

## Review

# PCAT-1: A Novel Oncogenic Long Non-Coding RNA in Human Cancers

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## Abstract

Long non-coding RNAs (lncRNAs) are transcripts longer than 200 nucleotides (nts) without obvious protein coding potential. lncRNAs act as multiple roles in biological processes of diseases, especially carcinomas. Prostate cancer associated transcript-1 (PCAT-1) is an oncogenic lncRNA that identified by RNA-Sequence in prostate cancer. High expression of PCAT-1 is observed in different types of cancers, including prostate cancer, colorectal cancer, hepatocellular cancer and gastric cancer. High expressed PCAT-1 is correlated with poor overall survival. Furthermore, PCAT-1 regulates cancer cell proliferation, apoptosis, migration and invasion. Additionally, PCAT-1 is involved in *EMT* and *Wnt/β-catenin*-signaling pathway. In this review, we focus on the implication of PCAT-1 in human cancers.

Key words: long non-coding RNA, PCAT-1, cancer, biomarker, therapeutic target

## Introduction

Cancer is a group of disease involving uncontrolled cell growth, and its high mortality and disability cause great personal suffering among patients and a huge burden to society [1]. Surgical treatment, chemotherapy and radiotherapy are currently the main treatments of cancer [2, 3]. However, the therapeutic effects of these primary treatments are still limited [4, 5]. Therefore, early diagnostic markers and novel therapies are urgently required to cure cancer.

lncRNAs are defined as transcripts longer than 200 nucleotides (nts) without obvious protein coding potential [6, 7]. The majority of lncRNAs are transcribed by RNA polymerase II and are frequently spliced and polyadenylated [8-10]. Compared with protein-coding sequence, most lncRNAs tend to be weakly evolutionary constraint [11]. The promoter sequence of lncRNA is strong conserved, while its transcript sequence is less conserved, indicating that

lncRNA transcription itself has a greater biological consequence than the transcript sequence [11]. lncRNA are involved in transcriptional regulation, epigenetic gene regulation, cellular addresses and disease, especially the growth and metastasis of cancers [11-14].

Various mutations of lncRNAs are implicated in multiple cancer types [15, 16], and lncRNAs are further considered as oncogenes or tumor suppressor genes in cancers [17, 18]. For example, lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is overexpressed in various cancers, associated with metastasis and poor prognosis, and acts as an oncogene in breast cancer by controlling the selective splicing process [19-21]. Moreover, MALAT1 is an interesting tumor marker and a potential target gene for anti-metastatic therapy [20, 22-25]. In contrast, lncRNA NF-KappaB Interacting lncRNA (NKILA) is a tumor suppressor and acts as a NF-κB

regulator to inhibit breast cancer metastasis [26-28]. Taken together, lncRNAs play important roles in cancer development, which may become diagnostic biomarkers and therapeutic targets.

Prostate cancer associated transcript-1 (PCAT-1) was originally identified in prostate cancer by large-scale RNA-Seq analyses, and functionally implicated in prostate cancer progression. The high expression of PCAT-1 has been found in several human tumor entities, and is associated with poor prognosis, including TNM stage. In addition, PCAT-1 has been implicated in regulating cancer cell proliferation, apoptosis, migration and invasion. PCAT-1 has also been shown to be involved in epithelial-mesenchymal transitions (EMT) and regulate cancer progression via the *Wnt*/ $\beta$ -catenin signaling pathway. In this review, we will focus on the implication of PCAT-1 in human cancers.

## Discovery of PCAT-1

In 2011, Prensner et al. discovered 121 unannotated prostate cancer-associated ncRNA transcripts (PCATs) by high-throughput RNA-Seq from a cohort of 102 prostate tissues and cells lines. The 121 unannotated transcripts were ranked and named as PCATs according to their fold-change in tumor versus normal tissue [29, 30]. PCAT-1 is significantly overexpressed in most prostate cancer tissues, particularly metastases.

PCAT-1 is a long non-coding RNA with a length of ~1900 nt. PCAT-1 gene consists of 2 exons. Exon 1 contains a retroviral long terminal repeat (LTR) sequence and exon 2 contains sequences from the HSMAR1 *mariner* family transposase bisected by an AluY repeat element [30]. PCAT-1 gene located at chromosome 8q24 and 725 kb upstream of the c-Myc

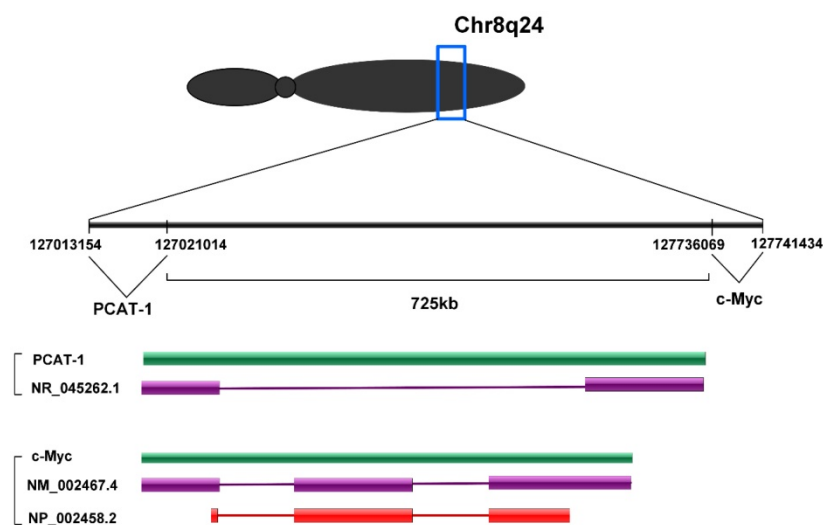
oncogene (Fig. 1). Chr8q24 locus is an area commonly studied in prostate cancer due to frequent amplification and the presence of prostate cancer susceptibility SNP loci [31, 32]. However, PCAT-1 outlier expression was not dependent on Chr8q24 amplification, as PCAT-1 highly expressing tumors often did not have 8q24 amplification and high copy number gain of 8q24 was not sufficient to upregulate PCAT-1 [30].

PCAT-1 promotes cell proliferation and is upregulated in major types of cancers, including esophageal squamous cell carcinoma (ESCC) [33], bladder cancer (BC) [34], hepatocellular cancer (HCC) [35], non-small cell lung cancer (NSCL) [36], glioblastoma, multiple myeloma (MM) [37], breast cancer, colorectal cancer (CRC) [38] and gastric cancer (GC) [39]. In addition, overexpression of PCAT-1 was closely associated with clinicopathological characteristics, including tumor size, lymphatic metastasis, distant metastasis, tumor-node-metastasis (TNM) stage and poor prognosis (Table 1). PCAT-1 functions predominantly as a transcriptional repressor. PCAT-1 negatively regulates the *BRCA2* tumor suppressor protein and positively regulates Myc oncoprotein [40]. It contains binding sites for microRNAs, and may act as a sponge for microRNAs that regulate cell growth pathways [30]. Thus, current evidence suggested that PCAT-1 is an oncogenic gene and played an important role in the regulation of cancer development.

## Expression distribution and transcription regulation of PCAT-1

PCAT-1 is expressed in a wide range of different tissues and is most highly expressed in the prostate, salivary gland [41]. In prostate cancer and osteosarcoma cells, PCAT-1 transcript is predominantly located in the cytoplasm and a smaller fraction is expressed in the nucleus [40]. PCAT-1 might play a role in both transcriptional and post-transcriptional regulation in cancer development.

As for the mechanism of PCAT-1 expression profiles in prostate cancer, Prensner et al. found that *SUZ12*, a core polycomb repressive complex 2 (*PRC2*) protein, directly binds to the PCAT-1 promoter ~1 kb upstream of the transcription start site [30]. *EZH2* knockdown by short hairpin (sh)RNA or pharmacologic inhibition caused a dramatic upregulation in PCAT-1 expression levels (Fig. 3). Otherwise, not much is known about the cellular factors and pathways that lead to the strong transcription of MALAT1, especially in human cancer cells.



**Figure 1.** PCAT-1 is located at chromosome 8q24 and 725 kb upstream of the c-Myc oncogene.

**Table 1.** Functional characterization of PCAT-1 in various cancers.

Cancer types	Expression	Effects	Related gene	Role	References
Prostate cancer	Upregulated	Proliferation, metastasis, DSB repair process	PRC2, cMyc protein, BRCA2, SUZ12, miR-3667-3p, miR-34a	Oncogene	30, 40, 47
Colorectal cancer	Upregulated	Proliferation, Cell arrest, apoptosis	Caspase-3, PARP, bax, bcl-2, cMyc protein	Oncogene	38
Hepatocellular cancer	Upregulated	Invasion, metastasis, apoptosis, TNM stage	HMGB1, mir-129-5p	Oncogene	59, 60, 61
Gastric cancer	Upregulated	Proliferation, migration, invasion, metastasis	CDKN1A	Oncogene	39, 67
Bladder cancer	Upregulated	Proliferation, apoptosis	-	Oncogene	34
Breast cancer	Upregulated	-	-	-	91
Esophageal squamous cell carcinoma	Upregulated	-	-	-	33
Non-small cell lung cancer	Upregulated	Proliferation, migration, invasion	-	Oncogene	36
Multiple myeloma (serum)	Upregulated	-	-	-	37
Osteosarcoma	Upregulated	Apoptosis, metastasis	E-cadherin, N-cadherin, EZH2, p21	Oncogene	72, 73, 74, 75, 83
Extrahepatic cholangiocarcinoma	Upregulated	Proliferation, apoptosis, metastasis	miR-122, WNT1	Oncogene	90

TNM: TNM Classification of Malignant Tumours; PRC2: Polycomb Repressive Complex 2; cMyc: MYC proto- oncogene, bHLH transcription factor; BRCA2: breast cancer 2, early onset; PARP: poly- ADP- ribose polymerase; Bax: BCL2- associated X protein; Bcl- 2: B- cell CLL/lymphoma 2 protein; HMGB1: high mobility group box 1; CDKN1A: cyclin-dependent kinase inhibitor 1A

In 2011, Gene expression profiling of PCAT-1 knockdown in LNCaP cells showed that PCAT-1 modulates the transcriptional regulation of 370 genes (255 upregulated, 115 downregulated; FDR ≤ 0.01) [30]. Since then, many studies have shown that PCAT-1 regulates transcription of various genes involved in cancer cell proliferation, apoptosis, migration and invasion, including *BRCA2* tumor suppressor, *Myc* oncoprotein and so on (Fig. 2).

## PCAT-1 in human cancers

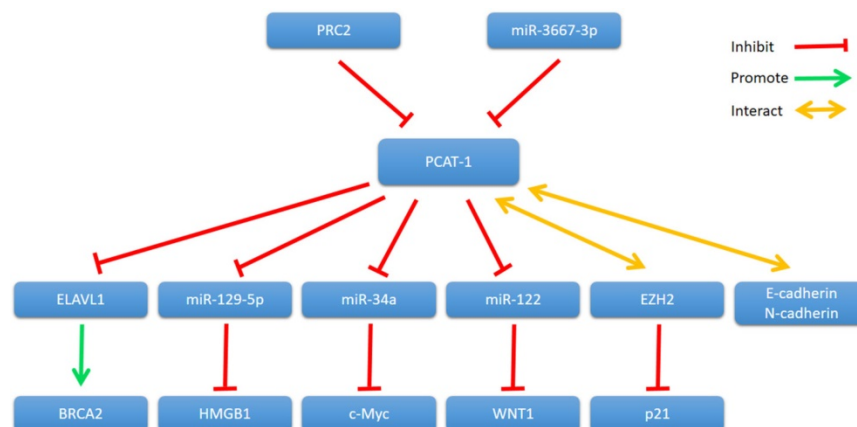
### Prostate cancer

Prostate cancer is the second most common malignancy in men and the second leading cause of cancer death in the United States and Europe. It is known for a disease of older man (aged >65years), and over 10% of new cases has been diagnosed in young men (aged ≤55 years) [42]. Surgery and radiotherapy are the traditional treatments to prostate cancer, but the effects of these treatments are still limited [43]. Therefore, biomarkers for early diagnosis

and novel targets for therapy are urgently required.

John et al. found that PCAT-1 was significantly overexpressed in most prostate cancer tissues, particularly metastases. It is well known that oncoprotein *EZH2* (a core protein of *PRC2*) is up-regulated in tumors and contributes to a metastatic phenotype [44-46]. They further investigated the relationship between PCAT-1 and *EZH2* [30]. They discovered that the expression of PCAT-1 and *EZH2* was almost mutually exclusive. Knockdown of *EZH2* by shRNA or pharmacologic inhibition of *EZH2* with the inhibitor 3-deazaneplanocin A (*DZNep*) up-regulated PCAT-1 expression levels. In addition, the expression level of three key PCAT-1 target genes (*BRCA2*, *CENPE* and *CENPF*) was up-regulated when PCAT-1 was knockdown in prostate cancer cells. Furthermore, another *PRC2* protein *SUZ12* was shown to bind directly to the promoter of PCAT-1 (Fig. 3). Further researches are required to elucidate the precise mechanism of the interplay between PCAT-1 and *PRC2*.

John et al. further reported that PCAT-1 posttranscriptional repressed the expression of the *BRCA2* tumor suppressor, leading to downstream impairment of homologous recombination (HR) [40]. In addition, Prensner et al. revealed that PCAT-1 promoted prostate cell proliferation by up-regulating the protein level of cMyc [47]. It is well known that cMyc is important transcription factor that is essential for cell cycle progression [48-51]. The oncogenic up-regulation of cMyc has a broad impact on cancer cell biology [52-54]. Evidence showed that PCAT-1 increased MYC 3'UTR activity through interfering the regulation of MYC by



**Figure 2.** PCAT-1 and its mechanisms of action.

microRNAs (miR-3667-3p and miR-34a), thereby promoting the proliferation of prostate tumor cells [47] (Fig. 4). In prostate cancer cells, PCAT-1 is predominantly expressed in the cytoplasm and is also expressed in a small amount in the nucleus [40]. This ubiquitous subcellular localization of PCAT-1 transcripts may contribute to the function of PCAT-1 both in nucleus and cytosol. To sum up, these results suggested that PCAT-1 may function as a potential prognostic biomarker and therapeutic target in prostate cancer.

### Hepatocellular cancer

Hepatocellular carcinoma (HCC) is the fifth most common cancer all around the world [55, 56]. Even after clinical treatment (including surgery, radiation therapy, and chemotherapy), recurrence and distant metastasis of HCC are still at high levels [57, 58]. In addition, current evidence suggests that the development of HCC is associated with genetic or epigenetic mutation [59]. Thus, it is urgent to seek for novel tumour biomarkers and further study the special mechanisms of HCC development.

Yan et al. illustrated that PCAT-1 was not only significantly up-regulated in HCC tissues and cell lines, but also related to TNM staging, metastasis and histological grade [35]. Wen et al. reported that PCAT-1 down-regulation significantly reduced the invasion and migration of HCC cell lines [60]. Zhang et al. found that PCAT-1 inhibits the repressive effect of miR-129-5p and reverses the expression of high mobility group box 1 (*HMGB1*), a target gene of miR-129-5p [61]. Importantly, *HMGB1* promotes metastasis and invasion in HCC (Fig. 5). In addition, evidence revealed that PCAT-1 was an independent prognostic factor of HCC in clinic research. Overexpression of PCAT-1 in HCC was associated with more malignant phenotypes and worse

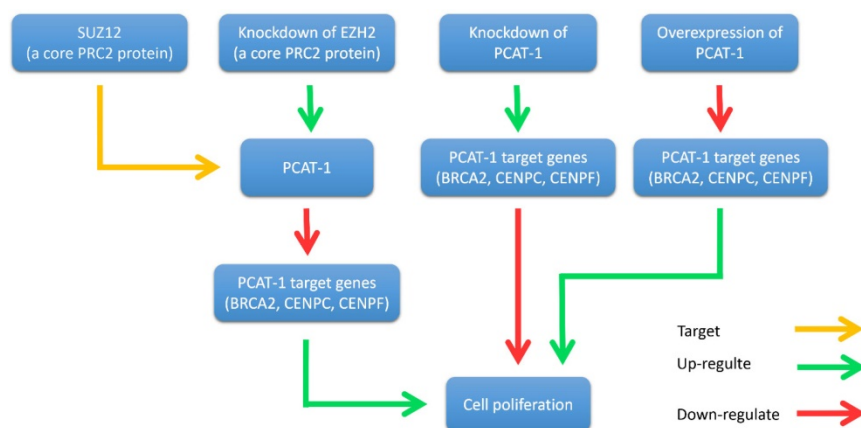
prognosis. These studies suggest that PCAT-1 is a potential diagnostic and therapeutic target in HCC.

### Gastric cancer

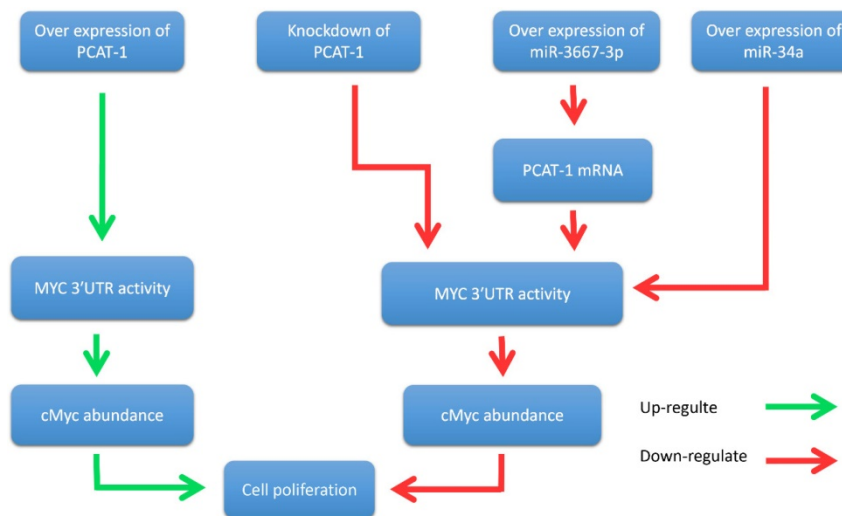
As an aggressive disease, gastric cancer (GC) is the third leading cause of cancer-related death worldwide [62, 63]. Surgery and chemotherapy are the main treatments for GC, but the 5-year survival rate is still low [64-66]. Therefore, it is necessary to find novel biomarkers for diagnosing GC.

Cui et al. observed that the PCAT-1 was high-expressed in GC tissues and cell lines, and overexpression of PCAT-1 was associated with poor overall survival [39]. *CDKN1A* acts as a regulator of cell cycle progression, and exerts tumor suppressive effects in several cancers. Bi et al. indicated that PCAT-1 promoted cell proliferation, migration and invasion in GC cells by regulating *CDKN1A* (Fig. 6). They found that inhibition of PCAT-1 in GC cells induced G1 arrests and apoptosis, and reduced cell migration and invasion. *CDKN1A* was up-regulated in PCAT-1 knockdown GC cells, and *CDKN1A* knockdown can rescue PCAT-1 knockdown-induced cell proliferation and migration inhibition [67]. These results indicate that PCAT-1 plays an oncogenic role in the progression of GC.

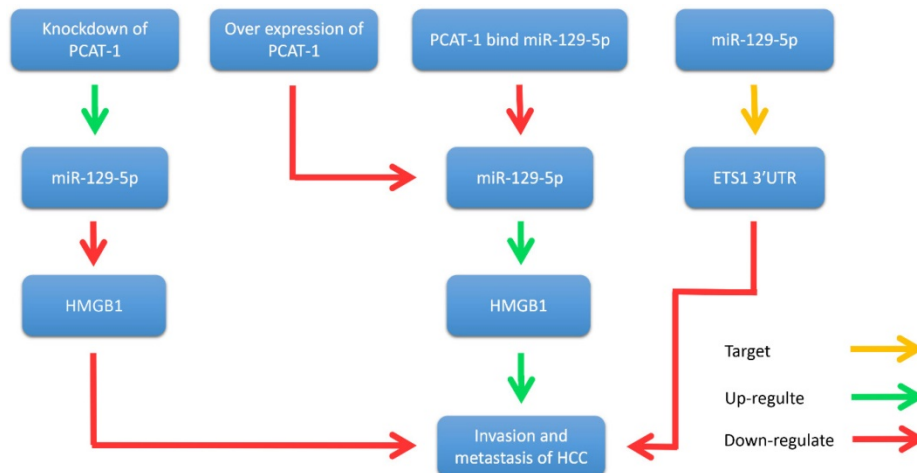
Cui et al. indicated that the expression level of PCAT-1 was closely correlated with the depth of invasion, TNM stage and lymph node metastasis of GC. Moreover, Kaplan-Meier analysis showed that GC patients with high PCAT-1 expression were significantly associated with lower overall survival (OS), suggesting that high expression of PCAT-1 is an independent prognostic factor for OS [39]. All these results indicate that the overexpression of PCAT-1 may be used as a biomarker for GC prognosis, which has important clinical significance.



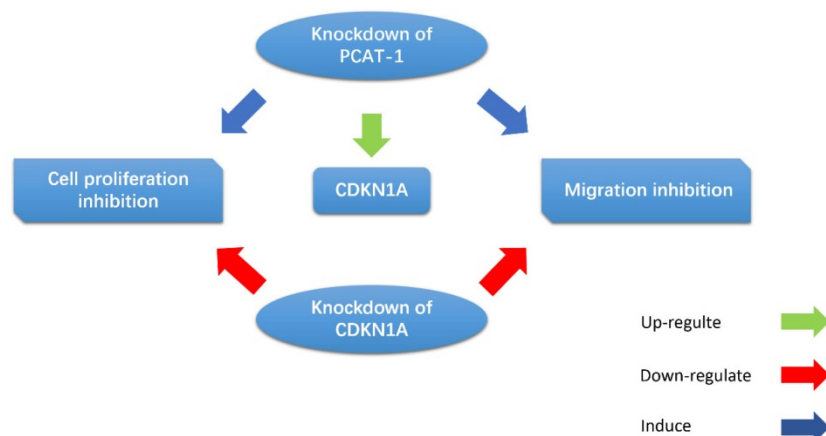
**Figure 3.** Interplay between PCAT-1 and the polycomb inhibitory complex 2 (PRC2). PCAT-1 overexpression promotes cell proliferation, while knockdown of PCAT-1 reduces cell proliferation. *EZH2* (a core PRC2 protein) knockdown up-regulates PCAT-1 expression and down-regulates PCAT-1 target genes (*BRCA2*, *CENPC*, *CENPF*). Similarly, PCAT-1 knockdown upregulates the target genes of PCAT-1. Another core PRC2 protein, *SUZ12*, binds directly to the promoter of PCAT-1.



**Figure 4.** PCAT-1 promotes prostate cancer cell proliferation through cMyc. Overexpression of PCAT-1 up-regulates MYC 3'UTR activity, increases cMyc abundance, and promotes prostate cancer cell proliferation. Conversely, PCAT-1 knockdown down-regulates this process and inhibits cancer cell proliferation. Overexpression of miRNA-3667-3p increases the expression level of PCAT-1 and suppresses MYC 3'UTR activity. Overexpression of miR-34a also inhibits MYC 3'UTR activity. Down-regulation of MYC 3'UTR activity reduces cMyc protein abundance and suppresses cancer cell proliferation.



**Figure 5.** PCAT-1 promotes metastasis and invasion in HCC. Overexpression of PCAT-1 down-regulates miR-129-5p, thereby increasing the expression of *HMGB1* and promoting the migration and invasion of hepatoma cells. Knockdown of PCAT-1 up-regulates miR-129-5p and reduces the expression of *HMGB1* protein, thereby inhibiting the migration and invasion of hepatoma cells. In addition, miR-129-5p inhibits the migration and invasion of hepatocellular carcinoma cells by directly targeting ETS1 3'UTR.



**Figure 6.** PCAT-1 promotes cell proliferation and migration in GC cells by regulating *CDKN1A*. *CDKN1A* was up-regulated in PCAT-1 knockdown GC cells, and *CDKN1A* knockdown can rescue PCAT-1 knockdown-induced cell proliferation and migration inhibition.

## Osteosarcoma

Osteosarcoma (OS) is a malignant primary bone cancer that is diagnosed in approximately 30 new cases per million people worldwide each year [68-70]. The 5-year survival rate of the patients with OS remains low [71]. The major treatments for OS are surgery, chemotherapy and palliative radiotherapy, but these treatments have limited efficacy [72]. Moreover, our understanding of the molecular mechanisms that underlies the development of OS remains limited. Therefore, we need to explore novel diagnostic and therapeutic targets for OS.

Zhang et al. reported that PCAT-1 was up-regulated in OS tissues and was correlated with several clinical features of patients with OS, including advanced clinical stage and tumor metastasis [73]. High expression level of PCAT-1 predicted poor prognosis, which may be an important prognostic factor for the clinical outcomes in patients with OS [73]. Moreover, knockdown of PCAT-1 promoted cell apoptosis. Cell cycle analysis showed that overexpression of PCAT-1 reduced the cell population at G<sub>0</sub>/G<sub>1</sub> phase and increased the cell population at S phase, while knockdown of PCAT-1 exerted the opposite effects. Additionally, PCAT-1 is associated with EMT by influencing the expression of EMT-related genes, including E-cadherin, N-cadherin [73]. EMT is considered as an important mechanism of tumor metastasis, which promotes tumor migration, invasion and metastasis [74, 75]. EMT was characterized by loss of cell polarity in epithelial cells and developing characteristics of interstitial cells, including 3 types: primary/type 1, secondary/type 2 and tertiary/type 3. Type 1 is related to embryogenesis, implantation and organogenesis; Type 2 is associated with wound healing, tissue regeneration and organ development;

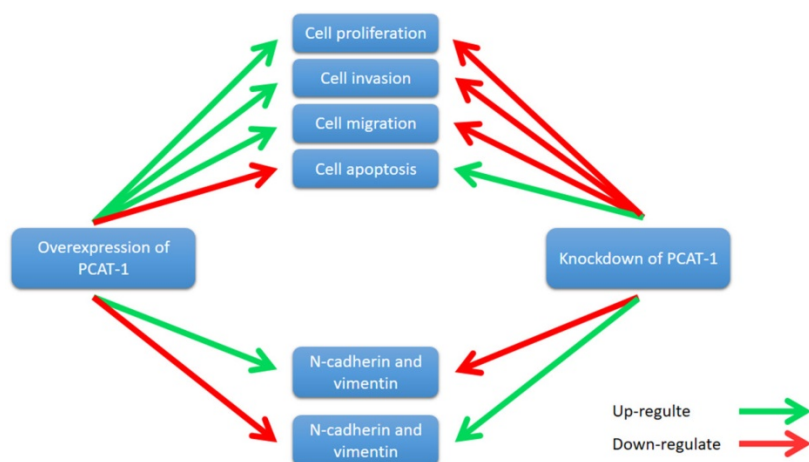
Type 3 regulates tumor metastasis [76-78]. Importantly, the expression of some EMT-related genes changes during cancer progression and metastasis, such as mesenchymal genes (fibronectin, N-cadherin and vimentin) and epithelial genes (E-cadherin and ZO-1) [79-82]. Zhang et al. observed that overexpression of PCAT-1 up-regulated the protein levels of N-cadherin and vimentin, and down-regulated the protein level of E-cadherin [73]. Knockdown of PCAT-1 down-regulated the protein levels of N-cadherin and vimentin, and up-regulated the protein level of E-cadherin [73]. These results showed that PCAT-1 was correlated with EMT in OS (Fig. 7).

In addition, Huang et al found that PCAT-1 was expressed in both cytoplasm and nucleus in OS cells, although the expression level of PCAT-1 in cytoplasm was lower than that of in nucleus [83]. Furthermore, they confirmed that PCAT-1 directly binds to *EZH2* in OS cells by RIP assays and RNA pulldown assays. The ChIP assays revealed that *EZH2* could bind to the p21 [83]. PCAT-1 knockdown reduced *EZH2* binding to the promoter region of p21, and increased p21 expression in OS cells [83]. These results suggest that PCAT-1 inhibits p21 expression through directly binding with *EZH2* and the promoter region of p21 in OS cells. Moreover, cellular functional assays revealed that the functions inhibited by PCAT-1 knockdown was partly abolished by transfected si-p21 [83]. These results indicate that the oncogenic function of PCAT-1 is partly dependent on p21 in OS cells. To sum up, PCAT-1 has potential value as a prognostic biomarker and therapeutic target in OS.

## Extrahepatic cholangiocarcinoma

Cholangiocarcinoma is a fatal cancer that can be divided into two types: intrahepatic and extrahepatic cholangiocarcinoma (ECC) [84]. ECC patients often receive conventional chemotherapy or radiotherapy, but the 5-year survival rate is only 10% [85]. However, the precise mechanism of ECC is still unclear.

*WNT1* is a member of the *WNT* family, which stimulates the *Wnt*/ $\beta$ -catenin-signaling pathway [86]. It is well known that *Wnt*/ $\beta$ -catenin signaling has been closely associated with the initiation and progression of many cancer types [87]. *Wnt*/ $\beta$ -catenin pathway mutations are frequently observed in different cancer types, such as adenomatous polyposis coli (*APC*) mutations in colorectal cancers and  $\beta$ -catenin gene mutations in colorectal cancers [88].

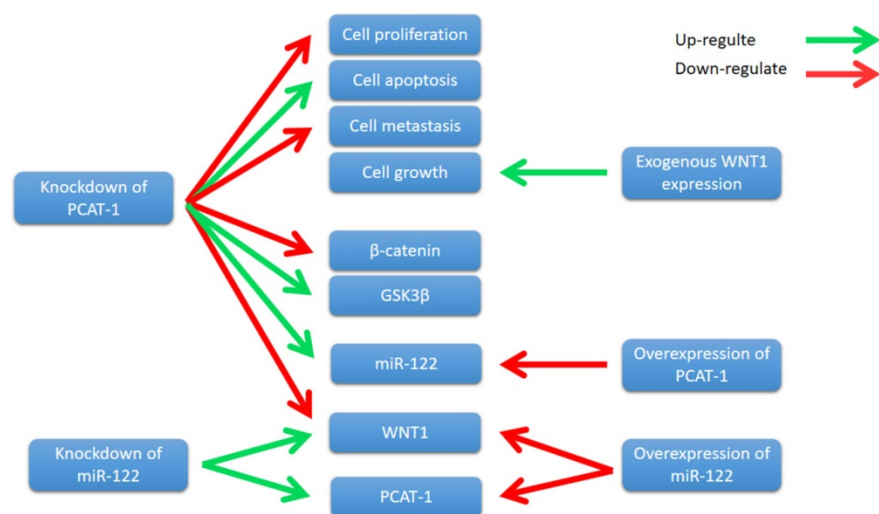


**Figure 7.** PCAT-1 promotes cell proliferation, invasion, migration and EMT in osteosarcoma. Overexpression of PCAT-1 up-regulates N-cadherin and vimentin and down-regulates E-cadherin (N-cadherin and vimentin, E-cadherin are EMT-related markers). By contrast, knockdown of PCAT-1 in OS cell lines exerted the opposite effect.

Importantly, abnormal *Wnt*/ $\beta$ -catenin signaling directly alters a number of regulators critical for the antitumor activities of T cells, thereby promoting cancer progression [89]. Zhang et al. showed that PCAT-1 was up-regulated in ECC tissue samples and cell lines. Knockdown of PCAT-1 suppressed ECC cell growth, induced apoptosis, and inhibited cell metastasis [90]. Moreover, PCAT-1 was associated with miR-122, and knockdown of PCAT-1 leads to an increase in miR-122 levels, whereas PCAT-1 overexpression down-regulated miR-122 expression [90]. Further study revealed that PCAT1 regulated *WNT1* expression via miR-122 [90]. Overexpression of miR-122 significantly down-regulated the *WNT1* expression, and knockdown of miR-122 up-regulated *WNT1* expression [90]. Zhang et al. also showed that knockdown of PCAT-1 significantly reduced  $\beta$ -catenin levels and increased glycogen synthase kinase 3 $\beta$  (*GSK3 $\beta$* ), and the expression of *WNT1* increased colony formation and inhibited cell apoptosis [90]. These results indicate that PCAT-1 knockdown inhibits ECC cells growth by reducing *Wnt*/ $\beta$ -catenin signaling pathway activity through miR-122 (Fig. 8). In conclusion, PCAT-1 may function as a potential prognostic biomarker and therapeutic target in ECC.

### Other cancers

The overexpression of PCAT-1 was also observed in other major cancer tissues and cell lines. For instance, Qiao et al. revealed that PCAT-1 acted as an oncogene in colorectal cancer (CRC), and down-regulation of PCAT-1 significantly reduced the proliferation of CRC cells [38]. However, our understanding of the roles of PCAT-1 in CRC is still at a preliminary stage, further experiments are required.



**Figure 8.** Knockdown of PCAT-1 inhibited cell proliferation, metastasis, and promoted cell apoptosis in ECC cell lines. PCAT-1 knockdown inhibits ECC cells growth by reducing *Wnt*/ $\beta$ -catenin signaling pathway activity through miR-122.

PCAT-1 is up-regulated in bladder cancer (BC) tissues, and PCAT-1 promotes BC cells growth and inhibits apoptosis [34]. In breast cancer, PCAT-1 has been reported to be up-regulated in cancer samples compared with adjacent normal tissues [91]. In esophageal squamous cell carcinoma (ESCC), the expression of PCAT-1 in tumor tissues is significantly higher than normal tissues. The high expression of PCAT-1 was closely associated with tumor invasion, clinical stage and lymph node metastasis. High expression of PCAT-1 indicates poor prognosis of ESCC [33]. In non-small cell lung cancer (NSCL), PCAT-1 is considered as an oncogenic role because its expression level is up-regulated in cancer tissues and cell lines. More experiments have shown that knockdown of PCAT-1 suppressed cell proliferation, migration and invasion in NSCL, whereas up-regulation of PCAT-1 exerted the opposite effect [36]. The relative expression level of PCAT-1 in serum of patients with multiple myeloma (MM) was higher than that of healthy controls, indicating that PCAT-1 can be used as an important biomarker for MM diagnosis [37].

### Conclusion and future perspectives

Aberrant of PCAT-1 expression was observed in major cancer tissues and cell lines. Overexpression of PCAT-1 was closely associated with tumor size, lymphatic metastasis, distant metastasis, tumor-node-metastasis (TNM) stage and poor prognosis. PCAT-1 plays an important role in the regulation of cancer development by regulating cell proliferation, metastasis, apoptosis, cell cycle, DNA repair and homologous recombination [30, 47, 61]. These results reveal that PCAT-1 acts as an oncogenic gene and plays an important role in the regulation of cancer development.

Current studies indicates that PCAT-1 is involved in *EMT* and *Wnt*/ $\beta$ -catenin signaling pathway [73, 90]. Potential cancer therapies targeting *EMT* and *Wnt*/ $\beta$ -catenin signaling pathways have been investigated [86, 92]. For instance, CTCs is a preliminary stage to metastatic development, and their *EMT*-related characteristics are emerging as novel therapeutic targets in cases of cancer chemoresistance over typical neoadjuvant therapies [92]. Since *Wnt*/ $\beta$ -catenin-signaling pathway is critical for cancer, therapies based on *Wnt* signaling may be a novel treatment [89]. Zhang et al. showed that in OS cell lines (MG-63 and U2OS), PCAT1 overexpression increased

the protein levels of *N*-cadherin and vimentin (*EMT* markers), and decreased the protein level of *E*-cadherin, while downregulation of PCAT1 decreased the protein levels of *N*-cadherin and vimentin, and increased the protein level of *E*-cadherin [73]. In the other paper, Zhang et al. reported that silencing of PCAT-1 inhibited the progression of ECC by reducing *Wnt*/ $\beta$ -catenin signaling through miR-122 repression and *Wnt* family member 1 (*WNT1*) expression [90]. Since Activation of *WNT* signaling often promote *EMT*-like changes in a subset of cancers, it is possible that PCAT1 target *WNT1* protein to induce *EMT* in ECC.

From the above researches on PCAT-1, we know a lot about the expression, regulation, and function of PCAT-1 in cancers, particular in prostate cancer, where it has been originally discovered. However, there are several questions that can be addressed to fully understand the function of PCAT-1: What is the molecular mechanism of PCAT-1 up-regulation in cancer? PCAT-1 seems to apply multiple mechanisms to fulfill its functions. How does PCAT-1 accomplish this and how is this controlled in different cancers? Which factors interact with PCAT-1 under which conditions and determine its function? Does PCAT-1 target *WNT1* protein to induce *EMT*?

Compare to other well-known lncRNAs, such as lncRNA MALAT1 [93], H19 [94] and HOX antisense intergenic RNA (HOTAIR) [95], our understanding of the role of PCAT-1 in cancer is still at a preliminary stage. For instance, HOTAIR promotes *EMT* in GC and induces cancer invasion and metastasis by regulating *PRC2* target genes in breast cancer [95, 96]. H19 is up-regulated in GC. Up-regulation of H19 is associated with miR-675, p53 and Isthmin1, which promote cell proliferation, migration and invasion in GC [97-99]. Therefore, to detect more functions of PCAT-1, further experiments should be carried out in cancers. Moreover, more cancer samples should be used to further analyze the relationship between PCAT-1 and the progression and survival of cancer patients. The relationship between PCAT-1 and target genes can also be investigated. Notably, previous studies showed that PCAT-1 interacts with *PRC2*, suggesting that relevant signaling pathway should be explored in cancer.

In conclusion, PCAT-1 is considered as an oncogenic gene, and whose up-regulation is associated with clinicopathological characteristics, including tumor size, lymphatic metastasis, distant metastasis, tumor-node-metastasis (TNM) stage and poor prognosis in human cancers. PCAT-1 may serve as a potential target for cancer diagnosis and treatment, and may be a potential biomarker for cancer.

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## Competing Interests

The authors have declared that no competing interest exists.

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