Long non-coding RNA PVT1 interacts with MYC and its downstream molecules to synergistically promote tumorigenesis

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Abstract
Numerous studies have shown that non-coding RNAs play crucial roles in the development and progression of various tumor cells. Plasmacytoma variant translocation 1 (PVT1) mainly encodes a long non-coding RNA (lncRNA) and is located on chromosome 8q24.21, which constitutes a fragile site for genetic aberrations. PVT1 is well-known for its interaction with its neighbor MYC, which is a qualified oncogene that plays a vital role in tumorigenesis. In the past several decades, increasing attention has been paid to the interaction mechanism between PVT1 and MYC, which will benefit the clinical treatment and prognosis of patients. In this review, we summarize the coamplification of PVT1 and MYC in cancer, the positive feedback mechanism, and the latest promoter competition mechanism of PVT1 and MYC, as well as how PVT1 participates in the downstream signaling pathway of c-Myc by regulating key molecules. We also briefly describe the treatment prospects and research directions of PVT1 and MYC.

Keywords PVT1 · MYC · Gene fusion · Positive feedback · Promoter · Enhancer

Abbreviations
PVT1    Plasmacytoma variant translocation 1
MYC    MYC or c-Myc
lncRNA    Long non-coding RNA
E-boxes    Enhancer box sequences
GWAS    Genome-wide association studies
SNPs    Single nucleotide polymorphisms
TAD    Topologically associated domain
BRD4    Bromodomain-containing protein 4
CDK4    Cyclin-dependent kinases 4
Miz1    Myc-interacting zinc finger protein-1
Snail1    Snail homolog 1
TFAP4    Transcription factor AP4
EZH2    Enhancer of zeste homolog 2
TSP1    Thrombospondin-1
VEGF    Vascular endothelial growth Factor
HIF-1    Hypoxia inducible factor-1
LDH    Lactate dehydrogenase
GLUT1    Glucose transporter 1
HK2    Hexokinase 2
PDK    Pyruvate dehydrogenase kinase
MDM2    Mouse double minute 2

Introduction
In the entire human genome, only 2% of the genes are used to encode proteins, and the vast majority of the human genome is transcribed into non-coding RNAs, such as long non-coding RNAs (lncRNAs), which are longer than 200 nucleotides (nt) [1]. These lncRNAs play an important role...
in regulating cellular activities by modulating gene expression, including cell differentiation, proliferation, cell cycle, apoptosis, migration, and invasion [2, 3]. However, abnormal expression of lncRNAs can contribute to the occurrence and development of various diseases, such as cancer [4–6].

The plasmacytoma variant translocation 1 (PVT1) gene encodes a lncRNA and was first discovered as an activator of MYC in murine plasmacytoma variant translocation in 1984 [7]. The human PVT1 is a large locus more than 30 kb in length and is located at 8q24.21 [8]. The locus constitutes a fragile site for genetic aberrations, including translocation, amplification, viral integration, and multiple risk loci in cancer or other diseases [8, 9].

Studies have shown that PVT1 is expressed at low levels in normal tissues, while it is highly expressed in various malignant tumors and tumor cell lines, such as gastric cancer, lung cancer, hepatocellular carcinoma, thyroid carcinoma, breast cancer, and pancreatic cancer [7, 9–16]. PVT1 can also serve as a potential predictor of cancer progression and patient prognosis [10, 14, 15]. Most studies have reported that PVT1 can promote proliferation, angiogenesis, apoptosis escape, and participate in DNA rearrangements, which might ultimately promote carcinogenesis [7, 10, 11, 13, 17, 18]. However, recent studies have shown that PVT1, also a microRNA Host gene, can encode miR-1204, miR-1205, miR-1206, miR-1207-5p, miR-1207-3p, and miR-1208 [7, 19–21]. Moreover, PVT1 can also engender a circRNA called circPVT1 by circularizing exon 3 along with long introns on each side [22]. CircPVT1 can act as a miRNA sponge to regulate gene expression and promote cell proliferation in cancer [22, 23].

In the human genome, MYC is located only 53 kb upstream of PVT1. Both genes have been reported to play a role in cancer [1]. High expression of PVT1 can increase c-Myc expression by regulating c-Myc stability, and they can also interact with each other to regulate their expression, which synergistically promotes the occurrence and development of tumors [7, 24]. MYC, a proto-oncogene, was first discovered as the cellular homolog of the Avian virus myelocytomatosis oncogene and plays various roles in protein synthesis, metabolism, and cellular differentiation [25, 26]. C-Myc, a transcription factor, is thought to regulate the expression of 15% of all genes by binding enhancer box sequences (E-boxes) [27]. Moreover, c-Myc can lead to genomic instability, gene amplification, cellular proliferation, and repression of apoptosis, which is observed in various tumors, including breast, lung, colon, and prostate cancers [25, 27]. Although numerous studies have examined the interaction of PVT1 and MYC, the detailed mechanisms of the interaction between them remain unclear. In this review, we update the more recent findings for PVT1 and MYC, with the aim of promoting modern studies and the development of clinical therapies.

**Cancer risk related to PVT1 fusion gene on 8q24**

Both human PVT1 and MYC are located at the 8q24 locus, a well-known cancer-associated chromosome segment and a common and preferred integration site for somatic cell expansion in many cancers (Fig. 1), such as prostate, colorectal, breast, ovarian, and cervical cancers [28–32]. The fragile sites are heritably specific chromosomal loci. When cells are undergoing mitosis, the chromatin region exhibits a loose state and high DNA flexibility, and the induction of fragile sites inhibits partial replication without blocking the cell cycle [33]. There are two common fragile sites in the 8q24 segment, FRA8C and FRC8D, where substantial amounts of DNA helix flexibility exist. When cells are under...
the influence of genetic changes or exposed to factors that interfere with DNA replication, such as hypoxia, viral invasion, and cytotoxic drugs, these sites induce chromosome breakage and amplification, translocation, and other chromosome structural variations [34]. As a gene sequence adjacent to the fragile site, PVT1 is also prone to gene rearrangement within the chromosome or interchromosomal segments during gene amplification, leading to an increase in its copy number. Cytogenetic analysis indicated that gene amplification was driven by recurrent breakage within the common fragile site via a break–fusion–bridge mechanism [35, 36]. Although no studies have specifically reported the mechanism of the increased PVT1 copy number, we predict that its amplification occurs through this general amplification mechanism at the fragile sites.

Amplification of the PVT1 locus often manifests as the fusion of sister chromatid ends to form double minute chromosomes or a homogeneously staining region [36]. Through either amplification process, PVT1 will generate new fusion genes, and these abnormal changes in the gene replication process play an important role in tumor development [37]. Numerous studies have shown that PVT1 can fuse to other genes by translocation in certain tumor tissues (Table 1). Although PVT1 is a nonprotein encoding gene, the fusion of other genes may produce abnormal protein that participates in the cancer process. For example, in small cell lung cancer, exon 1 or 2 of PVT1 fuses to exon 2 of AKT3 (1q44) to form a chimeric transcript PVT1-AKT3 [38]. It encodes a shorter AKT3 protein with a missing N-terminus and an incomplete PH domain, which changes the function of the protein and promotes tumor progression [38]. We also found that gene fusion of PVT1 with its neighboring gene MYC is most common in 8q24-amplified cancers [37, 39]. An increased MYC copy number and PVT1 expression occur in more than 98% of cancer cases with increased 8q24 copy numbers, which points to an interaction between PVT1 and MYC and that they are part of a common signaling pathway [40]. False DNA repair, referred to as chromothripsis, may occur during amplification of the PVT1 locus, producing fragmented 8q24 amplicons. In different tumors, these fragments, including PVT1 and MYC, fuse with different exons [39]. Thus, MYC can be regulated by the PVT1 promoter because of the loss of its partial exons [39]. In mice artificially transfected with copies of MYC-PVT1, the level of RSPO1, a key regulatory molecule in the Wnt/β-catenin pathway, was upregulated. Accelerating proliferation of breast cancer cells in mice was subsequently observed, and the increased copy number of each single gene separately did not have a proliferative effect [41]. Therefore, most studies have shown that PVT1 fusion genes exert the effect of affecting cancer risk mainly by driving protein expression. With respect to whether it affects the function of IncRNA, additional research is expected.

From the perspective of genetic epidemiology, genome-wide association studies (GWAS) indicate that 8q24 is a cancer susceptibility locus and single nucleotide polymorphisms (SNPs) in this region are associated with cancers, such as colorectal, prostate, breast, ovarian, and pancreatic cancers [52–58]. The cancer risk-associated SNPs are differentially located on 8q24 in different cancers; for example, rs1561927 in pancreatic cancer locates 455 kb telomeric of

| Cancer type                                      | Fusion locus | Fusion gene | References |
|-------------------------------------------------|-------------|-------------|------------|
| Colorectal cancer                               | 8q24/8q23.1 | PVT1-RSPO2  | [42]       |
|                                                 | 8q24/8q24.21| PVT1-MYC    | [37]       |
| Neuroendocrine bladder cancer                   | 8q24/17q12  | PVT1-ERBB2  | [43]       |
| Acute myeloid leukemia                           | 8q24/8q24.21| PVT1-CCDC26 | [44]       |
|                                                 | 8q24/8q24.13| PVT1-NSMCE2 | [45, 46]  |
| Gastric cancer                                  | 8q24/11p13  | PVT1-PDHX   | [47]       |
|                                                 | 8q24/10q26.13| PVT1-ATE1  | [47]       |
|                                                 | 8q24/11p13  | PVT1-APIP    | [47]       |
|                                                 | 8q24/10q26.12| PVT1-PPAPDC1A| [47]      |
| Blastic plasmacytoid dendritic cell neoplasm    | 8q24/6p21   | PVT1-SUPT3H  | [48]       |
| Burkitt lymphoma                                | t(2,8)or t(8,22) | PVT1-IGγ or IGk | [49]   |
| Small-cell lung cancer                          | 8q24/8q13.3 | PVT1-EYA1   | [50]       |
|                                                 | 8q24/8q12   | PVT1-CHD7   | [51]       |
|                                                 | 8q24/1q44   | PVT1-AKT3   | [38]       |
| Multiple myeloma                                | 8q24/13q13  | PVT1-NBEX   | [38]       |
|                                                 | 8q24/16q23  | PVT1-WwoX    | [38]       |
| Medulloblastoma                                  | 8q24/8q24.21| PVT1-MYC    | [39]       |
|                                                 | 8q24/8q24.3 | PVT1-NDRG1  | [39]       |
**Positive feedback between PVT1 and MYC**

Since PVT1 was discovered and received widespread attention, researchers have closely examined whether it is involved in the cancer-promoting pathway related to MYC. A large number of studies showed that PVT1 levels are higher in many cancers with increased MYC expression compared to normal tissues and are associated with poor prognosis [66–68]. Tissue microarray analysis of 8 primary tumors (lung, colon, rectum, stomach, esophagus, liver, kidney, and mammary gland) indicated a high correlation between PVT1 and c-Myc expression, providing strong evidence for the cooperation of PVT1 and MYC in different human cancers [40]. The gene fusion of MYC and PVT1 and the positive feedback mechanism between them can increase the transcription of PVT1, thereby enhancing the role of PVT1 in tumors.

Interestingly, when siRNA was used to knock down PVT1, low levels of c-Myc were found without significant changes in MYC mRNA levels, which indicates that c-Myc levels are closely related to PVT1 in high-copy 8q24 proliferating cancer cells. Phosphorylation of the threonine 58 (Thr58) site on c-Myc causes the degradation of itself through the ubiquitin proteasome pathway [69]. In tumor tissues, the major transcription product of the PVT1 gene, PVT1 (an IncRNA), increases the level of c-Myc by enhancing the stability of it via blocking the phosphorylation of the Thr58 site on c-Myc [8, 70, 71]. Furthermore, c-Myc is an important transcription factor that enhances PVT1 transcription. Carrausa et al. [72] found that the PVT1 promoter region contains two enhancer E-boxes that serve as c-Myc binding sites and E-box 2 clearly mediates the binding of c-Myc to the PVT1 promoter to promote PVT1 expression. Northcott et al. [39] subsequently confirmed that MYC positively regulates the expression of PVT1-encoded miRNA in medulloblastoma cells and MYC can enhance its own expression through the PVT1 promoter in tumors with PVT1-MYC gene fusion. Thus, the mechanism of co-amplification of PVT1 and MYC in tumor cells may involve a positive feedback pathway in which c-Myc increases the transcription of PVT1 by binding to E-boxes located in the PVT1 promoter region, which results in the increased expression of PVT1. PVT1 then prevents the degradation of c-Myc by blocking the phosphorylation of Thr58 in c-Myc and maintains a high c-Myc protein level (Fig. 2). Therefore, through this positive feedback mechanism, PVT1 and c-Myc in cancer cells can remain at a high level, which results in the synergistic promotion of tumorigenesis by PVT1 and c-Myc.

**Promoter-enhancer competition between PVT1 and MYC**

It has been known for many years that enhancers play an important role in genomic transcription. Their main function is to enhance the transcriptional initiation rate as a sequence element to enhance promoter activity. Initially, the understanding of enhancer–promoter interactions only existed at the linear level. With the development of high-throughput techniques and chromosome topology spatial structure detection techniques, researchers were able to detect the interaction among genomic components in 3D and discover more complex mechanisms [73, 74]. There are two mechanisms for the spatial interaction between the promoter and enhancer. One mechanism is to connect linearly distant loci with proteins, such as CTCF. In the other mechanism, for the topologically associated domain (TAD) scaffold, contact between the promoter and enhancer can coordinate the regulation of gene expression [75, 76]. Promoter-enhancer competition between PVT1 and MYC, described as follows, mainly occurs in the TAD.

Cho et al. [9] found that the PVT1 promoter can cis-competitively contact its own four intragenic enhancers, reducing competition from the MYC promoter and down-regulating the expression of MYC to inhibit the proliferation of tumor cells. Unexpectedly, they found that when the PVT1 promoter was silenced, tumor cell proliferation was significantly enhanced, which was contrary to the experimental conclusion from previous studies that “PVT1 has a
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"cancer-promoting effect" [8, 77]. Moreover, they also found that MYC mRNA was significantly upregulated in cells after silencing the PVT1 promoter and the role of PVT1 promoter was independent of its lncRNA function, which affects the transcription level of MYC. On chromosome 8, the distance between MYC and PVT1 is 53 kb, so how does the PVT1 promoter affect MYC transcription despite this relatively long distance barrier? Cho et al. used the Hi-ChIP method to target the enhancer-associated marker histone 3 lysine 27 acetylation. The promoter of PVT1 and its four intragenic enhancers and the MYC promoter are in the same TAD of discrete self-interacting units of three-dimensionally organized chromatin [78]. Normally, the four intragenic enhancers of PVT1 contact their own PVT1 promoter. However, in cells in which the PVT1 promoter is silent, the enhancers of PVT1 can contact the MYC promoter more readily and reduce their association with the PVT1 promoter. Silencing the enhancers of PVT1 could reverse the upregulation of MYC induced by silencing of the PVT1 promoter. According to the previously described experimental results, a "promoter-enhancer competition" model was proposed (Fig. 3), which sheds light on the recurrent chromosomal rearrangements within the MYC-PVT1 locus.

The transcription of PVT1 and MYC starts at the promoter core sequence for both genes, and RNA polymerase II (Pol II) is recruited by the transcription complex and accurately locates the specific region [79]. There is a promoter proximal pause mediated by a transcriptional pause-inducing factor...
during transcriptional elongation in RNA synthesis, and the epigenetic reading protein bromodomain-containing protein 4 (BRD4) recruits P-TEFb, a kinase-positive transcription elongation factor, to the pretranscriptional initiation complex [80]. BRD4 can bind to the carboxy terminal domain of Pol II and phosphorylate it at the Ser 2 site, and P-TEFb dissociates the pause-inducing factor from the transcription complex to synergistically promote transcription via Pol II [81]. In normal tissues, the four internal enhancers of PVT1 are preferentially contacted by the PVT1 promoter; thus, BRD4 will preferentially occupy the PVT1 promoter, reducing the occupation of BRD4 at the MYC promoter and decreasing the transcription of MYC.
Therefore, the PVT1 promoter can act as a tumor suppressor DNA element of MYC. In human breast cancer and malignant lymphoma, the PVT1 promoter is mutated. Thus, the MYC promoter predominate the promoter–enhancer competition, thereby increasing the MYC mRNA level (Fig. 3). According to the description of the topology structure, the PVT1 promoter, MYC promoter, and the four enhancers belong to the same TAD in normal tissues, while in cancer cells, the circumstance is different. Mutations in the PVT1 promoter lead to changes in chromosome 3D construction so that the four intragenic enhancers of PVT1 become closer to the MYC promoter and preferentially contact it. Thus, the promoter of PVT1 inhibits the expression of its “neighbor” gene MYC by competing for the four enhancers on the same chromosome. We hypothesize that the “promoter–enhancer competition” model is the initial step in the MYC-driven carcinogenic process. The high level of MYC transcripts is involved in the positive feedback mechanism previously described, activates the PVT1 promoter and promotes PVT1 expression, which is consistent with the high expression of both MYC and PVT1 in tumor cells.

Additionally, in some tumor tissues, the region near the PVT1 promoter shows more pronounced structural changes than other IncRNA promoters, such as deletions, inversions, or duplications, which alter the chromatin and TAD environment of the PVT1 promoter [9]. In human (ER−) HER2+ breast cancer, the PVT1 intron 1, which is close to the PVT1 promoter, is abnormally prone to cleavage, which might result in the fusion of PVT1 with another gene on the same chromosome leading to an abnormal transcription process not regulated by the PVT1 promoter.

In normal cells, studies have demonstrated low expression of PVT1 and MYC [72]. If the “promoter–enhancer competition” between PVT1 and MYC commonly exists in cells, the PVT1 promoter serves as a tumor suppressor, and will further down-regulate the expression of MYC, preventing the development of MYC-driven tumors. Thus, the mutation of PVT1 promoter will be the last straw in cancer development. However, the “promoter–enhancer competition” between PVT1 and MYC is currently only observed in breast cancer cell lines and mutation of the PVT1 promoter is only observed in breast cancer and malignant lymphoma. Thus, whether the competition mechanism acts as a complement and improves the positive feedback mechanism in common MYC-driven tumors requires further analysis.

**PVT1 participates in the downstream signaling pathway of c-Myc by regulating key molecules**

In addition to preventing the phosphorylation of c-Myc to maintain its stability, PVT1 can participate in the downstream signaling pathway of c-Myc by regulating its downstream key factors (Fig. 4). PVT1 may promote the tumorigenesis and development of tumors together with c-Myc by regulating key molecules in the downstream signaling pathway of c-Myc. Therefore, we adequately understand that PVT1 and c-Myc jointly regulate key molecules, which may contribute to the development of new and selective anti-cancer drugs for the targeted therapy of cancers with high expression of PVT1 and c-Myc.

**PVT1 participates in the proliferation-related signaling pathway downstream of c-Myc**

Malignant cell proliferation is one of the hallmarks of tumor cells [82–86]. Research has shown that c-Myc can promote the transcription of positive cell cycle regulatory factors, such as E2F transcription factors, cyclin D1, and cyclin-dependent kinase 4 (CDK4). They can promote activation of the cell cycle and thus cell proliferation [87–90]. By inhibiting cell cycle inhibitors, such as p15, p16, and p21, which inhibit the cyclin-cdk complex, c-Myc promotes cell proliferation. In cancer cells, a complex of c-Myc and c-Myc-interacting zinc finger protein-1 (Miz1) act on the promoter of p15 and p16, which, in turn, down-regulates the expression of p15 and p16, enabling the cell to enter the cell cycle phases. By binding to Miz1, c-Myc can also inhibit the expression of p21 [91]. C-Myc also inhibits the expression of p21 through miR-17, miR-20a, and miR-10b [92, 93]. Moreover, the transcription factor AP4 (TFAP4), induced by c-Myc, binds to the promoter of p21 and inhibits the expression of p21 [94, 95].

Recent studies showed that PVT1 affects the c-Myc-related pathway and influences the cell cycle. PVT1 can promote tumor proliferation by downregulating the expression of p15 and p21 [96]. PVT1 acts on the promoter of P15 and P16 by binding the enhancer of zeste homolog 2 (EZH2) to inhibit p15 and p16 expression [97]. In cancer cells, knockdown of PVT1 expression inhibits the expression of cyclin D1 and CDK4, which suggests that PVT1 positively regulates the expression of cyclin D1 and CDK4 [98]. PVT1 inhibits the promoter of miR-200c by recruiting EZH2, which leads to an upregulation of cyclin D1 expression [99]. Furthermore, Chen et al. [22] confirmed that circPVT1 competently binds to the miR-125 family and enhances the expression of the transcription factor E2Fs. Therefore, PVT1 participates in the proliferation-related signaling pathway downstream of c-Myc by regulating p21, p15/p16, CD4, and cyclin D (Fig. 4).

**PVT1 participates in the downstream angiogenesis-related signaling pathway of c-Myc**

Sustained angiogenesis is a key element in tumorigenesis. In an anoxic environment inside a tumor mass, hypoxia-inducible
Studies have shown that the high expression and metastasis of tumors typically lead to patient death. c-Myc amplification of the MYC gene can promote tumor metastasis, which is closely related to the epithelial–mesenchymal transition (EMT) of tumor cells. The EMT is a key process in the occurrence and development of tumors. PVT1 participates in the downstream signaling pathway of c-Myc by regulating the expression of key molecules. PVT1, similar to c-Myc, can promote tumor proliferation, angiogenesis, the EMT, and the Warburg effect. Moreover, PVT1 may inhibit c-Myc-induced apoptosis by regulating caspase9, caspase3, and MDM. In this figure; the blue arrow indicates promotion/upregulation, while the black line indicates inhibition/downregulation.

**PVT1 participates in the downstream signaling pathway of c-Myc by regulating key molecules.** In cancer cells, PVT1 not only exhibits a positive feedback interaction with c-Myc but also participates in the signal pathways downstream of c-Myc to promote the occurrence and development of tumors. PVT1 participates in the downstream signaling pathway of c-Myc by regulating the expression of key molecules. PVT1, similar to c-Myc, can promote tumor proliferation, angiogenesis, the EMT, and the Warburg effect. Moreover, PVT1 may inhibit c-Myc-induced apoptosis by regulating caspase9, caspase3, and MDM. In this figure; the blue arrow indicates promotion/upregulation, while the black line indicates inhibition/downregulation.

factor-1 (HIF-1) induces the expression of genes involved in angiogenesis [100–102]. HIF-1α is a crucial oxygen sensor and plays a leading role in angiogenesis. By binding to the promoter of vascular endothelial growth factor (VEGF), HIF-1α upregulates the expression of VEGF [103]. VEGF can act on the vascular endothelium, accelerating its proliferation and tube formation and increasing vessel permeability. In the angiogenesis signaling pathway, VEGF-A and thrombospondin-1 (TSP1) are angiogenesis inducers and inhibitors, respectively. TSP1 is a key balance factor in angiogenesis. It also binds to transmembrane receptors on endothelial cells, triggering inhibitory signals that counteract angiogenesis stimulation [104]. In cancer cells, c-Myc increases the transcriptional level of HIF-1α [105], thus increasing the expression of HIF-1α, further promoting the expression of VEGF, which participates in downstream signaling pathways and promotes tumor angiogenesis. c-Myc can also directly upregulate the expression of VEGF [106] and inhibit the transcription of TSP1 [107], further promoting tumor angiogenesis. High expression of PVT1 in tumor cells can be used as a competing endogenous RNA sponge to adsorb miR-199a-5p or miR-186 and subsequently upregulate the expression of HIF-1α [108, 109]. PVT1 can recruit EZH2 to the miR-200b promoter and inhibit miR-200b expression [110]. MiR-200b reduces the VEGF level [111]. Thus, PVT1 may upregulate the expression level of VEGF through inhibiting miR-200b. Moreover, PVT1 may increase the expression of VEGF by inhibiting miR-20a [13, 112]. Therefore, PVT1 participates in the downstream angiogenesis-related signaling pathway of c-Myc and can promote tumor angiogenesis (Fig. 4).

**PVT1 participates in the downstream Warburg effect-related signaling pathway of c-Myc**

Cancer is often accompanied by deregulating cellular energy [129–133]. The pyruvate produced by glycolysis does not enter the mitochondria and is converted to lactic acid by lactate dehydrogenase (LDH), which typically occurs when normal cells are in a low-oxygen state. However, in cancer cells, the production of lactic acid under aerobic conditions is referred to as “aerobic glycolysis” or the Warburg effect. Many genes involved in glucose metabolism have been reported to be directly upregulated by the induction of c-Myc, particularly glucose transporter 1 (GLUT1) and hexokinase 2 (HK2) [134]. C-Myc also regulates pyruvate dehydrogenase kinase (PDK), which blocks pyruvate from entering the TCA cycle. C-Myc activates lactate dehydrogenase A, which converts pyruvate to lactic acid. PVT1 acts as an endogenous competitive RNA to inhibit miR-497 whose downstream target is HK2, which results in elevated HK2 expression, increasing glucose consumption and glycolysis [135]. Therefore, PVT1 can regulate HK2 expression to...
participate in the downstream Warburg effect-related signaling pathway of c-Myc (Fig. 4).

**PVT1 participates in the downstream apoptosis-related signaling pathway of c-Myc**

In most human cancers, c-Myc expression is deregulated and/or significantly increased. Interestingly, high levels of c-Myc overexpression not only induce ARF transcription but also stabilize ARF by inhibiting ubiquitin ligase, which, in turn, leads to p53 activation, induces apoptosis, and limits c-Myc-induced carcinogenesis [136]. Mouse double minute 2 homolog (MDM2) downregulates p53 by binding to and inhibiting the transactivation domain of p53 and promoting its degradation [137]. However, ARF can promote the degradation of MDM2, which, in turn, leads to p53 activation. Inactivation of the Arf-Mdm2-p53 tumor suppressor pathway is believed to be a crucial step in tumorigenesis [138]. C-Myc induces apoptosis by regulating the ARF-MDM2-p53 pathway to limit its own carcinogenic potential [136]. However, PVT1 can increase the stability of EZH2 protein by binding to EZH2, which promotes the expression of MDM2 protein. In cancer cells, high expression of PVT1 enhances the expression of EZH2 and MDM2, inhibits the expression of P53 protein in cancer cells, and thus exerts anti-apoptotic effects [139, 140]. C-Myc can also inhibit anti-apoptotic proteins, such as BCL-2 and BCL-XL, leading to a certain amount of tumor apoptosis [141]. When c-Myc exerts a pro-apoptotic function, it can further activate caspase-9 and caspase-3 to induce apoptosis by increasing the expression of and activating the pro-apoptotic protein Bax [142]. PVT1 can downregulate the expression of caspase-9, caspase-7, and poly ADP-ribose polymerase, thereby inhibiting apoptosis and ultimately leading to radiation tolerance [14]. Studies have also shown that PVT1 can downregulate the expression of caspase-3 to inhibit apoptosis [143, 144]. Therefore, PVT1 may participate in the downstream apoptosis-related signaling pathway of c-Myc by affecting MDM, caspase-9, and caspase-3 (Fig. 4).

**Perspectives**

In addition to the interaction between PVT1 and MYC, the newly discovered molecule CircPVT1 is also associated with MYC [145–149]. CircPVT1 is highly expressed in cancer and can mediate the expression of c-Myc [22, 150]. Let-7 can target MYC mRNA and downregulate its expression; however, circPVT1 can impede let-7 through its sponge adsorption effect and increase c-Myc expression [22, 151]. In acute lymphocytic leukemia, circPVT1 can upregulate the expression of c-Myc and anti-apoptotic Bcl-2 proteins [23]. After deletion of circPVT1, the expression levels of c-Myc and Bcl-2 proteins were significantly reduced, while the level of PVT1 RNA was not changed [23]. However, CircPVT1 has many other mechanisms that have not been elucidated. It is worth further investigating whether CircPVT1 has similar mechanisms to PVT1 in cancer cells, whether CircPVT1 interacts with MYC, and which molecules CircPVT1 can regulate to participate in the downstream signaling pathway of c-Myc. Moreover, there are no studies on PVT1-encoded microRNAs that indicate whether they interact with MYC (including miR-1204, miR-1205, miR-1206, miR-1207-5p, miR-1207-3p, and miR-1208) [20, 21].

Currently, the mechanism of action of PVT1 in cancer and the interaction mechanism with MYC are not completely clear; however, in-depth studies of PVT1 can contribute to the development of new therapeutic targets. C-Myc is an important protein in cells and participates in many important metabolic pathways. Overexpression of c-Myc in cancer substantially enhances certain metabolic pathways. If c-Myc is directly inhibited, therapeutic interventions will have a strong impact on patients [152]. Therefore, utilizing a small molecular drug to inhibit PVT1, compared to treatment that directly targets MYC, would fine-tune the level of c-Myc in cancer and reduce toxic side effects or exert an influence on the c-Myc downstream biological phenotype, which is another therapeutic target in MYC-driven cancer. Recently, antisense LNA GapmeRs have been used by researchers to degrade PVT1 in acute erythroleukemia cell lines, which can increase apoptosis and necrosis of tumor cells. They suggested that PVT1 antisense LNA GapmeRs can be used alone or combined with chemotherapeutic drugs in the treatment of acute erythroleukemia [153]. PVT1 promotes the development of cisplatin resistance in colorectal cancer; thus, silencing PVT1 inhibits tumorigenesis and cisplatin resistance in colorectal cancer [154]. Knockdown of PVT1 to a certain extent enhances the radiosensitivity of non-small cell lung cancer cells through inhibiting cell proliferation and promoting apoptosis, which provides a new therapeutic target for improving the efficiency of radiotherapy in patients with non-small cell lung cancer [155]. In addition, studies have found that gemcitabine can inhibit the growth of pancreatic cancer cells by decreasing PVT1 levels and increasing PVT1 encoded miRNAs, such as the miR-1207 pair (miR-1207-5p/3p) [156, 157]. Therefore, there is a bright future for research on how to use PVT1 as a therapeutic target. It is necessary to develop drugs that target PVT1. In the future, we can interfere with the function of PVT1 in tumor cells using siRNAs or antisense LNA GapmeRs against PVT1. Further in vivo studies and clinical trials are required to evaluate the feasibility of this strategy. Moreover, according to the latest promoter competition mechanism, the PVT1 promoter, as a “non-standard” tumor suppressor, is a novel candidate for designing a new therapeutic strategy for tumors in which MYC serves as a carcinoma driver.
Furthermore, the high and specific expression of PVT1 in human cancer indicates its potential as a biomarker in early clinical diagnosis. PVT1 is considered an indicator of poor prognosis in cancer because PVT1 has been shown to play a role in cell proliferation, cell apoptosis, and cell migration, which are key elements of poor prognosis in human cancer [13, 128]. The expression of PVT1 is upregulated in gastric cancer tissues and significantly associated with advanced tumor and lymph node metastasis. Upregulated PVT1 in gastric cancer can promote the proliferation and invasion of gastric cancer cells, which is associated with poor prognosis [97, 108, 158]. A high PVT1 expression level in patients with prostate cancer has been shown to be associated with low overall survival. PVT1 expression is significantly correlated with tumor stage and can promote tumor cell proliferation, invasion, and metastasis in prostate cancer [128, 144]. The expression of PVT1 in ovarian cancer tissues is higher than that in normal ovarian tissue and is related to the advanced stage of ovarian cancer and lower overall survival. The high expression of PVT1 in ovarian cancer cells promotes the proliferation, migration, and invasion ability of ovarian cancer cells [159, 160]. In gliomas, PVT1 is also highly expressed. PVT1 can promote the development of glioma cells through various mechanisms, resulting in a worse prognosis for patients with glioma and high PVT1 expression [18, 161, 162]. Multiple meta-analyses have also shown that PVT1 can be used as a new tumor biomarker and a predictor of poor prognosis in different cancers [163–167].

Conclusions

We have summarized the latest research regarding the relationship between PVT1 and MYC. At the chromosomal level, PVT1 is easily fused with other genes to form a fusion gene that drives the abnormal expression of cancer-associated proteins. Moreover, GWAS also indicated that PVT1 and MYC located in the 8q24 segment are associated with cancer risk. Furthermore, there is a synergistic effect of positive feedback between MYC and PVT1, which results in increased expression levels of these genes in cancer. With the development of 3D technology, the latest research shows that PVT1 and MYC have a “promoter-enhancer competition mechanism” in a three-dimensional structure. Moreover, PVT1 can also participate in the c-Myc downstream signaling pathway by acting on key molecules downstream of c-Myc.

However, the interaction between PVT1 and MYC has not been fully understood, and further studies are needed. Studies have shown that PVT1 can inhibit the phosphorylation and degradation of c-Myc to promote its stability; however, are there ways that PVT1 impacts the transcription and translation of c-Myc? In addition to gene fusion, the positive feedback mechanism, coamplification and the “promoter-enhancer competition mechanism”, are there other mechanisms of that mediate the PVT1 and MYC interaction? The “promoter-enhancer competition” between PVT1 and MYC is currently only found in breast cancer cell lines and, thus, requires further exploration regarding whether this competition commonly exists in other MYC-driven cancers. Moreover, the key molecules that are at the c-Myc downstream signaling pathway and regulated by PVT1 are needed to further verify and clarify to develop anticancer drugs by inhibiting these key molecules. In addition, it is worth elaborating on whether microRNAs and the circPVT1 encoded by PVT1 interact with MYC.

Although the increasing number of mechanisms of action for PVT1 and its interaction with MYC in cancer are being discovered, there is no application for PVT1 in clinical treatment to date, and only one clinical trial on PVT1 is recruiting subjects. Thus, the findings resulting from such studies are expected to be transformed into methods of early cancer diagnosis and treatment applications in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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