Biomedicine & Pharmacotherapy 142 (2021) 112010

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

A review on the role of PCAT6 lncRNA in tumorigenesis

Soudeh Ghafouri-Fard [a], Tayyebeh Khoshbakht [b], Mohammad Taheri [c,*], Kaveh Ebrahimzadeh [d,*]

[a] Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Men's Health and Reproductive Health Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Urology and Nephrology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[d] Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
PCAT6
lncRNA
Cancer
Biomarker

ABSTRACT

Prostate cancer-associated transcript 6 (PCAT6) is a long non-coding RNA (lncRNA) firstly identified in 2013 through an integrative genomic analysis of different cancer tissues. This oncogenic lncRNA has been found to regulate carcinogenesis process in different tissues, including breast, ovary, stomach, bladder, colon, pancreas and liver. The role of PCAT6 in sequestering certain microRNAs has been well established. For instance, miR-4723-5p, miR-185-5p, miR-143-3p, miR-30, miR-15a, miR-513a and miR-204, and miR-326 are among those being sequestered by PCAT6. Over-expression of PCAT6 has been associated with poor clinical outcomes in diverse types of cancers including ovarian, bladder, colorectal and pancreatic cancers. In the present review, we summarize the impact of PCAT6 in the development of diverse types of cancers, based on the results of functional studies in cell lines, experiments in xenograft models of cancers and expression studies in samples obtained from human subjects.

1. Introduction

Long non-coding RNAs (lncRNAs) functionally affect pathogenesis of human disorders, particularly malignant conditions [1]. Indeed, lncRNA genes exceed protein-coding genes in terms of quantity [2]. With sizes of more than 200 nucleotides, the vast majority of lncRNAs have no noticeable peptide product [3]. Thus, the man functional effects of lncRNAs are attributed to the transcript itself. Through binding with chromatin and altering its architecture, lncRNAs affect expression of genes. Moreover, they can recruit regulatory molecules to certain chromatin regions, interact with proteins, affect gathering of constituents of protein complexes, interact with mRNAs and regulate their splicing, stability, or translation. Finally, they can serve as molecular sponges for microRNAs (miRNAs) [1]. Several lncRNAs have been recognized that influence the carcinogenic process via different mechanisms [1].

Being firstly identified through an integrative genomic analysis of cancer tissues, prostate cancer-associated transcript 6 (PCAT6) is an lncRNA located on 1q32.1 cytogenetic band [4]. The longest isoform of this lncRNA is 764 bps long (NR_046325.1). A number of other isoforms have also been identified for PCAT6 including ENST00000417262.5 (748 bps), ENST00000425295.1 (634 bps) and ENST00000553157.1 (551 bps). In addition to prostate cancer, PCAT6 has been found to actively participate in the pathoetiology of several cancer types [5]. In the present review, we summarize the impact of PCAT6 in the development of diverse types of cancers, based on the results of functional studies in cell lines, experiments in xenograft models of cancers and expression studies in samples obtained from human subjects.

2. Cell line studies

PCAT6 has been found to boost proliferation, migration and angiogenic processes in triple negative breast cancer. Notably, VEGF secreted from M2 macrophages has been shown to induce expression of PCAT6, therefore enhancing angiogenesis in this type of cancer. Functionally, PCAT6 acts as a sponge for miR-4723-5p to up-regulate expression of VEGFR2 and participate in VEGFR/AKT/mTOR pathway to induce angiogenic process. Furthermore, PCAT6 binding with USP14 accelerates deubiquitination of VEGFR2 [6]. Another experiment in this type of breast cancer has shown up-regulation of PCAT6 and TPD52, while down-regulation of miR-185–5p in these cells. Notably, PCAT6 silencing has suppressed proliferation of these cells, induced apoptosis and promoted their sensitivity to

* Corresponding authors.
E-mail addresses: mohammad_823@yahoo.com (M. Taheri), dr.kavehmay1980@gmail.com (K. Ebrahimzadeh).

https://doi.org/10.1016/j.biopha.2021.112010
Received 18 July 2021; Received in revised form 2 August 2021; Accepted 3 August 2021

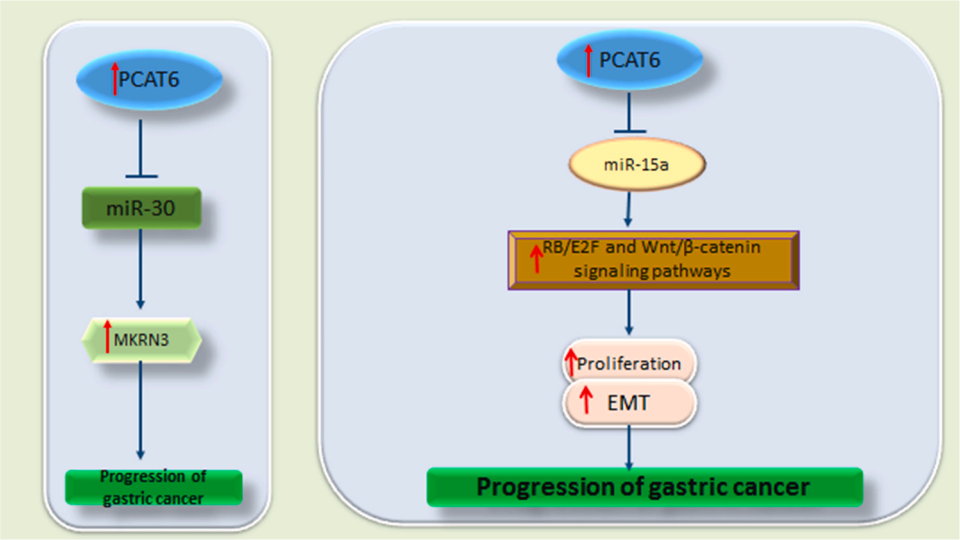

Fig. 1. PCAT6 contributes in the pathogenesis of gastric cancer via sponging miR-30 [10] and miR-15a [11].

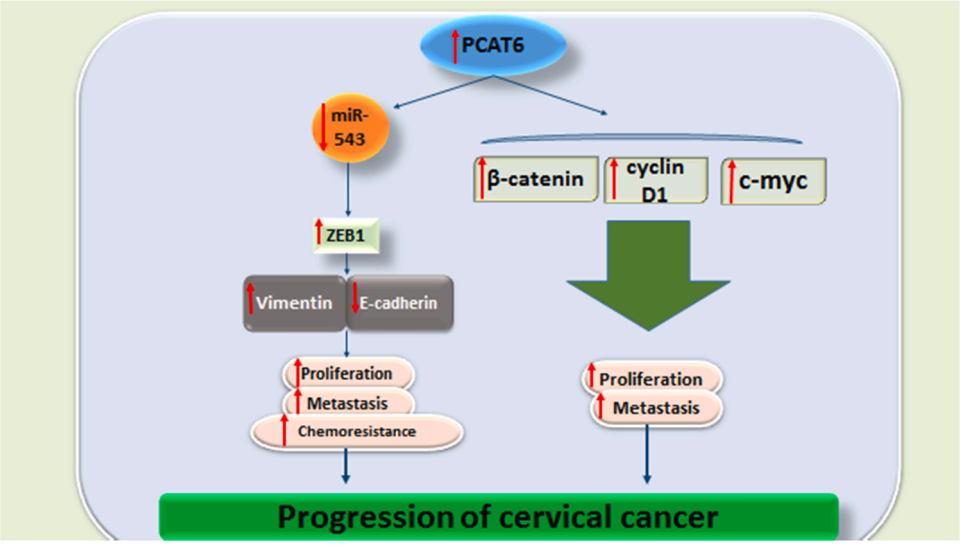

Fig. 2. PCAT6 participates in the pathogenesis of cervical cancer via sponging miR-543 [12]. Moreover, it can regulate growth and metastasis of cervical cancer cells through modulation of Wnt/β-catenin pathway [13].

radiotherapy via influencing miR-185-5p/TPD52 axis [7].

Suppression of PCAT6 expression in ovarian cancer cells has led to significant reduction in their proliferation capacity as well as their metastatic ability and invasiveness. Since expression of PTEN has been remarkably induced following PCAT6 knock-down, down-regulation of this tumor suppressor has been suggested as a possible route of carcinogenic activity of PCAT6 [8]. Another experiment in ovarian cancer cells has shown the sequestering effect of PCAT6 on miR-143-3p and subsequent impact of this lncRNA on levels of TGF-β-activated kinase 1 [9].

In gastric cancer, PCAT6 sequesters miR-30, thus regulating expression of MKRN3 [10]. PCAT6 also regulates cell proliferation and epithelial-mesenchymal transition (EMT) in this kind of cancer. These effects are exerted through sequestering miR-15a. PCAT6 can also regulate RB/E2F and Wnt/β-catenin signaling [11]. Fig. 1 demonstrates the impact of PCAT6 on gastric carcinogenesis.

In cervical cancer cell lines, miR-543 has been recognized the target of PCAT6 through which PCAT6 regulates proliferation, metastatic aptitude and resistance to cisplatin. Since ZEB1 is targeted by miR-543, the sequestering effect of PCAT6 on this miRNA leads to up-regulation of ZEB1 [12]. Fig. 2 shows the mechanism of participation of PCAT6 in the pathogenesis of cervical cancer.

In lung cancer, PCAT6 promotes proliferation, migratory aptitude, and invasiveness through sequestering miR-330–5p [14]. PCAT6 silencing has lessened growth of lung cancer through arresting cells at G1 phase of cell cycle and inducing cell apoptosis. These effects are mediated through its interaction with the epigenetic repressor EZH2 and subsequent suppression of LATS2 [15]. Fig. 3 shows the impact of PCAT6 in progression of lung cancer.

Table 1 shows the outlines of research papers which judged expression of PCAT6 in cell lines.

3. Animal studies

In accordance with the results of functional studies in cell lines, experiments in mouse models of different cancers have confirmed that PCAT6 silencing diminishes tumor size and decreases the metastatic aptitude of malignant cells. On the other hand, forced over-expression of

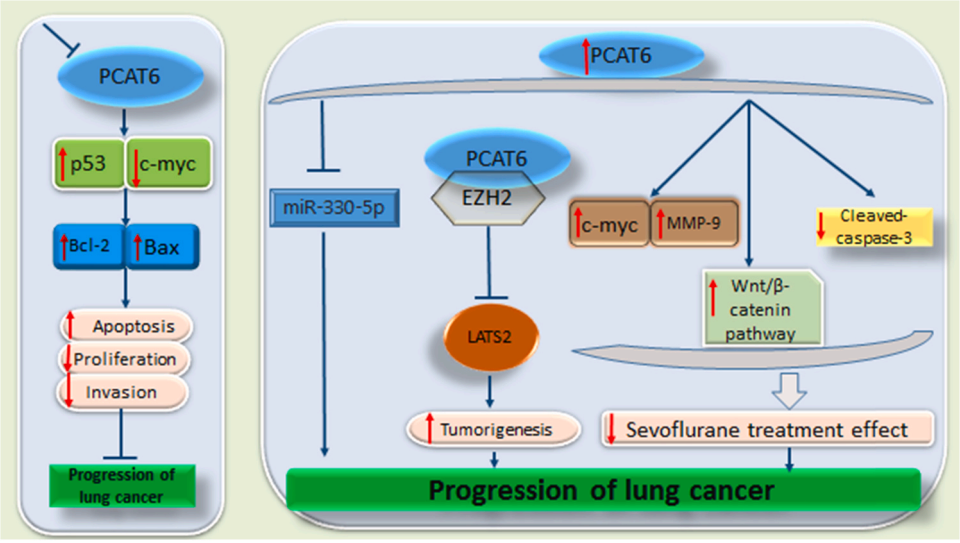

Fig. 3. The impact of PCAT6 in progression of lung cancer is exerted through regulation of expression of miR-330-5p [14], its binding with EZH2 and suppression of LATS2 expression [15], regulation of expressions of c-Myc and p53 [16], and regulation of the activity of Wnt-β catenin [17].

PCAT6 has increased malignant behaviors of cancer cells (Table 2).

4. Human studies

Over-expression of PCAT6 has been reported in almost all kinds of tumoral tissue obtained from a wide range of cancers. Kaplan–Meier analysis has shown correlation between over-expression of PCAT6 and poor survival of patients in terms of overall, progression-free and disease-free survival rates. Univariate/multivariate cox regression analyses have confirmed PCAT6 expression levels as determinant of patients' survival in colorectal cancer, cervical cancer, liver cancer and osteosarcoma (Table 3).

Another aspect of PCAT6 which has been assessed in human subjects is its potential in separation of malignant tissues from normal or non-malignant tissues. Significant up-regulation of PCAT6 in lung cancer samples has provided this lncRNA the ability to distinguish cancer tissues from non-affected tissues. Such ability has been appraised through depicting receiver operating characteristic (ROC) curves and measurement of area under these curves (AUC). These values ranged from 0.9210 to 0.9942 in different datasets or patients cohorts, representing nearly ideal values. Furthermore, circulatory levels of PCAT6 could differentiate lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) from non-cancerous controls with AUC values of 0.9213 and 0.9583, respectively [36].

Another study has measured expression levels of SLC9A3-AS1 and PCAT6 in circulatory extracellular vesicles of patients with lung cancer and normal subjects. Combination of SLC9A3-AS1 and PCAT6 expression levels as measured by multi-colour fluorescence digital PCR method could separate these two groups with AUC value of 0.811. This value was superior to what obtained through qPCR method [39]. Table 4 shows the diagnostic value of PCAT6 in cancers.

5. Discussion

PCAT6 is an lncRNA whose expression is suppressed in normal tissues except for testis, while being up-regulated in cancerous tissues. Thus, this lncRNA belongs to the group of cancer-testis genes [40]. Expression of most of genes attributed to this family has been shown to be regulated by epigenetic mechanisms including DNA methylation and acetylation [41]. Yet, the impact of these epigenetic markers on expression of PCAT6 has not been assessed yet. Instead, gene amplification has been reported as a mechanism for up-regulation of PCAT6 in some types of cancers [24].

Data presented above indicate the oncogenic role of PCAT6 in diverse cancers. Most notably, PCAT6 can affect response of cancer cells to both radiotherapy [7] and chemotherapy [20]. Cisplatin and 5-fluorouracil are two chemotherapeutic agents whose cytotoxic effects on cancer cells are modulated by PCAT6 expression levels. Therefore, therapeutic manipulation of PCAT6 expression not only directly affects carcinogenesis but also enhances efficacy of conventional therapeutics. Several miRNAs including miR-4723-5p, miR-185-5p, miR-143-3p, miR-30, miR-15a, miR-513a and miR-204, and miR-326, miR-139-3p and miR-513 have been reported to be sponged by PCAT6. Notably, miR-185-5p mediates the effects of PCAT6 in breast cancer, pancreatic cancer and osteosarcoma. Moreover, miR-143-3p has been found to be sponged by PCAT6 in ovarian cancer, osteosarcoma and gastrointestinal stromal tumor. Therefore, the functionality of PACT6/miR-185-5p and PCAT6/miR-143-3p axes has been validated in different tissues, suggesting these axes as putative targets for therapeutic interventions.

PCAT6 has also been reported to influence activity of Akt/mTOR, NF-κB, Wnt/β-catenin, TGF-β and RhoA-ROCK pathways most probably through sponging diverse miRNAs. The eminent role of PCAT6 in regulation of EMT has been validated in breast and gastric cancers, potentiating this lncRNA as a target for combating cancer recurrence and metastasis. The impact of PCAT6 up-regulation on induction of stemness further shows its role in cancer metastasis [31].

Diagnostic value of PCAT6 has been best validated in lung cancer, since its transcript levels could appropriately separate affected tissues from adjacent tissues. Most notably, plasma levels of PCAT6 could also discriminate patients with lung cancer from healthy controls. Since early detection of cancer is an important step in reduction of mortality of cancer, particularly highly deadly cancers such as lung cancer, assessment of expression of PCAT6 in the peripheral blood/plasma is a promising non-invasive approach for reduction of burden of malignancies. Serum exosomes also provide a source of biomarker discovery. Expression levels of PCAT6 in these vesicles can be used for cancer detection. However, this approach has been only used in lung cancer.

Independent studies in colorectal cancer, cervical cancer and osteosarcoma have shown the impact of PCAT6 over-expression in reduction of survival of patients. Therefore, prior assessment of PCAT6 expression in tumor samples might guide clinicians in design of highly aggressive versus less aggressive therapeutic regimens.

In brief, PCAT6 is a cancer-testis lncRNA with potential application as diagnostic/prognostic marker. PCAT6 silencing has efficiently reduced tumor burden in xenograft models of breast, colorectal, lung,

Table 1
Concise review of research papers which judged expression of PCAT6 in cell lines (Δ: knock-down, EMT: epithelial-mesenchymal transition).

Cancer type	Targets/regulators and signaling pathways	Cell line	Function	Ref.
Triple-negative breast cancer	miR-4723-5p, USP14, VGEFR2, Akt/mTOR signaling	MCF-10A, MDA-MB-231, MDA-MB-468, MDA-MB-436, and HCC-1937	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process, ↓ angiogenesis	[6]
	miR-185-5p, TPD52	MDA-MB-468, MDA-MB-231, MCF-10A	Δ PCAT6: ↑ Radiosensitivity	[7]
Ovarian cancer	PTEN	SKOV3, OVCAR3, PEO1, A2780, 3AO, CAOV3, HOSEPiCs	Δ PCAT6: ↓ invasion, ↓ migration	[8]
	miR-143-3p, TAK1, NF-κB signaling	SKOV3, A2780, HEK293T	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion ↑ PCAT6: ↑ proliferation, ↑ migration, ↑ invasion	[9]
Gastric cancer	miR-30, MKRN3	BGC-823, SGC-7901, HGC-27, MKN45, GES-1	↑ PCAT6: ↑ proliferation, ↑ migration, ↑ invasion, ↑ EMT process, ↓ apoptosis	[10]
	miR-15a, RB/E2F signaling pathway, Wnt/β-catenin signaling pathway, E-cad, N-cad, Vimentin, Snail, ZEB1	MKN45, SGC-7901, AGS, MKN28, GES-1	Δ PCAT6: ↓ proliferation, ↓ EMT process	[11]
Bladder cancer	miR-513a	SV-HUC-1, T24, EJ, 253j, 5637, 293T	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion, ↓ viability	[18]
	_	RT4, T24, J82, UM-UC-3, 5637, SV-HUC-1	Δ PCAT6: ↓ proliferation, ↑apoptosis	[19]
Colorectal cancer	miR-204, HMGA2/PI3K/p-Akt signaling	HCT116, HT-29, SW620, SW480, DLD-1, RKO, CCD-112CoN, HEK293	Δ PCAT6: ↓ proliferation, ↓ chemoresistance to 5–FU	[20]
	EZH2, H3K4me3, anti-apoptotic protein ARC	HCT116, RKO, COLO320HSR, SW480, SW620, NCM460	Δ PCAT6: ↓ growth, ↑ apoptosis, ↑ cleaved caspase 3 activation	[21]
Pancreatic ductal adenocarcinoma	miR-185-5p/CBX2 pathway	Capan-2, AsPC-1, PANC1, BxPC-3, HPDE	Δ PCAT6: ↓ proliferation, ↓ migration, ↓invasion ↑ PCAT6: ↑ growth	[22]
Hepatocellular carcinoma	_	SMMC-7721, HuH-7, Hep3B, HepG2, PLC/PRF/5, LO2	Δ PCAT6: ↓ proliferation, ↑cell cycle arrest, ↑ apoptosis ↑ PCAT6: ↑ proliferation, ↓cell cycle arrest, ↓ apoptosis	[23]
	_	HepG2, SMMC-7721	Δ PCAT6: ↓ proliferation, ↓ migration	[24]
Non-small-cell lung carcinoma	miR-330–5p	A549, H1975, H1650, HCC827, BEAS-2B, 293T	Δ PCAT6: ↓ proliferation, ↓ cell growth, ↓ migration, ↓ invasion	[14]
	EZH2, LATS2	A549, SPC-A1, H1299, H1975, H1703, SK-MES-1, H520	Δ PCAT6: ↓ proliferation, ↓ colony-forming ability, ↓ migration, ↓ invasion, ↑ G1 cell cycle arrest, ↑ apoptosis ↑ PCAT6: ↑ growth, ↑ colony-forming ability	[15]
Lung cancer	c-Myc, p53 protein, Bcl-2, Bax	H292, PC-9, CL1–5, H460, H1650, A549, H446, H1975, NHBE	Δ PCAT6: ↓ proliferation, ↓ invasion, ↑ early apoptosis	[16]
	miR-326, Wnt5a, Wnt/β-catenin pathway	16HBE, H446, H1975	↑ PCAT6: ↓ suppressing effects of sevoflurane on proliferation, migration, invasion, apoptosis	[17]
Cervical Cancer	miR-543, ZEB1	SiHa, HeLa, ME180, C-33A, Ect1/E6E7	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion, ↓ chemoresistance to cisplatin, ↑ apoptosis, ↑ cleaved-caspase 3 activation ↑ PCAT6: ↑ proliferation, ↑ metastasis, ↑ chemoresistance to cisplatin, ↓ apoptosis	[12]
	β-catenin, cyclin D1 and c-myc (Wnt/β-catenin pathway)	Caski, SW756, HeLa, ME-180, SiHa, C33A, Ect1/E6E7	Δ PCAT6: ↓ proliferation, ↓ colony-forming ability, ↓ migration, ↓ invasion, ↑ apoptosis	[13]
Osteosarcoma	miR-143-3p, ZEB1	MG-63, Saos-2, 143B, U2OS, hFOB 1.19	Δ PCAT6: ↓ proliferation, ↓ growth, ↓ metastasis, ↓ migration, ↓ invasion, ↓ the number of cells in S phase, ↑ the number of cells in the G0/G1 phase	[25]
	miR-185-5p, TGFBR1/2 (TGF-b pathway)	U2OS, 143B cells	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion	[26]
	MDM2, P53, P21	hFOB1.19, Saos2, MG63, U2OS, HOS	↑ PCAT6: ↑ proliferation, ↑ migration, ↑ invasion	[27]
Cholangiocarcinoma	miR-330-5p	ICC-9810	↑ PCAT6: ↑ proliferation, ↑ invasion	[28]
	miR-326, RhoA-ROCK pathway	HuCCT1, THP-1	↑ PCAT6: ↑ M2 Polarization of Macrophages, ↑ ROS production, ↑ mitochondrial and metabolic dysfunction	[29]
Liver cancer	miR-326, hnRNPA2B1	MHCC97H, HepG2, Huh7, THLE-3, 293T	Δ PCAT6: ↓ proliferation, ↓ invasion	[30]
Gastrointestinal stromal tumor (GIST)	miR-143-3p, PRDX5, Wnt/β-catenin pathway	GIST-H1, GIST-882, GIST-T1, GIST-48	Δ PCAT6: ↓ proliferation, ↓ stemness ↑ PCAT6: ↑ proliferation, ↑ stemness, ↓ apoptosis	[31]
Pituitary adenomas	miR-139-3p, BRD4	RC-4B/C (CRL-1903), GH3 (CCL-82.1)	Δ PCAT6: ↓ proliferation, ↓ migration, ↓ invasion, ↓ viability	[32]
Glioblastoma	YY1, miR-513, IGF2BP1, AKT signaling	A172, U251, LN229, U87, NHA	Δ PCAT6: ↓ proliferation, ↑ apoptosis ↑ PCAT6: ↑ proliferation, ↓ apoptosis	[33]

Table 2
Summary of the results of animal studies about the oncogenic roles of PCAT6.

Cancer type	Animal models	Results	Ref.
Breast cancer	male BALB/C nude mice	Δ PCAT6: ↓ tumor volume, ↓ tumor weight, ↓ metastasis	[6]
Colon cancer	xenograft mouse model/nude mice	Δ PCAT6: ↓ tumor volume, ↓ onset of primary tumor formation ↑ PCAT6: ↑ tumor volume, ↑ tumor weight, ↑ tumor growth	[21]
Non-small-cell lung carcinoma	nude mice	Δ PCAT6: ↓ tumor weight, ↓ tumor growth	[14]
	nude mice	Δ PCAT6: ↓ tumor weight, ↓ tumor growth	[15]
Cervical Cancer	murine xenograft model	Δ PCAT6: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth	[12]
Osteosarcoma	Nude Mouse Model of Tibia Orthotopic Tumor	Δ PCAT6: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth	[25]
	BALB/c nude mice	↑ PCAT6: ↑ proliferation, ↑ tumor volume, ↑ tumor weight	[27]
Cholangiocarcinoma	xenograft mouse model/nude mice	Δ PCAT6: ↓ tumor growth, ↑ immune response	[29]
Liver cancer	xenograft nude mice	Δ PCAT6: ↓ tumor weight, ↓tumor growth	[30]
Pituitary adenomas	xenograft mouse model/nude mice	Δ PCAT6: ↓tumor volume, ↓ tumor weight	[32]

Table 3
Summary of human studies that assessed role of PACT6 (ANTTs: adjacent non-tumoral tissues, OS: overall survival, DFS: disease-free survival, PFS: progression-free survival).

Cancer type	Numbers of clinical samples	Expression (tumor vs. normal)	Kaplan–Meier analysis	Univariate cox regression	Multivariate cox regression	Ref.
Breast cancer	86 pairs of tumor tissues and ANTTs	up	_	_	_	[6]
	70 pairs of tumor tissues and ANTTs	up	_	_	_	[7]
Ovarian cancer	42 pairs of tumor tissues and ANTTs	up	_	_	_	[8]
	GEO analysis: 8 pairs of primary ovarian tumors and matched normal fallopian tubes, 11 benign tissues, 79 serous ovarian cancer tumors, 32 ascites.	up	High expression of PCAT6 was correlated with poor OS and PFS.	_	_	[9]
Gastric cancer	72 gastric cancer tissues and ANTTs	up	_	_	_	[10]
	20 GC tissues and ANTTs	up	_	_	_	[11]
Bladder cancer	21 pairs of tumor tissues and ANTTs	up	High expression of PCAT6 was correlated with poor prognosis of BC patients.	_	_	[18]
	106 pairs of BC tissues and ANTTs	up	High expression of PCAT6 was correlated with shorter OS and PFS.	_	_	[19]
Colorectal cancer	73 pairs of CRC tissues and ANTTs	up	_	High expression of PCAT6 and TNM stage caused significant differences in OS in CRC patients.	High expression of PCAT6 was a determinant of poor survival.	[20]
	63 CRC patients and 40 controls	not significantly different	_	_	_	[34]
Colon cancer	GEO and TCGA analysis: 58 pairs of colon cancer tissues and adjacent normal tissues	up	_	Age, stage, and PCAT6 expression were significantly associated with worse OS.	Age, stage, and PCAT6 expression were associated with worse OS.	[21]
Pancreatic ductal adenocarcinoma (PDAC)	67 PDAC tissues and ANTTs	up	Patients with higher PCAT6 expression possessed worse OS.	_	_	[22]
Hepatocellular carcinoma	TCGA-LIHC analysis: 374 HCC patients and 50 ANTTs	up	Patients with lower levels of PCAT6 expression had significantly longer OS and DFS.	_	_	[23]
	GEO analysis: 30 pairs of tumor tissues and ANTTs	up	_	_	_	
	29 pairs of HCC tissues and ANTTs	up	_	_	_	
	_	up	_	Patients with higher PCAT6 had poorer PFS.	_	[35]
Liver hepatocellular carcinoma (LIHC)	TCGA-LIHC analysis: 364 LIHC samples and adjacent samples (paired and unpaired tissues)	up	_	_	_	[24]
Lung cancer	26 pairs of NSCLC tissues and ANTTs	up	_	_	_	[14]
	60 pairs of NSCLC tissues and ANTTs	up	_	_	_	[15]
	73 LUAD tissues and 39 normal counterparts	up	_	_	_	[36]
	51 LUSC tissues and 39 normal counterparts	up	_	_	_	
		up	_	_	_	[37]

(*continued on next page*)

Table 3 (*continued*)

Cancer type	Numbers of clinical samples	Expression (tumor vs. normal)	Kaplan–Meier analysis	Univariate cox regression	Multivariate cox regression	Ref.
	82 NSCLC patients and normal samples					
	535 LUAD patients and 59 controls	up	_	_	_	[38]
	58 lung cancer tissues and 23 ANTTs	_	Patients with high PCAT6 expression had a significantly lower OS rate.	_	_	[16]
	45 pairs of lung cancer tissues and ANTTs	_		_	_	[17]
	32 lung cancer tissues and 30 healthy controls	_	_	_	_	[39]
Cervical cancer	44 pairs of CC tissues and ANTTs	_	_	_	_	[12]
	114 pairs of tumor tissues and ANTTs	_	Patients with higher PCAT6 expression levels had shorter OS and DFS.	High expression of PCAT6, FIGO stage, lymph node metastasis and depth of cervical invasion were associated with poor OS.	High PCAT6 expression was as an independent indicator of unfavorable prognosis for CC patients.	[13]
Osteosarcoma	106 pairs of tumor tissues and ANTTs	up	Patients with high expression of PCAT6 had worse OS and PFS.	_	PCAT6 overexpression was revealed as an independent prognostic factor for the poor outcome of patients with OS.	[25]
	25 pairs of osteosarcoma tissues and ANTTs	up	Patients with higher PCAT6 expression levels had shorter OS and PFS.	_	_	[26]
Cholangiocarcinoma	_	up	_	_	_	[28]
	20 pairs of cholangiocarcinoma tissues and ANTTs	up	_	_	_	[29]
Liver cancer	117 pairs of liver cancer tissues and ANTTs	up	Patients with higher PCAT6 expression possessed poor OS.	_	_	[30]
Gastrointestinal stromal tumor (GIST)	72 pairs of GIST tissues and ANTTs	up	_	_	_	[31]
Pituitary adenomas	20 tumor tissues and ANTTs	up	_	_	_	[32]
Glioblastoma	53 pairs of GBM tissues and ANTTs	up	_	_	_	[33]

Table 4
Diagnostic value of PCAT6 in cancers (ANTTs: Adjacent non-tumoral tissues, LUAD: lung adenocarcinoma, LUSC: lung squamous cell carcinoma).

Cancer type	Numbers of clinical samples	Distinguish between	Area under curve	Sensitivity (%)	Specificity (%)	Accuracy (%)	Ref.
Non-small-cell lung carcinoma (NSCLC)	GSE19804 analysis: 60 pairs of tumor tissue samples and ANTTs	LUAD patients vs. controls	0.9578	96.67	85.00	90.83	[36]
	GSE27262 analysis: 25 pairs of tumor tissue samples and ANTTs	LUAD patients vs. controls	0.9584	92.00	96.00	94.00	
	GSE30219 analysis: 85 tumor tissue samples and 14 normal noncancerous tissue samples	LUAD patients vs. controls	0.9210	98.82	78.57	95.96	
	GSE19188 analysis: 45 tumor tissue samples and 65 normal noncancerous tissue samples	LUAD patients vs. controls	0.9333	86.67	90.77	89.09	
	73 pairs of tumor tissue samples and ANTTs	LUAD patients vs. controls	0.9574	95.89	87.67	91.78	
	73 tumor plasma samples and 39 normal plasma samples	LUAD patients vs. controls	0.9213	87.67	97.44	90.18	
Non-small-cell lung carcinoma (NSCLC)	GSE30219 analysis: 61 tumor tissue samples and 14 normal noncancerous tissue samples	LUSC patients vs. controls	0.9567	100	85.71	97.33	
	GSE19188 analysis: 27 tumor tissue samples and 65 normal noncancerous tissue samples	LUSC patients vs. controls	0.9795	96.30	92.31	93.48	
	51 tumor tissue samples and ANTTs	LUSC patients vs. controls	0.9942	100	98.04	99.02	
	51 tumor plasma samples and 39 normal plasma samples	LUSC patients vs. controls	0.9583	94.12	100	96.67	
Lung cancer	32 tumor tissue samples and 30 ANTTs	Patients with lung cancer vs. controls	0.705	_	_	_	[39]

cervical and liver cancers. These studies encourage biologists to continue to explore the mechanistic aspects of PCAT6 oncogenic roles and design highly efficient therapeutic methods for application in clinical settings.

CRediT authorship contribution statement

Mohammad Taheri: wrote the draft and revised it. **Soudeh Ghafouri-Fard:** wrote the draft and revised it. **Kaveh Ebrahimzadeh:** collected the data and designed the figures and tables. **Tayyebeh Khoshbakht:** collected the data and designed the figures and tables. All the authors read and approved the submitted version.

Conflict of interest statement

The authors declare they have no conflict of interest.

Acknowledgements

This study was financially supported by shahid beheshti university of medical sciences.

References

[1] A.M. Schmitt, H.Y. Chang, Long noncoding RNAs in cancer pathways, Cancer Cell 29 (4) (2016) 452–463.
[2] T. Derrien, R. Johnson, G. Bussotti, A. Tanzer, S. Djebali, H. Tilgner, G. Guernec, D. Martin, A. Merkel, D.G. Knowles, The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression, Genome Res. 22 (9) (2012) 1775–1789.
[3] B. Bánfai, H. Jia, J. Khatun, E. Wood, B. Risk, W.E. Gundling, A. Kundaje, H. P. Gunawardena, Y. Yu, L. Xie, Long noncoding RNAs are rarely translated in two human cell lines, Genome Res. 22 (9) (2012) 1646–1657.
[4] Z. Du, T. Fei, R.G. Verhaak, Z. Su, Y. Zhang, M. Brown, Y. Chen, X.S. Liu, Integrative genomic analyses reveal clinically relevant long noncoding RNAs in human cancer, Nat. Struct. Mol. Biol. 20 (7) (2013) 908–913.
[5] M. Li, X. Yu, Q. Zheng, Q. Zhang, Y. He, W. Guo, Promising role of long non-coding RNA PCAT6 in malignancies, Biomed. Pharmacother. Biomed. Pharmacother. 137 (2021), 111402.
[6] S.R. Fang Dong, Jinlong Wang, Yun Xia, Kehao Le, Xiaoyun Xiao, Ting Hu, Qiong Wang, M2 macrophage-induced lncRNA PCAT6 facilitates tumorigenesis and angiogenesis of triple-negative breast cancer through modulation of VEGFR2, Cell Death Dis. (2020).
[7] P.W. Rui Shi, Miaomiao Liu, Bing Chen, Longjiao Cong, Knockdown of lncRNA PCAT6 enhances radiosensitivity in triple-negative breast cancer cells by regulating miR-185-5p/TPD52 axis, OncoTargets Ther. 13 (2020) 3025–3037.
[8] Y.-H.L.F.-R. Kong, H.-M. Yao, H.-Y. Zhang, Y. Zhou, S.-E. Liu, LncRNA PCAT6 promotes occurrence and development of ovarian cancer by inhibiting PTEN, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 8230–8238.
[9] Y.S. Xiaofang Tan, Yue Teng, Siyu Liu, Weijian Li, Lu Xue, Yuepeng Cao, Chongqi Sun, Jinhong Zhang, Jing Han, Xiaoli Wu, Hanzi Xu, Kaipeng Xie, The cancer-testis long non-coding RNA PCAT6 facilitates the malignant phenotype of ovarian cancer by sponging miR-143-3p, Front. Cell Dev. Biol. (2021).
[10] J.-Y.S.Y. Xu, Y.-F. Jin, H. Yu, PCAT6 participates in the development of gastric cancer through endogenously competition with microRNA-30, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 5206–5213.
[11] Y.L. Dongfang Dong, Bo Sun, Haiyuan Sun, Qunying Wang, Gang Yuan, Jingzi Quan, Silencing of long non-coding RNA PCAT6 restrains gastric cancer cell proliferation and epithelial-mesenchymal transition by targeting microRNA-15a, Gen. Physiol. Biophys. 39 (2020) 1–12.
[12] G.G. Zhongping Ma, Weikang Pan, Xiaoxiang Chen, LncRNA PCAT6 accelerates the progression and chemoresistance of cervical cancer through up-regulating ZEB1 by sponging miR-543, OncoTargets Ther. (2020) 1159–1170.
[13] Q.T.X.-J. Lv, Y.-Q. Tu, D.-D. Yan, Q.-C. Wei, Long noncoding RNA PCAT6 regulates cell growth and metastasis via Wnt/β-catenin pathway and is a prognosis marker in cervical cancer, Eur. Rev. Med. Pharmacol. Sci. 23 (2019) 1947–1956.
[14] H.R.X. Li Hua Cui, Wu Yang, Li Jiang Yu, lncRNA PCAT6 promotes non-small cell lung cancer cell proliferation, migration and invasion through regulating miR-330-5p, OncoTargets Ther. 11 (2018) 7715–7724.
[15] Z.L. Xuefei Shi, Zhicong Liu, Xueren Feng, Feng Hua, Xixian Hu, Bin Wang, Kaihua Lu, Fengqi Nie, Long noncoding RNA PCAT6 functions as an oncogene by binding to EZH2 and suppressing LATS2 in non-small-cell lung cancer, EBioMedicine (2018) 177–187.
[16] L.Z. Li Wan, Kai Fan, Zai-Xing Cheng, Quan-Chao Sun, Jian-Jun Wang, Knockdown of long noncoding RNA PCAT6 inhibits proliferation and invasion in lung cancer cells, Oncol. Res. 24 (2016) 161–170.
[17] G. Su, Z. Yan, M. Deng, Sevoflurane inhibits proliferation, invasion, but enhances apoptosis of lung cancer cells by Wnt/β-catenin signaling via regulating lncRNA PCAT6/miR-326 axis, Open Life Sci. 15 (2020) 159–172.
[18] C.C.W. Xia, M.-R. Zhang, L.-N. Zhu, LncRNA PCAT6 aggravates the progression of bladder cancer cells by targeting miR-513a-5p, Eur. Rev. Med. Pharmacol. Sci. 24 (2020) 9908–9914.
[19] D.D. Dairong Zhang, Sisi Yi, Xiaofeng Li, LncRNA PCAT6: a potential biomarker for diagnosis and prognosis of bladder cancer, Ann. Diagn. Pathol. (2020).
[20] Q.Z. Haijun Wu, Hong He, Yu Liang, Mingjun Lei, Qin Zhou, Dan Fan, Liangfang Shen, Long non-coding RNA PCAT6 targets miR-204 to modulate the chemoresistance of colorectal cancer cells to 5-fluorouracil-based treatment through HMGA2 signaling, Cancer Med. (2019) 2484–2495.
[21] G.S. Weimei Huang, Xiaoxian Huang, Angru Zou, Jingfang Wu, Yunchu Yang, Yaru Zhu, Shumei Liang, Deyu Li, Feng Ma, Linlang Guo, Long noncoding RNA PCAT6 inhibits colon cancer cell apoptosis by regulating anti-apoptotic protein ARC expression via EZH2, Cell Cycle 18 (2019) 69–83.
[22] X.L. Weina Wang, Canghai Guan, Zengtao Hu, Yuqiao Zhao, Wenzhi Li, Xingming Jiang, LncRNA PCAT6 promotes the proliferation, migration and invasion of pancreatic ductal adenocarcinoma via regulating miR-185-5p/CBX2 axis, Pathol. Res. Pract. (2020).
[23] J.L. Yue Luo, Yueqi Zhang, Guanqi Dai, Aimin Li, Xinhui Liu, LncRNA PCAT6 predicts poor prognosis in hepatocellular carcinoma and promotes proliferation through the regulation of cell cycle arrest and apoptosis, Cell Biochem. Funct. (2020).
[24] Y.C. Shuaizhou Chen, Qufei Qian, Xuewei Wang, Yuting Chang, Sihan Ju, Yide Xu, Chang Zhang, Na Qin, Hui Ding, Yayun Gu, Jing Han, Cheng Wang, Erbao Zhang, Zhibin Hu, Gene amplification derived a cancer-testis long noncoding RNA PCAT6 regulates cell proliferation and migration in hepatocellular carcinoma, Cancer Med. 8 (2019) 3017–3025.
[25] Q.F. Kai Wu, Liang Li, Yanfei Xiong, Shihong Liu, Jie Liu, Qing Wu, Long-noncoding RNA PCAT6 aggravates osteosarcoma tumourigenesis via the MiR-143-3p/ZEB1 axis, OncoTargets Ther. (2020) 8705–8714.
[26] L.H. Chengdong Zhu, Fei Xu, Ping Li, Pengfei Li, Fangyong Hu, LncRNA PCAT6 promotes tumor progression in osteosarcoma via activation of TGF-β pathway by sponging miR-185-5p, Biochem. Biophys. Res. Commun. (2020) 463–470.
[27] Y.X. Xiliang Guan, Jufen Zheng, Long non-coding RNA PCAT6 promotes the development of osteosarcoma by increasing MDM2 expression, Oncol. Rep. 44 (2020) 2465–2474.
[28] X.H. Yongjie Xin, Wei Zhao, Meixiao Zhan, Yong Li, Jing Xiao, Ke He, Ligong Lu, LncRNA PCAT6 increased cholangiocarcinoma cell proliferation and invasion via modulating miR-330-5p, Am. J. Transl. Res. (2019) 6185–6195.
[29] F.W. Jianfei Tu, Li Chen, Liyun Zheng, Yang Yang, Xihui Ying, Jingjing Song, Chunmiao Chen, Xianghua Hu, Zhongwei Zhao, Jiansong Ji, Long non-coding RNA PCAT6 induces M2 polarization of macrophages in cholangiocarcinoma via modulating miR-326 and RhoA-ROCK signaling pathway, Front. Oncol. (2021).
[30] J. Luo, J. Zheng, W. Hao, H. Zeng, Z. Zhang, G. Shao, lncRNA PCAT6 facilitates cell proliferation and invasion via regulating the miR-326/hnRNPA2B1 axis in liver cancer, Oncol. Lett. (2021).
[31] N.Z. Fangyun Bai, Wei Fang, Xiangyi He, Yan Zheng, Donghua Gu, PCAT6 mediates cellular biological functions in gastrointestinal stromal tumor via upregulation of PRDX5 and activation of Wnt pathway, Mol. Carcinog. (2020) 661–669.
[32] J.C. Peng Zhao, Bin Li, Ding Nie, Hongyun Wang, Chuzhong Li, Songbai Gui, Yazhuo Zhang, LncRNA PCAT6 regulates the progression of pituitary adenomas by regulating the miR-139-3p/BRD4 axis, Cancer Cell Int. 21 (2021) 14.
[33] P.Z. Peng Liu, Bing Li, Dianxiang Xu, Kun Wang, LncRNA PCAT6 regulated by YY1 accelerates the progression of glioblastoma via miR-513/IGF2BP1, Neurochem. Res. (2020) 2894–2902.
[34] A.A.-G. Halima Siddique, Hani Choudhry, Suzan AlTurki, Huda Alshaibi, Huda Al Doghaither, Hadeil Alsufiani, Long noncoding RNAs as prognostic markers for colorectal cancer in Saudi patients, Genet. Test. Mol. Biomark. 23 (2019) 509–514.
[35] X.S. Hao Jiang, Guochao Ye, Yongcan Xu, Jiewei Xu, Jun Lu, Wei Lu, Up-regulated long non-coding RNA DUXAP8 promotes cell growth through repressing Krüppel-like factor 2 expression in human hepatocellular carcinoma, OncoTargets Ther. 12 (2019) 7429–7436.
[36] L.Z. Li Wan, Kai Fan, Jian-Jun Wang, Diagnostic significance of circulating long noncoding RNA PCAT6 in patients with non-small cell lung cancer, OncoTargets Ther. 10 (2017) 5695–5702.
[37] B.U. Amelia Acha-Sagredo, Paschalia Pantazi, Naiara G. Bediaga, Chryssanthi Moschandrea, Lucille Rainbow, Michael W. Marcus, Michael P. A. Davies, John K. Field, Triantafillos Liloglou, Long non-coding RNA dysregulation is a frequent event in non-small cell lung carcinoma pathogenesis, Br. J. Cancer 122 (2020) 1050–1058.
[38] W.K. Guoqiang Qi, Xiaoyang Mou, Shuaiqun Wang, A new method for excavating feature lncRNA in lung adenocarcinoma based on pathway crosstalk analysis, J. Cell. Biochem. (2019) 9034–9046.
[39] Y.Q. Yanan Bai, Zhenhua Wu, Yijiu Ren, Zule Cheng, Yunxing Lu, Jie Hu, Jiatao Lou, Jianlong Zhao, Chang Chen, Hongju Mao, Absolute quantification and analysis of extracellular vesicle lncRNAs from the peripheral blood of patients with lung cancer based on multi-colour fluorescence chip-based digital PCR, Biosens. Bioelectron. (2019).
[40] C. Wang, Y. Gu, K. Zhang, K. Xie, M. Zhu, N. Dai, Y. Jiang, X. Guo, M. Liu, J. Dai, Systematic identification of genes with a cancer-testis expression pattern in 19 cancer types, Nat. Commun. 7 (1) (2016) 1–12.
[41] S. Ghafouri-Fard, M.H. Modarressi, Cancer-testis antigens: potential targets for cancer immunotherapy, Arch. Iran. Med. 12 (4) (2009) 395–404.