1 to stabilize its expression or promote FOXM1 expression by binding to miR-370 through a sponging effect, ultimately leading to OC progression and chemotherapy resistance (Fig. 5J). Another study reported that PVT1 silencing inhibits OC cell growth,
metastasis, and cisplatin resistance by downregulating the JAK2/STAT3/programmed
dead-ligand (PD-L1) pathway. The authors suggested that combination therapy target-
ing PVT1 and the PD-L1 immune checkpoint blockade may have a synergistic effect on
the clinical treatment of patients with OC (Fig. 5K) [159].

Martini et al. [160] analyzed the expression of multiple lncRNAs in 202 cases of early-
onset OC and found that lncRNA PVT1 predicted a poor prognosis in patients with
early-onset OC. Conversely, Yamamoto et al. [52] argued that high PVT1 and MYC
expression predicted a good prognosis in patients with early-onset OC. High PVT1 and
MYC expression may predict a good prognosis because of cell senescence induced by
oncogenes and DNA damage caused by excessive replication stress in oncogenes. ATM-
Chk1 and ATR-Chk2 pathway activation leads to p53 and retinoblastoma protein upreg-
ulation, which has a synergistic effect on cell growth arrest.

In conclusion, PVT1 may provide new insights for future treatment strategies and
cisplatin resistance in OC. PVT1 may be a powerful biomarker for OC diagnosis and
prognosis.

PVT1 in cervical cancer
CC is the second leading cause of cancer-related deaths among women aged 20–39 years
[1]. Therefore, identifying the molecular markers and therapeutic targets is important.
Sun et al. [161, 162] showed that PVT1 could be used as a new non-invasive biomarker
for the early diagnosis of CC. Iden et al. [17] showed that PVT1 may promote cell pro-
liferation, migration, and invasion through interaction with nucleolar proteins, and is
associated with poor prognosis of CC. Zhang et al. [46] revealed that PVT1 downregu-
lates miR-200b by recruiting EZH2 to the miR-200b promoter region, thereby promot-
ing CC cell cycle progression and migration (Fig. 5L). Subsequently, Shen et al. [163]
confirmed that PVT1 attenuates miR-195 by binding EZH2 to increase the H3K27me3
level in the promoter region (Fig. 5M). They also found that PVT1 acts as a sponge to
attract miR-195 and that PVT1 inhibition reduced paclitaxel-induced EMT and chemo-
therapy resistance. Moreover, Gao et al. [164] reported that PVT1 promotes the progres-
sion and invasion of CC by targeting miR-424 (Fig. 5N). Another study demonstrated
that PVT1 promotes CC cell growth and invasion by downregulating TGF-β1 expres-
sion [165]. Further studies demonstrated that PVT1 regulated CC cell growth, invasion,
and apoptosis by upregulating the nuclear factor-κB, ECM1, ARL2, and Smad3 pathways
by modulating miR-16, miR-486-3p, miR-503, and miR-140-5p (Fig. 5O–R) [166–169],
respectively.

These data demonstrate that PVT1 is an important molecular marker and significant
therapeutic target for CC.

PVT1 in endometrial cancer
Endometrial cancer is the most common metastatic malignant tumor among women,
and originates from endometrial epithelial cells [170]. Therefore, there is an urgent need
to elucidate the underlying molecular mechanisms.
Kong et al. [18] demonstrated that the PVT1-miR-195-5p-FGFR1/FGF2 axis plays an
important role in endometrial cancer (Fig. 5S). They found that cell proliferation, migra-
tion, and invasion were inhibited by PVT1 knockdown.
In conclusion, PVT1 plays a key role in endometrial cancer and is expected to become a new therapeutic target and be included in diagnostic screening methods in the future.

Role of PVT1 in the urinary system

**PVT1 in renal cell carcinoma**

By 2022, 79,000 new cases of kidney and pelvic cancer will be diagnosed in the USA, and 13,920 people will die from the disease [1]. Approximately 85% of kidney tumors are RCC [171]. RCC is classified into three subtypes: clear cell RCC (ccRCC), papillary carcinoma, and chromophobe RCC. RCC is associated with late detection and poor prognosis; therefore, new and effective detection methods must be explored [172].

One study pointed out that hypomethylation of the PVT1 promoter leads to its upregulation in patients with RCC. PVT1 upregulation stabilizes MYC expression, promotes tumor occurrence, and predicts a poor prognosis [20]. Subsequently, Li et al. [173] further demonstrated that PVT1 regulates the RCC cell cycle as well as apoptosis, and proliferation by upregulating EGFR expression and affecting its downstream proteins, AKT and MYC. Another study showed that PVT1 promotes RCC growth and inhibits RCC cell apoptosis by upregulating Mcl-1 [174]. Recently, Zhang et al. [175] found that HIF-2α promotes PVT1 expression by binding to the PVT1 enhancer; similarly, PVT1 can protect HIF-2α from ubiquitin-dependent degradation. This PVT1/HIF-2α loop promotes tumorigenesis and metastasis in RCC (Fig. 6A). Wang et al. [176] showed that PVT1 is significantly associated with a poor prognosis in patients with ccRCC. Furthermore, Wu et al. [177] found a 5-lncRNA signature, including lncRNA PANDAR, PVT1, LET, PTENP1, and linc00963, which was used to differentiate benign and malignant

![Fig. 6](image-url) The role of PVT1 in the urinary system. A PVT1 forms a positive feedback loop with HIF2α protein. B PVT1 promotes BMI1, ZEB1, and ZEB2 by targeting miR-200s. C PVT1 can directly target miR-16-5p. D PVT1 promotes the expression of CDK1 by targeting miR-31. E PVT1 promotes the expression of VEGF by targeting miR-128. F PVT1 promotes the expression of BCLAF1 by targeting miR-194-5p. G PVT1 leads to chemoresistance in BCa by activating the Wnt/β-catenin signaling pathway. H PVT1 represses NOV expression by recruiting EZH2 to the promoter region of NOV. I PVT1 promotes Twist1 expression by targeting miR-186 and ultimately leads to EMT. J PVT1 promotes the expression of KIF23 by targeting miR-15a-5p. K PVT1 can directly target miR-146a
renal masses. Similarly, Liu et al. [178] proved that PVT1 combined with TCL6, miR-155HG, and HAR1B could be used as biomarkers to evaluate the prognosis of ccRCC. Yang et al. [179] reported that PVT1 promotes the proliferation and metastasis of RCC by competitively binding miR-200s to upregulate BMI1, ZEB1, and ZEB2 (Fig. 6B). Another study showed that PVT1 acts as a sponge for miR-16-5p to regulate apoptosis and EMT in RCC cells (Fig. 6C) [180].

In summary, PVT1 was specifically upregulated in RCC, especially ccRCC. Many studies have shown that PVT1 combined with other lncRNAs is an efficient and accurate method for RCC diagnosis and prognosis prediction.

**PVT1 in bladder cancer**

Bladder cancer is the sixth most common cancer in men, with approximately 500,000 new cases and 200,000 deaths worldwide each year [181]. Current diagnostic markers, such as bladder tumor antigen and nuclear matrix protein, are not suitable for early bladder cancer owing to their lack of specificity and sensitivity [182]. Therefore, identifying new biomarkers is necessary for early diagnosis.

Zhuang et al. [21] reported that downregulation of PVT1 inhibits bladder cancer growth and induces apoptosis. Another study showed that elevated PVT1 was significantly associated with poor prognosis in muscle-invasive bladder cancer [183]. Tian et al. [184] demonstrated that the PVT1/miR-31/CDK1 pathway is responsible for the invasion, metastasis, and occurrence of bladder cancer (Fig. 6D). VEGFC is a lymphatic vasculature growth factor involved in lymphangiogenesis, angiogenesis, and regional lymphatic metastasis. Subsequently, Yu et al. [185] reported that PVT1 promotes the growth and metastasis of bladder cancer cells by upregulating VEGFC expression by acting as a ceRNA of miR-128 (Fig. 6E). Recently, Chen et al. [186] reported that PVT1 expression was significantly increased in bladder cancer. The PVT1/miR-194-5p/BCLAF1 axis was reportedly involved in the malignant progression and development of bladder cancer (Fig. 6F).

Another study indicated that PVT1 promotes the expression of MDR1 and MRP1 in bladder cancer by activating the Wnt/β-catenin pathway, ultimately reducing the response of bladder cancer cells to doxorubicin and cisplatin (Fig. 6G) [187].

In conclusion, PVT1 plays an important role in bladder cancer and is a new biomolecular marker that may be used as a new therapeutic target and diagnostic tool.

**PVT1 in prostate cancer**

According to the analysis of the 2022 Cancer Statistics, the incidence of PCa in American men ranked first among all cancers, accounting for 27% of all cases [1]. Although prostate-specific antigen can detect PCa early, recurrence in patients with advanced PCa is still an important factor that affects prognosis. Therefore, the underlying mechanisms of PCa need to be further explored.

A study suggested that exon 9 of PVT1 may be closely associated with invasive PCa in men of African descent [22]. Four years later, Pal et al. [188] demonstrated that exon 9 of PVT1 induced the proliferation and migration of prostate epithelial cells and was correlated with castration resistance after androgen deprivation therapy. A year later, Videira et al. [47] pointed out that PVT1 upregulation downregulated the expression of the
androgen suppressor gene NOV through epigenetic modifications that recruited EZH2 to its promoter. This eventually led to the progression of androgen-independent castration-resistant PCa (Fig. 6H). Moreover, Yang et al. [189] reported that the knockdown of PVT1 significantly inhibited PCa cell growth, promoted apoptosis, and reduced c-Myc expression in cells. Subsequently, Chang et al. [190] found that PVT1 acts as a sponge of miR-186 to promote the expression of the EMT-related transcription factor TWIST1 (Fig. 6I). Wan et al. [191] showed that PVT1 downregulation inhibited PCa cell proliferation by reducing the phosphorylation of mitosis-related molecule P38. Another study discovered that PVT1 upregulated the expression of tumor metastasis-related protein NOP2 and promoted the invasion and metastasis of PCa [192]. Recently, Wu et al. [193] demonstrated that PVT1 promotes PCa progression by mediating the miR-15a-5p/KIF23 pathway (Fig. 6J). In addition, another study pointed out that PVT1 promotes tumor growth by regulating miR-146a methylation (Fig. 6K) [194].

In conclusion, high PVT1 expression plays an important role in promoting tumorigenesis in castrate-resistant prostate cancer and PCa.

**Role of PVT1 in the immune system**

The immune system is important as it regulates the body’s immune responses and functions. It is composed of immune organs, cells, and molecules. Changes in the immune system may affect the occurrence and development of various diseases, including cancer. Therefore, studying the effect of PVT1 on the immune system is of considerable significance for the future treatment of tumors through immune regulation [195].

Sjogren’s syndrome is a chronic autoimmune disease characterized by highly activated CD4$^+$ T cells in the salivary glands. Fu et al. [196] found that PVT1 overexpression in patients with Sjogren’s syndrome promoted CD4$^+$ T-cell activation (Fig. 7A). Lu et al. [197] showed that PVT1 promotes regulatory T-cell autophagy and ultimately

**Fig. 7** The role of PVT1 in the immune system. A PVT1 can activate CD4$^+$ T cells. B PVT1 can promote autophagy of regulatory T cells by targeting miR-146a. C PVT1 can promote the expression of HMGB1 and promote the polarization of M1 macrophages by targeting miR-29a. D PVT1 can reduce TH17 differentiation by attenuating NOTCH1 expression. E PVT1 can promote the effect of MDSCs to achieve tumor immune suppression.
inhibits allograft rejection by acting as a sponge for miR-146a (Fig. 7B). Luo et al. [198] reported that PVT1 promotes M1 macrophage polarization and aggravates myocardial injury through the miR-29a/HMGB1 axis in sepsis-induced myocardial injury. Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by a significant increase in T helper 17 (Th17) cells in peripheral blood (Fig. 7C). Yu et al. [199] found that PVT1 overexpression reduced Th17 differentiation by downregulating NOTCH1 levels, thereby alleviating the occurrence of ITP. Myeloid-derived suppressor cells (MDSCs) can impair the antitumor response induced by T cells, thereby achieving tumor immunosuppression (Fig. 7D). Zheng et al. [200] found that the knockdown of PVT1 significantly inhibited the immunosuppressive ability of MDSCs (Fig. 7E).

Role of PVT1 in tumors of other systems

**PVT1 in glioma**

Glioma is the most aggressive malignant tumor of the central nervous system and occurs mainly in the brain and glial tissues. The 5-year survival rate of glioma is only 0.05–4.7%. Therefore, exploring the pathogenesis of glioma is of great significance for improving its therapeutic effect in the future [201].

One study showed that PVT1, as a ceRNA, binds to miR-190a-5p and miR-488-3p to upregulate myocyte enhancer factor 2C expression. It then promotes the expression of JAGGED1, which ultimately leads to increased malignant behavior in glioma cells (Fig. 8A) [202]. A year later, Han et al. [203] showed that PVT1 promotes glioma

![Fig. 8](image-url) The role of PVT1 in the other systems. A PVT1 promotes the expression of MEF2C by targeting miR-190a-5p and miR-488-3p. B PVT1 can directly target miR-424. C PVT1 can directly target miR-200a. D PVT1 promotes the expression of GREM1 by targeting miR-128-3p. E PVT1 promotes PTBP1 by targeting miR-128-1-5p. F PVT1 promotes TMBIM6 by targeting miR-1301-3p. G PVT1 promotes HNF1B by targeting miR-1207-3p. H PVT1 promotes Atg7 and Beclin1 by targeting miR-186. I PVT1 promotes the expression of ELF4 by targeting miR-365 to regulate the expression of SOX2. J PVT1 represses its expression by recruiting EZH2 to the promoter region of TSHR. K PVT1 can directly target miR-30a. L PVT1 promotes the expression of PAK3 by targeting miR-423-5p. M PVT1 promotes the expression of PTBP1 by targeting miR-484. N PVT1 promotes the expression of ERG by targeting miR-183-5p. O PVT1 promotes the expression of the c-MET/PI3K/AKT signaling pathway by targeting miR-152, which leads to chemoresistance.
progression as a ceRNA of miR-424 (Fig. 8B). Another study came to a similar conclusion that PVT1 acted as a sponge of miR-200a and promoted glioma proliferation and invasion (Fig. 8C) [204]. A study by Lv et al. [205] indicated that PVT1 promotes glioma progression by downregulating UPF1 expression.

Many studies have revealed the important role of the lncRNA–miRNA–mRNA pathway in gliomas. Specifically, PVT1 reportedly promotes glioma cell proliferation, invasion, metastasis, and EMT by upregulating GREM1, PTBP1, TMBIM6, HNF1B, and Atg7/Beclin1 by modulating miR-128-3p, miR-128-1-5p, miR-1301-3p, miR-1207-3p, and miR-186, respectively (Fig. 8D–H) [23, 206–209].

PVT1 is also involved in chemotherapy resistance in glioma. Gong et al. [210] found that PVT1 upregulated ELF4 expression by acting as a ceRNA of miR-365, which then directly activated stem cell-related protein SOX2 expression, ultimately promoting stem cell characteristics and temozolomide resistance in gliomas (Fig. 8I).

Taken together, these studies demonstrate that PVT1 is an oncogene in glioma and may be a target for future therapy.

**PVT1 in thyroid cancer**

TC is the most common malignant tumor of the endocrine glands. According to the latest cancer statistics, an estimated 43,800 new cases were reported in 2022 [1]. Primary TCs include papillary TC (PTC), follicular TC, medullary TC, and anaplastic TC. PTC accounts for 85–90% of all TCs and has a good prognosis. Anaplastic TC is the most aggressive TC and has a poor prognosis and low survival rate [211]. Exploring the molecular mechanism of TC is of great significance for discovering new therapeutic targets in the future.

One study showed that PVT1 promotes TC cell proliferation by recruiting EZH2 and affecting TSHR expression (Fig. 8J) [26]. Another study showed that high PVT1 levels promoted TC cell growth and invasion by targeting the miR-30a/IGF1R axis and was associated with higher TNM and LNM stages (Fig. 8K) [212]. Two years later, Lin et al. [213] showed that PVT1 promoted malignant proliferation and migration of TC through the miR-423-5p/PAK3 pathway (Fig. 8L). In addition, Possier et al. [214] showed that co-expression of MALAT1, PVT1, and HOTAIR could be used to distinguish benign and malignant thyroid nodules.

In conclusion, these results suggest that PVT1 plays a significant role in promoting TC, which is related to TNM and LNM stages, and TC tumor invasion, and can be used in the diagnosis of thyroid nodules.

**PVT1 in osteosarcoma**

OS is a rare tumor that often occurs in children and adolescents. Approximately 400 children and adolescents are diagnosed with OS in the USA every year, and as many as 25% of patients have metastasis by the time they are diagnosed. Therefore, exploring the mechanism of metastasis of OS is important for the development of future treatments [215, 216].

Zhou et al. [24] showed that PVT1 upregulates the expression of BCL2 by inhibiting miR-195, thereby inducing OS cell cycle arrest, inhibiting apoptosis, and promoting cell migration and invasion (Fig. 8M). Another study indicated that PVT1 upregulated HK2
by binding miR-497 and increasing glucose uptake and lactate production in OS cells, which ultimately accelerated cell proliferation and invasion (Fig. 8N) [217]. Similarly, Zhao et al. [218] showed that PVT1, as a ceRNA, inhibits its degradation and ubiquitination by binding to miR-183-5p, thereby upregulating ERG and ultimately promoting OS progression and metastasis (Fig. 8O). A year later, Yan et al. [219] found that PVT1 promoted metastasis in OS by targeting miR-484 (Fig. 8P). Xun et al. [220] demonstrated that PVT1 promotes EMT in OS cells and is highly correlated with TNM stage and distant metastases, which may be used as an independent prognostic risk marker of OS. In addition, Chen et al. [221] reported that the expression of PVT1 was upregulated in OS. Functionally, ALKBH5-mediated upregulation of PVT1 promotes OS cell growth in vitro and in vivo. Sun et al. [222] demonstrated that PVT1 enhanced the chemoresistance of OS by targeting miR-152 to activate the c-MET/PI3K/AKT signaling pathway (Fig. 8Q).

Taken together, these studies show that PVT1 is a significant factor in promoting OS progression and chemoresistance.

**PVT1 in multiple myeloma**

MM is a malignant tumor that originates from mutations in the bone marrow plasma cells and is characterized by abnormal proliferation and production of monoclonal immunoglobulins or light chains. Although current treatments can greatly improve remission rates, patients have a high risk of relapse or progression. Therefore, exploration of its pathogenesis is urgently needed to develop further treatments for this disease [223].

Yang et al. [25] demonstrated that PVT1 promotes MM cell proliferation by competitively binding to miR-203a. Handa et al. [224] showed that MYC and PVT1 synergistically promote MM progression.

Overall, these data suggest that PVT1 may serve as a future therapeutic target in patients with MM.

**PVT1 in lymphoma**

Lymphoma is a malignant tumor originating from lymphatic tissue and is mainly divided into Hodgkin’s and non-Hodgkin’s lymphoma (NHL). Hodgkin’s lymphoma is nearly twice as common as NHL, whereas the opposite is true for children with Hodgkin’s lymphoma [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common and aggressive NHL subtype, accounting for 40% of NHL cases. Owing to the lack of effective treatments, survival rates remain very low [225].

Yang et al. [27] showed that overexpression of PVT1 promoted the proliferation of DLBCL cells and predicted poor prognosis.

This evidence suggests that PVT1 acts as an oncogene to promote lymphoma growth.

**PVT1 in leukemia**

Leukemia is a malignant tumor of the hematopoietic system. Leukemia can be classified as acute or chronic leukemia. Acute leukemia can be further classified as acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Chronic leukemia can be classified as chronic myeloid leukemia and chronic lymphocyte leukemia (CLL). The
5-year survival rates are 27.4% and 84.2% for AML and CLL, respectively. Identifying new gene targets is important for improving leukemia cure rates [226].

Houshmand et al. [28] showed that PVT1 knockout in hematologic malignancies results in c-Myc degradation, decreased proliferation, increased apoptosis, and cell cycle arrest. PVT1 expression was higher in patients with AML than in healthy controls. In addition, PVT1 expression levels in the high-risk AML group were higher than in the medium- and low-risk AML groups. Similarly, Izadifard et al. [227] reported that PVT1 expression was higher in patients with AML than in healthy controls. PVT1 expression levels in the high-risk AML group were higher than in the medium- and low-risk AML groups. A subsequent study also confirmed that PVT1 and CCAT1 were highly expressed in patients with AML and were associated with poor prognosis [228]. Salehi et al. [229] showed that the inhibition of PVT1 significantly induced AML cell apoptosis and necrosis and reduced proliferation and C-MYC expression in AML cells. A year later, another study confirmed the relationship between PVT1 and c-Myc and suggested that the PVT1 blockade might be a potential treatment for AML [230]. In addition, Cheng et al. [231] found that PVT1 promotes the malignant progression of AML through the miR-29 family/WAVE1 axis, suggesting that PVT1 may be a potential therapeutic target for AML. Another study showed that PVT1 knockout significantly promoted apoptosis of ALL cells, blocked the cell cycle at G0/G1, reduced the proliferation rate, and downregulated the expression of oncogene c-Myc [232].

In conclusion, PVT1, as an oncogene, plays an important role in the development of leukemia and may be a therapeutic target in the future.

**Circular RNA PVT1 in various human tumors**

The PVT1 gene located on chromosome 8 encodes IncRNA PVT1 as well as circular RNA PVT1 (circPVT1), obtained by circularization of its exon 2. circPVT1 is also a non-coding RNA that is widely present in the occurrence and development of various tumors [233].

In the respiratory system, circPVT1 has oncogenic effects in patients with NSCLC, lung adenocarcinoma, and lung squamous cell carcinoma (LSCC). Qin et al. [234] reported that circPVT1, as a ceRNA of miR-497, indirectly regulates Bcl-2 expression to promote the proliferation of NSCLC and inhibit cell apoptosis. Zheng et al. [235] demonstrated that circPVT1 regulates cisplatin and pemetrexed resistance in lung adenocarcinoma by acting as a sponge for miR-145-5p. Gao et al. [236] reported similar results, showing that circPVT1 enhances cisplatin resistance in lung adenocarcinoma cells by regulating miR-429/forkhead box K1 expression. Finally, Shi et al. [237] revealed that circPVT1 was significantly upregulated in the tissues, serum, and cell lines of patients with LSCC and promoted LSCC progression by increasing cyclin F expression, acting as a sponge for miR-30d and miR-30e.

In the digestive system, circPVT1 is closely related to the occurrence, development, and drug resistance of various tumors. He et al. [238] showed that circPVT1 regulates STAT3 levels by acting as a sponge for miR-125b and ultimately increases OSCC cell proliferation. Wang et al. [239] revealed that circPVT1 promotes OSCC progression by regulating the miR-143-3p/SLC7A11 axis and affecting the MAPK signaling pathway. Zhong et al. [240] found that circPVT1 regulated the progression of EC by influencing
miR-4663 levels to modulate Paxs and peroxisome proliferator-activated receptor levels. Yao et al. [241] revealed that circPVT1 increased EC cell resistance to 5-fluorouracil by inhibiting ferroptosis through miR-30a-5p/Frizzled3. Chen et al. [242] found that circPVT1 was significantly upregulated in patients with GC and modulated the proliferation of GC cells by acting as a sponge for miR-125. These results suggested that circPVT1 expression is an independent prognostic marker. Liu et al. [243] showed that circPVT1 enhanced the resistance of GC cells to paclitaxel through the miR-124-3p/ZEB1 axis. Similarly, Wang et al. [244] showed that circPVT1 regulates the expression of HCC-derived growth factors by targeting miR-152-3p, leading to cisplatin resistance in GC cells. Zhu et al. [245] found that upregulation of circPVT1 regulates the proliferation and invasion ability of HCC cells by affecting the miR-203/homeobox D3 axis. Bu et al. [246] found that circPVT1 regulated HCC cell proliferation and glycolysis through sponging of miR-377. Wang et al. [247] found that circPVT1 regulated CRC cell metastasis by acting as a sponge for miR-145.

CircPVT1 also plays an important role in the endocrine and urinary systems [248]. Bian et al. [249] reported that circPVT1 regulated BC cell invasion and EMT by acting as a ceRNA of miR-204-5p. Wang et al. [250] revealed that circPVT1 promotes the ARG2/HIF-1α axis by regulating miR-29a-3p, thereby enhancing BC cell proliferation, invasion, and metastasis. In addition, Sun et al. [251] found that circPVT1 inhibited apoptosis and promoted OC cell proliferation by sponging miR-149. Zheng et al. [252] showed that circPVT1 affects ccRCC cell growth and metastasis by targeting the miR-145-5p/TX15 axis.

Leukemia is a disease that occurs mainly in the region of chromosome 8q24. Therefore, studying circPVT1, which is also located on chromosome 8, is of great significance for further exploration of the pathogenesis of leukemia [253]. Hu et al. [254] found that circPVT1 was significantly upregulated in patients with ALL and promoted cell proliferation by promoting the expression of c-Myc and Bcl-2. Gaffo et al. [255] showed that circPVT1 was significantly upregulated in children with B-precursor ALL. Moreover, a study by Chen et al. [256] revealed that circPVT1 was significantly upregulated in 68 patients with AML, and patients with high circPVT1 expression had significantly shortened overall and event-free survival rates, suggesting that circPVT1 may be used as a biomarker to assess prognosis.

Osteosarcoma (OS) is a common primary bone malignancy. Noncoding RNA, as an oncogenic factor, also plays an important role in OS [257]. Wan et al. [258] demonstrated that circPVT1 inhibited miR-423-5p, thereby promoting the Wnt5a/Ror2 signaling pathway and affecting OS cell glycolysis, proliferation, migration, and metastasis. Huang et al. [259] found that circPVT1 inhibition significantly inhibited proliferation and induced apoptosis of OS cells through the miR-26b-5p/CCNB1 axis. Li et al. [260] validated that circPVT1 enhances the resistance of OS cells to doxorubicin by regulating the miR-137/TRIAP1 axis.

The abnormal expression of circPVT1 in patients with TC also warrants further investigation. Tao et al. [261] confirmed that circPVT1 inhibited PTC progression by sponging miR-126. Subsequently, Zeng et al. [262] showed that circPVT1 acted as a sponge for miR-195 to regulate VEGFA expression. circPVT1 promotes the Wnt/β-catenin signaling pathway and proliferation, migration, and invasion of PTC. In addition, Zheng et al.
reported that circPVT1 regulates EMT by targeting the miR-455-5p/CXCL12/CXCR4 signaling pathway and promotes thyroid medullary cancer cell proliferation, invasion, and migration.

Conclusions
Cancer is one of the greatest risks to human health. By 2022, 1,918,030 new cases and 609,360 cancer-related deaths are estimated to occur in the USA [1]. Owing to delayed diagnosis, recurrence, metastasis, chemotherapy resistance, and other problems, patients tend to have poor prognosis and low survival rates. Therefore, the discovery of new biomarkers for early diagnosis and new targets in the treatment of cancer is vital for improving the survival rates of patients with cancer.

With the development of second-generation sequencing and bioinformatics, lncRNAs have gradually emerged in our field of vision, and have been found to play important roles in tumor progression. Previously, lncRNAs were reported to directly regulate chromatin topology or act as scaffolds for RNA and protein expression. Many studies have found that lncRNAs, including PVT1, are differentially expressed in tumor tissues compared with non-tumor tissues. However, the upstream and downstream regulatory mechanisms and how they affect the occurrence and development of tumors remain unclear. This study provides a new perspective for understanding the mechanisms underlying tumorigenesis and its development.

This review describes the mechanisms of action of PVT1 in various cancers. We found that PVT1 acts as a ceRNA to bind miRNAs and regulate downstream gene expression. PVT1 can also bind directly to the promoter region of the target gene, thereby promoting its methylation to regulate its expression. PVT1 also promotes the proliferation, invasion, and EMT of various tumor cells. For example, Wang et al. [87] pointed out that PVT1 promotes EMT in GC cells through the miR-30a/Snail axis. PVT1 is a biomarker that can be detected in serum. Wu et al. [177] constructed a model based on five lncRNAs (LET, PVT1, PANDAR, PTENP1, and linc00963), which are highly valuable in the diagnosis of ccRCC. In addition, PVT1 plays an important role in chemotherapy resistance. For example, tumor tissues with high PVT1 expression are resistant to GEM, cisplatin, adriamycin, and other chemotherapy drugs [40, 72, 149]. Some studies have also shown that PVT1 is a critical regulatory molecule in radiotherapy resistance. For instance, Wang et al. [70] showed that PVT1 significantly improved the radioresistance of NSCLC cells.

In summary, PVT1 plays an oncogenic role in many cancers. PVT1 is closely associated with the onset, development, invasion, migration, and treatment of cancer. PVT1 is an emerging biomarker for the diagnosis and treatment of cancer.

Abbreviations
ALL Acute lymphoblastic leukemia
AML Acute myeloid leukemia
BC Breast cancer
Bcl-2 B-cell lymphoma
CC Cervical cancer
CCA Cholangiocarcinoma
cCRCC Clear cell renal cell carcinoma
celRNA Competitive endogenous RNA
circPVT1 Circular RNA PVT1
CLL Chronic lymphocyte leukemia
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