Review

PCAT6 May Be a Whistler and Checkpoint Target for Precision Therapy in Human Cancers

Feng Jiang 1,2, Qiaoyi Lv 1,2, Cexun Hu 1,2, Zhanghui Li 1,2, Haojie Wu 1,2, Shujun Gao 1,2, Hui Wang 1,2, Yangjing Zhao 1,2,* and Qixiang Shao 1,2,3,*

1 Jiangsu Key Laboratory of Medical Science and Laboratory Medicine, Department of Immunology, Reproductive Sciences Institute, School of Medicine, Jiangsu University, Zhenjiang 212013, China; jiang_wax@163.com (F.J.); 2212113104@stmail.ujs.edu.cn (Q.L.); 2211913059@stmail.ujs.edu.cn (C.H.); 2212013001@stmail.ujs.edu.cn (Z.L.); whjsnow1990@126.com (H.W.); gaoshujun95@163.com (S.G.);
2 Jiangsu Key Laboratory of Medical Science and Laboratory Medicine, Department of Pathology, School of Medicine, Jiangsu University, Zhenjiang 212013, China
3 Institute of Medical Genetics and Reproductive Immunity, School of Medical Science and Laboratory Medicine, Jiangsu College of Nursing, Huai’an 223002, China
* Correspondence: 1000005289@ujs.edu.cn (Y.Z.); shao_qx@ujs.edu.cn (Q.S.)

Simple Summary: Prostate cancer-associated transcript 6 (PCAT6), as a newly discovered carcinogenic long non-coding RNA (lncRNA), is abnormally expressed in multiple diseases. With the accumulation of studies on PCAT6, we have a deeper understanding of its biological functions and mechanisms. Therefore, in this review, the various molecular mechanisms by which PCAT6 promotes multiple tumorigenesis and progression are summarized and discussed. Furthermore, its potential diagnostic, prognostic, and immunotherapeutic values are also clarified.

Abstract: LncRNAs are involved in the occurrence and progressions of multiple cancers. Emerging evidence has shown that PCAT6, a newly discovered carcinogenic lncRNA, is abnormally elevated in various human malignant tumors. Until now, PCAT6 has been found to sponge various miRNAs to activate the signaling pathways, which further affects tumor cell proliferation, migration, invasion, cycle, apoptosis, radioresistance, and chemoresistance. Moreover, PCAT6 has been shown to exert biological functions beyond ceRNAs. In this review, we summarize the biological characteristics of PCAT6 in a variety of human malignancies and describe the biological mechanisms by which PCAT6 can facilitate tumor progression. Finally, we discuss its diagnostic and prognostic values and clinical applications in various human malignancies.

Keywords: lncRNA; PCAT6; biological function; molecular mechanism; signaling pathway; oncogenic biomarker

1. Introduction

In recent years, with the development of RNA sequencing (RNAseq) technology, such as next-generation sequencing (NGS) and the third generation sequencing (TGS), more and more non-coding RNAs (ncRNAs) have been discovered, which occupy the majority of the transcriptome (~90%) [1]. Unlike protein-coding genes, ncRNAs do not encode proteins or short peptides. According to whether they are more than 200 nucleotides in length, ncRNAs are divided into two categories: short ncRNAs and long ncRNAs (lncRNAs) [2,3]. LncRNAs participate in a variety of biological processes, such as individual ontogenetic development, cell or tissue development and differentiation, cell proliferation, cell death, cell cycle, migration, and invasion [4–6], and numerous pathological conditions, including cancer [7–9]. Moreover, lncRNAs play indispensable roles in regulating gene expression via epigenetic modification, transcriptional activation or interference, and post-transcriptional
mechanism [10]. For example, lncRNAs can affect biological processes in various cancers by acting as competing endogenous RNAs (ceRNAs) or the sponge of microRNAs [11–13], or by directly regulating target proteins [14,15]. Recently, increasing evidence has revealed that lncRNAs are closely related to the clinicopathological features of various diseases, and have better diagnostic and prognostic value [16,17]. In short, lncRNAs are likely to serve as tumor biomarkers and therapeutic targets [18,19].

Prostate cancer-associated transcript 6 (PCAT6) is a novel lncRNA that extensively promotes multiple cancer progression. Many investigations have demonstrated that the expression of PCAT6 is up-regulated in a variety of cancers and closely related to the occurrence and development of tumors [20,21]. Therefore, PCAT6 may be a potential target for cancer diagnosis and treatment. This review aims to summarize the abnormal expression and subcellular localization of PCAT6, and to further understand the underlying mechanisms, and its diagnostic or prognostic values in multiple human cancers.

2. The Discovery of PCAT6

PCAT6, a newly discovered lncRNA, is also named KDM5B-AS1, KDM5BAS1, PCAN-R1, ncRNA-a2, or onco-lncRNA-96. It was first described as ncRNA-a2 in 2010 [22]. The gene of PCAT6 is located on chromosome 1q32.1 and contains two exons. It consists of 968 bp and has two transcript variants: transcript variant 1 (NR_046325.1) and transcript variant 2 (NR_046326.1). The transcription direction of PCAT6 is positive (Figure 1a), and some transcription factors that bind to the promoter region can be found near the upstream 2000 bp (chr1:202808946) and downstream 100 bp (chr1:202811046) of its transcription start sites (chr1:202810946). In addition, the histones H3K4Me3 and H3K27Ac that recognize the promoter sequences are also found in this region, which further proves the existence of an active promoter. Moreover, the transcription factors near these regions are more likely to become the upstream transcription factors of PCAT6 to regulate its transcription (e.g., nescent helix-loop-helix 2, NHLH2) (Figure 1b). By analyzing the RNAseq data of normal tissue from the Human Protein Atlas database, it was found that human testis tissues had the highest expression level of PCAT6 [23]. Subsequently, Wan et al. first found that knockdown of PCAT6 inhibited cell proliferation, invasion, and increased early apoptosis in lung cancer [20]. Increasing numbers of studies have illustrated that high expression levels of PCAT6 are associated with many human cancers.

Figure 1. Transcription direction and upstream transcription factors of PCAT6. (a) The red arrow following PCAT6 points in the direction of transcription. Reference information comes from the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/gene/100506696 (accessed on 13 July 2021)). (b) Transcription factors that may regulate PCAT6, including NHLH2. Reference information comes from the University of California Santa Cruz (UCSC) Genome Browser (http://genome.ucsc.edu/ (accessed on 13 July 2021)).
3. Expression and Subcellular Localization of PCAT6

3.1. The Abnormal Expression of PCAT6 in Cancers

The expression of PCAT6 is found to be aberrantly elevated in various human tumor tissues and cell lines compared with matched normal ones, including bladder cancer (BC) [21,24,25], breast cancer (BrCa) [26,27], cervical cancer (CC) [28,29], colorectal cancer (CRC) [30,31], gastrointestinal stromal tumor (GIST) [32], gastric cancer (GC) [33,34], glioblastoma (GBM) [35], hepatocellular carcinoma (HCC) [36–38], lung cancer (LC) [20,39–43], osteosarcoma (Osa) [44–46], ovarian cancer (OvCa) [47,48], cholangiocarcinoma (CCA) [49], pituitary adenoma (PA) [50], pancreatic ductal adenocarcinoma (PDAC) [51], and prostate cancer (PCa) [52,53]. In subsequent experiments on the biological functions of tumor cells, it has been revealed that a high level of PCAT6 has strong cancer-promoting effects, mainly including the promotion of cell proliferation, enhancement of migration, invasion and EMT process, as well as the inhibition of cell apoptosis. Meanwhile, PCAT6 has been shown to promote tumor growth and metastasis in xenograft mouse models (Table 1) [26,29,30,38–40,43,44,46,50,52–54]. However, Amelia et al. reported that the expression level of PCAT6 was opposite in lung tumor tissues and lung cancer cell lines compared with the normal control group [55]. Compared with paired normal tissue, PCAT6 expression level is higher in lung tumors, while its level is lower in non-small cell lung cancer (NSCLC) cell lines compared to the normal human fetal lung fibroblast cell line (IMR-90) [55]. Interestingly, Tu et al. found that, compared to T cells, B cells, dendritic cells, and neutrophils, PCAT6 expression was the highest in macrophages which derived from patients of CCA, especially M2 macrophages [54]. Furthermore, PCAT6 expression level is also significantly higher in the blood samples of some cancer patients, including BC [24] and LC [41,56]. Contradictorily, Siddique et al., testified that PCAT6 level had no significant difference in the blood between Saudi CRC patients and healthy donors [57]. It is speculated that the cause of this result may be ethnically related, and the expression level of PCAT6 in CRC patients of different races might be different.

Table 1. Functional characterization of PCAT6 in multiple human cancers.

| Tumor Types | Expression | Sample Type | Role | Functional Role in Vitro | Functional Role in Vivo | Related Genes/Protein/Pathways | Ref. |
|-------------|------------|-------------|------|--------------------------|-------------------------|-------------------------------|------|
| Bladder cancer | Up | cells (RT4, T24, J82, UMUC3, 5637), patient tissue and serum | Tumor promoter | Cell proliferation and apoptosis | NA | [24] |
| | Up | Cells (T24, EJ, 253j, 5637), patient tissue | Tumor promoter | Cell proliferation, migration, and invasion | miR-513a-5p | [21] |
| | Up | Cells (T24T, EJ, UMUC3, 5637), patient tissue | Tumor promoter | Cell proliferation, migration, and invasion | miR-143-3p, PDIA6 | [25] |
| Breast cancer | Up | Cells (MDA-MB-231, MDA-MB-468, MDA-MB-436, HCC-1937), patient tissue | Tumor promoter | Cell proliferation, migration, invasion, EMT process, and angiogenesis | Tumor growth, metastasis, and angiogenesis | VEGF, VEGFR2/Akt/mTOR, miR-4723-5p, USP14, E-cadherin, N-cadherin, Slug, Twist, | [26] |
| | Up | Cells (MDA-MB-468, MDA-MB-231), patient tissue | Tumor promoter | Cell proliferation, apoptosis, cell cycle, and radiosensitivity | miR-185-5p, TP53 | [27] |
| Cervical cancer | Up | Cells (Caski, SW756, HeLa, ME-180, SiHa, C-33A), patient tissue | Tumor promoter | Cell proliferation, apoptosis, migration, and invasion | Wnt/β-catenin, β-catenin, cyclin D1, c-myc | [28] |
| | Up | Cells (SiHa, HeLa, ME180, C-33A), patient tissue | Tumor promoter | Cell proliferation, apoptosis, migration, invasion, and chemoresistance | Tumor growth | miR-543, Bcl-2, cleaved-caspase 3, ZEB1 | [29] |
Table 1. Cont.

| Tumor Types                  | Expression | Sample Type                                      | Role                | Functional Role in Vitro                          | Functional Role in Vivo | Related Genes/Protein/Pathways                | Ref. |
|------------------------------|------------|--------------------------------------------------|---------------------|-------------------------------------------------|-------------------------|---------------------------------------------|------|
| Colorectal cancer            | Up         | Cells (SW628, SW480, RKO, COLO320HSR, HCT116), patient tissue | Tumor promoter      | Cell proliferation and apoptosis                 | Tumor growth            | Cleaved-caspase 3, ARC, EZH2               | [30] |
|                              | Up         | Cells (HCT116, HT-29, SW620, SW480, DLD-1, RKO, LoVo), patient tissue | Tumor promoter      | Cell proliferation and chemoresistance          |                         | miR-204, HMGA2, PI3K, Akt                | [31] |
| Gastrointestinal stromal tumor | Up         | Cells (GIST-H1, GIST-882, GIST-T1, GIST-48), patient tissue | Tumor promoter      | Cell proliferation, stemness, and apoptosis     |                         | Wnt/β-catenin, miR-143-3p, PRDX5           | [32] |
| Gastric cancer               | Up         | Cells (BGC-823, SGC-7901, HGC-27, MKN45), patient tissue | Tumor promoter      | Cell proliferation, migration, EMT, and apoptosis |                         | Cyclin D1, p53, Bax, cleaved caspase 3, E-cadherin, N-cadherin, Vimentin, Snail, ZEB1, Snail | [34] |
|                              | Up         | Cells (MKN45, SGC-7901, AGS, MKN28), patient tissue | Tumor promoter      | Cell proliferation, EMT, and apoptosis          |                         | miR-30, MKRN3, caspase 3, caspase 9, Bax, Bcl-2, E-cadherin, N-cadherin, Vimentin, ZEB1, Snail | [33] |
| Glioblastoma                 | Up         | Cells (A172, U251, U87, LN229), patient tissue   | Tumor promoter      | Cell proliferation and apoptosis                |                         | YY1, miR-513, IGF2BP1, Akt                | [35] |
| Hepatocellular carcinoma     | Up         | Patient tissue                                   | Tumor promoter      | Cell proliferation and migration                |                         | NA                                         | [36] |
|                              | Up         | Cells (HuH7, SMMC-7721, Hep3B, HepG2, PLC/PRF/5), patient tissue | Tumor promoter      | Cell proliferation, cycle, apoptosis, and migration |                         | PCNA, CCND1, Bcl-2                        | [37] |
|                              | Up         | Cells (MHCC97H, HepG2, HuH7), patient tissue      | Tumor promoter      | Cell proliferation and invasion                 |                         | miR-326, hnRNPA2B1                        | [38] |
| Lung cancer                  | Up         | Cells (H1650, HCC827, H1975, A549), patient tissue | Tumor promoter      | Cell proliferation, migration, and invasion    | Tumor growth            | miR-330-5p                                 | [39] |
|                              | Up         | Cells (SK-MES-1, H1703, H520, H1299, H1975, SPCA1, A549), patient tissue | Tumor promoter      | Cell proliferation, cycle, apoptosis, and invasion | Tumor growth            | EZH2, LAT52                                | [40] |
|                              | Up         | Cells (H292, PC-9, CL1-5, H460, H1650, A549, H446, H1975) | Tumor promoter      | Cell proliferation, apoptosis, and invasion     | Tumor growth            | Bcl-2, Bax, c-myc, p53                    | [20] |
|                              | Up         | Cells (H446, H1975), patient tissue              | Tumor promoter      | Cell proliferation, migration, invasion, and apoptosis |                         | c-myc, MMP9, cleaved-caspase-3, Wnt5a, β-catenin, miR-326. | [42] |
|                              | Up         | Cells (H1838, H522, H2228, H358, H1299, A549), patient tissue | Tumor promoter      | Cell proliferation, migration, and apoptosis    | Tumor growth            | Caspase-3, Ki-67                           | [43] |
| Osteosarcoma                 | Up         | Cells (MG-63, Saos-2, 143B, U2OS), patient tissue | Tumor promoter      | Cell proliferation, migration, invasion, and cell cycle | Tumor growth            | ZEB1, miR-143-3p                           | [44] |
|                              | Up         | Cells (Saos2, MG63, U2OS, HO8), patient tissue   | Tumor promoter      | Cell proliferation, migration, and invasion     | Tumor growth            | MMP2, MMP9, p53, p21, MDM2                | [46] |
|                              | Up         | Cells (Saos2, HO8, U2OS, 143B, KHOS/240S, MG63, SK-ES-1), patient tissue | Tumor promoter      | Cell proliferation, migration, and invasion     |                         | miR-185-5p, TGF-β, p-SMAD, TGFBR1/2         | [45] |
### Table 1. Cont.

| Tumor Types              | Expression | Sample Type                                                                 | Role                                      | Functional Role in Vitro            | Functional Role in Vivo | Related Genes/Protein/Pathways | Ref. |
|--------------------------|------------|------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------|--------------------------|---------------------------------|------|
| Ovarian cancer           | Up         | Cells (OVCAR3, PEO1, A2780, 3AO, CAOV3, SKOV3), patient tissue              | Tumor promoter                            | Cell proliferation, migration, and invasion |                          | PTEN                            | [47] |
|                          | Up         | Patient tissue                                                              | Tumor promoter                            | Cell proliferation, migration, and invasion |                          | miR-143-3p, TAK1                | [48] |
| Cholangiocarcinoma       | Up         | Patient-derived macrophages, patient tissue                                 | Tumor promoter                            | M2 polarization of macrophages, cellular reactive oxygen species production, mitochondrial and metabolic dysfunction | Tumor growth           | miR-326, RhoA, ROCK1, ROCK2     | [54] |
| Pituitary adenomas       | Up         | Cell (ICC-9810, CCLP1, HuCC-T1, QBC939), patient tissue                     | Tumor promoter                            | Cell proliferation and invasion      |                          | miR-330-5p                      | [49] |
| Pancreatic ductal adenocarcinoma | Up         | Cell (Capan-2, AsPC-1, PANC1, BxPC-3), Patient tissue                      | Tumor promoter                            | Cell proliferation, migration, invasion |                          | miR-185-5p, CBX2                | [51] |
| Prostate cancer          | Up         | Cell (NCI-H660), patient tissue                                             | Tumor promoter                            | Cell NED, proliferation, and invasion | Tumor growth and metastasis | NSE, SYP, ChgA, miR-326, hnRNPA2B1 | [52] |

PDIA6, protein disulfide isomerase family A number 6; EMT, epithelial-mesenchymal transition; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2; Akt, serine/threonine kinase; mTOR, mammalian target of rapamycin; USP14, ubiquitin-specific protease-14; TPD52, tumor protein D52; Bcl-2, B-cell lymphoma-2; ZEB1, zinc finger E-box binding homeobox 1; ARC, activity regulated cytoskeleton associated protein; EZH2, enhancer of zeste homolog 2; HMGA2, high mobility group AT-hook 2; PRDX5, peroxiredoxin 5; MDM2, mouse double minute 2 homolog; TGF-β, transforming growth factor β; TGFβR1/2, transforming growth factor β receptor 1/2; PTEN, phosphatase and tensin homolog; TAK1, TGF-β activated kinase 1; RhoA, ras homolog family member A; ROCK1/2, Rho associated coiled-coil containing protein kinase 1/2; BRD4, bromodomain containing 4; CBX2, chromobox 2; NED, neuroendocrine differentiation; SYP, synaptophysin; ChgA, chromogranin A; BM, bone metastasis; IGF1R, insulin like growth factor 1 receptor; METTL3, methyltransferase 3; N6-adenosine-methyltransferase complex catalytic subunit; ALKBH5, alkB homolog 5.

#### 3.2. The Subcellular Localization of PCAT6 in Cancer Cell Lines

LncRNAs play diverse functions depending on different subcellular or extracellular compartmental localizations. Most studies indicate that PCAT6 is primarily located in the cytoplasm of BC [25], GIST [32], GBM [35], Osa [44,45], PA [50], and Pca [52] cells. Cytoplasmic lncRNAs regulate genes at the translational and post-transcriptional levels, such as interaction with cytoplasmic proteins [58], and interaction with microRNAs to regulate downstream mRNA levels [59–63]. Shi et al. determined that PCAT6 was principally distributed in the nucleus of NSCLC cells [40]. Nuclei lncRNAs regulate genes at the epigenetic and transcriptional levels, including histone modifications [64,65], DNA methylation [66], and chromatin remodeling [67]. Furthermore, Dong and Lang et al. demonstrated that PCAT6 was located in both the cytoplasm and nucleus of BrCa and Pca cells by fluorescence in situ hybridization (FISH) and subcellular fraction assays, which was different from most studies [26,53]. This is similar to the lncRNA HOTAIR, which regulates...
genes at both the epigenetic and transcriptional levels, as well as at the post-transcriptional level [68].

As shown in Figure 1a, PCAT6 is an antisense RNA of KDM5B, so it is also known as KDM5B-AS1. The RNAs PCAT6 and KDM5B are adjacent in chromosome position. Several antisense lncRNAs have been found to form RNA–RNA dimers with adjacent mRNA, thus improving the stability of mRNA and upregulating mRNA expression levels. For instance, IncRNA BACE1-AS1 can reduce the degradation of BACE1 by forming a dimer with BACE1 [69]; IncRNA FGFR3-AS1 promotes Osa through increasing FGFR3 stability [70]. Hence, we speculate that PCAT6 may also maintain the stability of KDM5B mRNA and upregulate the expression of the KDM5B protein, thus promoting disease progression, but this hypothesis needs to be further confirmed. Furthermore, PCAT6 is also regulated by different transcription factors. In addition to NHLH2 near H3K4Me3 and H3K27Ac (Figure 1b), transcription factors that have been confirmed to regulate PCAT6 include the Sp1 transcription factor (SP1) [71] and the enhancer of zeste homolog 2 (EZH2) [30,40].

4. PCAT6 Promotes Cancer Progression by ceRNA Mechanisms

LncRNAs can participate in the process of tumor progression via various molecular mechanisms, including by interacting with DNA, RNA, and protein. They play different regulatory roles by serving as different functional molecules, such as signals, decoys, guides, and scaffolds in multiple tumor cellular processes [22,72]. In recent studies, mounting evidence indicates that the lncRNA-miRNA-mRNA axis is present in cancers [73–77]. LncRNAs can mediate competitive mRNAs crosstalk by sharing microRNA response elements (MREs), which are also known as competing endogenous RNA (ceRNA) regulatory network mechanisms. Wang et al. first confirmed the existence of the lncRNA-related ceRNA mechanism in liver cancer. They determined that IncRNA HULC promoted liver cancer progression by regulating the miR-372/PRKACB axis [78]. Later on, Selmena et al. proposed the ceRNA hypothesis based on previous investigations [79]. Subsequently, more and more cancer-associated lncRNAs mediated ceRNA networks have been revealed. So far, more than 11,700,000 pairs of ceRNA have been included in the starBase database (http://starbase.sysu.edu.cn/index.php (accessed on 28 July 2021)). The ceRNA regulatory networks have been proven to be the indispensable regulators of multiple tumors growth [80], and the PCAT6-centric ceRNA networks have attracted wide attention. PCAT6 promotes tumorigenesis through the PCAT6/miRNA/mRNA axis, which in turn affects different biological behaviors of tumor cells [27,44]. As shown in Figures 2–4, 11 miRNAs have been verified to interact with PCAT6, thus participating in the ceRNA networks of PCAT6. Meanwhile, as members of ceRNA, the miRNAs downstream of lncRNAs can directly or indirectly regulate mRNAs and thus affect the biological behaviors of tumor cells, such as proliferation, migration, invasion, apoptosis, cell cycles [27,37,43,44,50,53], epithelial-mesenchymal transitions (EMT) [26,33,34,50], radiosensitivity [27], and chemoresistance [29,31].

4.1. PCAT6 Boosts the PI3K/Akt/mTOR Signaling Pathway

Phosphatidylinositol 3-kinase (PI3K), protein kinase B (PKB, also known as Akt), the mammalian target of the rapamycin (mTOR) signaling pathway, is vital for the regulation of cell biological functions in cancers, including cell proliferation, metastasis, cell apoptosis, autophagy, and glucose and lipid metabolism [81–83]. They are considered potential therapeutic targets and are involved in various biological processes in neoplasms. As shown in Figure 2, Dong et al. revealed that M2 macrophages secreted the vascular endothelial growth factor (VEGF) and upregulated the PCAT6 expression level in BrCa. PCAT6 overexpression further induced the Akt/mTOR pathway by absorbing miR-4723-5p to elevate vascular endothelial growth factor receptor 2 (VEGFR2) levels, which in turn promoted triple-negative breast cancer (TNBC) cell proliferation, migration, invasion, and angiogenesis in vitro, as well as tumor growth, metastasis, and angiogenesis in vivo [26]. Shi et al., also proved that PCAT6 increased the expression of tumor protein
D52 (TPD52) by interacting with miR-185-5p in TNBC [27]. Another study suggested that TPD52 may exert a biological function via the PI3K/Akt signaling pathway [84]. In CRC, PCAT6 can increase the expression level of HMGA2 via absorbing miR-204, while depletion of PCAT6 can dramatically reduce the protein levels of HMGA2, p-PI3K, and p-Akt. Inhibition of miR-204 partially abolishes the suppressive effects of PCAT6 knockdown on these proteins. This evidence indicates that PCAT6 activates PI3K/Akt signaling by regulating the miR-204/HMGA2 axis and further promotes proliferation of CRC cells [31]. In addition, Liu et al. confirmed that PCAT6 was transcriptionally upregulated by the Yin Yang 1 (YY1) protein in GBM, which further activated Akt signaling by increasing insulin-like growth factor 2 mRNA binding protein 1 (IGF2BP1) expression via inhibition of miR-513. Simultaneously, the stability of PCAT6 is enhanced by interacting with IGF2BP1. Furthermore, PCAT6, transcriptionally activated by YY1, promoted the proliferation and prevented the apoptosis of GBM cells through the PCAT6/miR-513/IGF2BP1 positive loop [35]. PCAT6 promotes HCC cell proliferation and invasion in vitro, and tumor growth in vivo by attenuating miR-326 and upregulating heterogeneous nuclear ribonucleoprotein A2/B1 (HNRNPA2B1) [38]. Moreover, enzalutamide induced PCAT6 also promotes PCa cell proliferation, metastasis, and neuroendocrine differentiation (NED) via the miR-326/HNRNPA2B1 axis in vitro or in vivo [52]. Several studies have clarified that HNRNPA2B1 can activate the PI3K/Akt/mTOR pathway [85–88], which further indicates that PCAT6 may induce this pathway through the ceRNA mechanism. In Osa, PCAT6 upregulates the transforming growth factor β receptor 1/2 (TGFBR1/2) expression by attenuating miR-185-5p, which further activates transforming growth factor β (TGF-β) pathway-related proteins such as p-SMAD, thereby promoting the proliferation, migration, and invasion of Osa cells [45]. TGF-β is verified to be associated with the PI3K/Akt signaling pathway [89–91]. Zhao et al., validated that PCAT6 promoted the progression of PA through miR-139-3p/bromodomain-containing protein 4 (BRD4) axis. Interference of PCAT6 or the accumulation of miR-139-3p impedes tumor growth, induces apoptosis and promotes the EMT process in vivo. The MiR-139-3p inhibitor significantly attenuates the regulatory effects of PCAT6 knockdown on cell viability, proliferation, apoptosis, and cell cycle arrest. The depletion of BRD4 reverses the promoting effects of the miR-139-3p inhibitor on PA cell viability, proliferation, migration, and invasion [50]. BRD4 has been experimentally confirmed to be associated with PI3K/Akt signaling [92–94]. Additionally, a study has elucidated that PI3K/Akt pathway can be activated by circ_0007841/miR-338-3p/BRD4 axis [95], which indicates PCAT6 may activate the PI3K/Akt pathway through the BRD4 ceRNA mechanism. Wang et al. clarified that PCAT6 acted as a sponge for miR-185-5p to increase chromobox 2 (CBX2) expression and promote PDAC cell proliferation, migration, and invasion in PADC [51]. Nevertheless, CBX2 exerts biological functions by activating the PI3K/Akt signaling pathway in tumorigenesis [96]. Taken together, PCAT6 boosts the PI3K/Akt/mTOR signaling pathway.
Figure 2. *PCAT6* promotes PI3K/AKT/mTOR signaling Pathway. By sponging miRNAs, *PCAT6* affects the PI3K/AKT/mTOR signaling pathway in multiple cancers, including BrCa, CRC, GBM, HCC, PCa, Osa, PA, PDAC. *: *PCAT6* is likely to activate the PI3K/AKT/mTOR signaling by regulating ceRNA mechanisms.

4.2. *PCAT6* Promotes the Wnt/β-Catenin Signaling Pathway

The Wnt signaling pathway plays an indispensable role in embryonic development and stem cell regulation. Therefore, dysregulated Wnt signaling activity leads to a variety of serious diseases, including cancers [97, 98]. Deregulation of Wnt signaling is correlated with tumor growth, metastasis, and chemoresistance, ultimately resulting in poor prognosis of patients [99, 100]. As shown in Figure 3, TPD52, HNRNPA2B1, BRD4, and CBX2, which may participate in the PI3K/Akt/mTOR pathway by the ceRNA mechanism, have also been found to be related to Wnt signaling [101–108]. *PCAT6* activates Wnt/β-catenin signaling and promotes GIST cell proliferation, maintaining stemness, and hampering GIST cell apoptosis. Meanwhile, *PCAT6* upregulates the expression level of peroxiredoxin (PRDX5) by acting as a ceRNA for miR-143-3p, while downregulation of *PCAT6* will hinder GIST cell proliferation and stemness and promote cell apoptosis. The inhibition of miR-143-3p or the accumulation of PRDX5 counteract the suppressive effects of loss of *PCAT6*, indicating that *PCAT6* mediates GIST cell proliferation, stemness, and apoptosis through the miR-143-3p/PRDX5 axis [32]. Additionally, it has been revealed that PRDX5...
influences cellular biological behavior by activating the Wnt/β-catenin pathway [109], which suggests that PCAT6 can activate the Wnt/β-catenin pathway through the ceRNA network of PRDX5. Dong et al. discovered that PCAT6 excited Wnt/β-catenin and RB/E2F signaling by targeting miR-15a in GC. Decreased expression of PCAT6 represses GC cell proliferation and accelerates cell apoptosis, whereas a miR-15a inhibitor reverses the performance [33]. Su et al. found that sevoflurane inhibited LC cell proliferation, migration, and invasion, conversely accelerating cell apoptosis, and inactivated the Wnt/β-catenin pathway. However, PCAT6 abolishes the effects of sevoflurane on cell biology function. Analogously, miR-326, acting as a ceRNA for PCAT6, also rescues the effects of PCAT6 on sevoflurane-treated cells. Furthermore, Wnt5a, a downstream target of miR-326, restores the regulatory role of miR-326 in LC cells. Hence, sevoflurane inhibits the PCAT6 that absorbs miR-326, further downregulates Wnt5a, deactivates Wnt/β-catenin signaling, and impairs LC cell biology function [42].

Figure 3. PCAT6 accelerates the Wnt/β-catenin signaling pathway. By sponging miRNAs, PCAT6 affects the Wnt/β-catenin signaling pathway in various cancers, including BrCa, HCC, Pca, PA, PDAC, GIST, GC, LC. #: PCAT6 is likely to activate Wnt/β-catenin signaling by absorbing miRNAs.

4.3. PCAT6 Facilitates the EMT Process

The epithelial-to-mesenchymal transition (EMT), an indispensable cellular program, exerts a specific role in embryonic development and tissue homeostasis. The EMT process is activated by wound healing, fibrosis, and tumors. The EMT process, which is aberrantly induced by cancer cells, enhances cell metastatic and invasive capacity [110–113]. Acting as a sponge for miR-4723-5p in TNBC, PCAT6 upregulates the VEGFR2/Akt/mTOR signaling pathway, leading to significantly decreased E-cadherin expression and significantly increased N-cadherin, Slug, and Twist expression (Figure 4). Hence, PCAT6 enhances cell migration and invasion by partly accelerating the transformation of the EMT process [26]. It has been revealed that PCAT6 upregulates makorin ring finger protein 3 (MKRN3) by endogenously competing with miR-30 in GC. The introduction of PCAT6 impairs the protein expression of caspase-3, caspase-9, Bax, and E-cadherin, and promotes the expression of Bcl-2, N-cadherin, Vimentin, zinc finger E-box binding homeobox 1 (ZEB1), and Snail, which validates the indication that PCAT6 facilitates the GC cell EMT process and hampers apoptosis via the miR-30/MKRN3 axis [34]. Similarly, Dong et al. also found that PCAT6 decreased GC cell apoptosis and EMT by endogenously competing with miR-15a. Defi-
ciency of PCAT6 promotes apoptosis by conspicuously restraining the Cyclin D1 protein level and enhancing the protein levels of p53, Bax, and cleaved caspase-3. The silence of PCAT6 impedes cell EMT process by decreasing the expression of N-cadherin, Vimentin, Snail, and ZEB1 except for E-cadherin [33]. This evidence proves that PCAT6 induces the EMT process by the ceRNA mechanism in GC. Moreover, the results of a subcutaneous xenotransplanted PA mice model have demonstrated that PCAT6 knockdown and miR-139-3p overexpression can induce the increase of the E-cadherin protein level and the decrease of the N-cadherin level in tumor tissues. The inhibition of miR-139-3p reverses its suppressive effect and decrease of PCAT6 on the PA cell EMT process in vitro [50]. ZEB1, as a transcriptional regulator, has been confirmed to be involved in the EMT process [114]. It also have observed that lncRNAs affect the EMT process by regulating the miRNAs/ZEB1 axis [115,116]. In CC, PCAT6 promotes cell proliferation and metastasis in vitro, and tumor growth in vivo through the miR-543/ZEB1 axis [29]. In addition, PCAT6 also upregulates the ZEB1 level by absorbing miR-143-3p in Osa, promoting cell proliferation, migration, invasion, and cell cycle in vitro, and tumor growth in vivo [44]. Hence, PCAT6 participates in the EMT process by regulating the miRNAs/ZEB1 axis and further influences cell migration and invasion. Moreover, PCAT6 also targets miR-143-3p to activate TGF-β-activated kinase 1 (TAK1) in OvCa, and then accelerates cell proliferation and enhances cell metastasis [48]. Previously, TAK1 has been reported to induce the EMT process in various diseases [117,118]. Therefore, these results confirm that PCAT6 regulates the EMT process by acting as a ceRNA for miRNAs.

4.4. PCAT6 Leads to Radioresistance and Chemoresistance

Currently, radiotherapy remains the preferred therapy for many cancers. However, many patients who are resistant to radiation have poor prognosis, with cancer recurrence and attenuating radiotherapy effectiveness [119]. Hence, the radiosensitivity of patients is the key to radiotherapy for malignant tumors. Radioresistance is a complex process involving various molecular mechanisms [120]. Recently, increasing amounts of evidence have demonstrated that many lncRNAs are closely associated with radiotherapies, including RBM5-AS1 [121], HOTAIR [122], and PVT1 [123]. Shi et al. also found that there was a relationship between PCAT6 and radioresistance in TNBC. The interference of PCAT6, up-regulation of miR-185-5p, or inhibition of TPD52 enhances the radiosensitivity of TNBC.

Figure 4. PCAT6 expedites the EMT process. By sponging miRNAs, PCAT6 promotes the EMT process in multiple cancers, including BrCa, GC, PA, CC, Osa, OvCa. ▲: PCAT6 is likely to promote the EMT process by absorbing miRNAs.
cells, inhibits cell proliferation, arrests the cell cycle in the G0/G1 phase, and accelerates cell apoptosis (Figure 2) [27].

Chemotherapy is an effective anticancer treatment. However, patients can also develop resistance to drug treatment like radioresistance, leading to a dismal prognosis [124,125]. Chemoresistance is influenced by tumor properties, biological behavior, and microenvironments [126]. To date, many drugs have been used in chemotherapy, such as platinum, paclitaxel, and 5-fluorouracil (5-FU). Exploring new mechanisms of chemotherapeutic drugs to overcome chemoresistance is urgently needed. Recently, lncRNA dysregulation has been associated with drug resistance, including UCA1 [127], CYTOR [128], and TINCR [129]. Furthermore, the aberrant expression of PCAT6 was also verified to be related to chemoresistance in cancers. It has been demonstrated that both the intervention of PCAT6 and the introduction of miR-543 impair CC cell chemoresistance to cisplatin. Moreover, PCAT6 rescues the suppressive effect of miR-543 on cell chemoresistance [29]. ZEB1, with significant negative correlation with miR-543 and with positive correlation with PCAT6, was confirmed to be a downstream target of miR-543 [29]. Furthermore, the over-expression of ZEB1 partially counteracts the inhibitory effect of PCAT6 downregulation on cell chemoresistance to cisplatin (Figure 4) [29]. Wu et al. found that loss of PCAT6 reversed the chemoresistance of CRC cells to 5-fluorouracil (5-FU), while this performance could be partially abrogated by depression of miR-204. Moreover, PCAT6 activates HMGA2/PI3K signaling by absorbing miR-204, thus reducing the CRC cells’ chemosensitivity to 5-FU (Figure 2) [31]. Consequently, PCAT6 may be a new effective target for treatment in cancer patients undergoing clinical radiotherapy and chemotherapy resistance.

4.5. Other ceRNA Mechanisms of PCAT6

In addition to those mentioned above, it has been eluted that PCAT6 boosts cancer progress via various signal pathways. PCAT6 can act as a sponge for miR-513a to facilitate BC progression. The inhibition of miR-513a partially offsets the proliferation, migration, and invasion induced by the knockdown of PCAT6 [21]. Moreover, PCAT6 promotes cell proliferation, migration, and invasion by inhibiting miR-143-3p and upregulating protein disulfide isomerase family A member 6 (PDIA6), in BC [25]. In NSCLC PCAT6 absorbs miR-330-5p and promotes cell proliferation, migration, invasion in vitro, and tumor growth in vivo [39]. PCAT6 has also been found to have a competitive binding relationship with miR-330-5p, which in turn induced CCA cell proliferation and invasion [49].

Furthermore, increasing evidence has indicated that dozens of lncRNAs are associated with immune cell function. For instance, XIST [130] and SBF2-AS1 [131] can the induce M2 polarization of tumor-associated macrophages, which are indispensable cells within the tumor immune microenvironment. Similarly, Tu et al. validated that PCAT6 overexpression induced the M2 polarization of macrophages deriving from CCA patients, and indicated the effect could be reversed by miR-326. Simultaneously, miR-326 mimics can abolish the promoting impacts of PCAT6 introduction on macrophage cellular reactive oxygen species production and mitochondrial and metabolic dysfunction. Furthermore, RhoA has been confirmed to be a downstream target of miR-326, which further activates the RhoA-ROCK signaling pathway and promotes tumor progression. The results of animal experiments uncovered that depletion of PCAT6 inhibited tumor growth by activating the T cell response in vivo, which was mainly manifested by the increase of CD3+ T cells and IFN-γ-producing CD4+ T and CD8+ T cells. These findings suggest that PCAT6 may serve as a potential immune-therapeutic target for CCA (Figure 5) [54].
Figure 5. PCAT6 exerts biological behaviors by other ceRNA and beyond ceRNA mechanisms in various cancers, including BC, LC, CCA, CC, CRC, HCC, Osa, OvCa.

5. The Mechanisms of PCAT6 above ceRNA

In addition to absorbing miR-4723-5p, PCAT6 also activates the VEGFR2/Akt/mTOR axis by recruiting USP14 to stabilize VEGFR2 and further elicits biological functions in vitro and in vivo in BrCa (Figure 2) [26]. TOP/FOP flash reporter assays have revealed that silence of PCAT6 inactivates Wnt/β-catenin signaling pathway in CC. Meanwhile, the results from real-time fluorescence quantitative PCR (qRT-PCR) and Western blot analyses indicate that several pivotal genes of Wnt/β-catenin signaling (e.g., β-catenin, cyclin D1, and c-myc), are remarkably suppressed in CC cells transfected with siRNA targeting for PCAT6 [28]. PCAT6 upregulates the activity regulated cytoskeleton associated protein (ARC) via binding to EZH2 in CRC. It also impedes cell apoptosis and promotes cell proliferation [30]. In HCC, PCAT6 promotes cell proliferation, increases the proportion of the S phase, and decreases cell apoptosis. In addition, PCAT6 also affects the expression of the protein related to the proliferation, cycle, and apoptosis, including proliferating cell nuclear antigen (PCNA), cyclin D1 (CCND1), and B-cell lymphoma-2 (Bcl-2) [37]. Bioinformatics analyses indicate that PCAT6 may be associated with Wnt, HIF-1, and metabolic pathways. Also, it may correlate with p53 and participate in the apoptotic signaling pathways [37]. PCAT6 indirectly regulates c-myc and p53 genes to affect Bcl-2 and Bax expressions, which further prevent sLC cell early apoptosis and induce cell proliferation [20]. Moreover, in NSCLC, PCAT6 transcriptionally impairs large tumor suppressor kinase 2 (LATS2) promoter activity by binding to EZH2, which mediates H3K27 trimethylation and accelerates the cell cycle, promoting cell proliferation, tumor growth and metastasis, and hindering cell apoptosis [40]. In Osa, overexpression of PCAT6 enhances cell proliferation, migration, and invasion in vitro, and tumor growth in vivo, while depression of MDM2 proto-oncogene (MDM2) exerts an opposite influence. Moreover, upregulation of PCAT6 decreases p53 and p21 expression, and further induces tumorgenesis [46]. However, this performance
is rescued by the depletion of MDM2 [46]. In OvCa, PCAT6 increases the capacity of cell proliferation and metastasis by decreasing the phosphatase and tensin homolog (PTEN) level. Moreover, both the mRNA and protein levels of PTEN are upregulated by depleting PCAT6. Meanwhile, knockdown of PTEN rescues the inhibition of the metastatic capability of OvCa cells induced by PCAT6 suppression (Figure 5) [47]. Lang et al. discovered that PCAT6 upregulating by methyltransferase 3 (METTL3), a catalytic subunit of the N6-adenosine-methyltransferase complex that induces m^6A modification, promoted PCa cell proliferation and metastasis in vitro, and accelerated tumor growth and bone metastasis (BM) in vivo. Upregulation of PCAT6 can interact with insulin like growth factor 2 mRNA binding protein 2 (IGF2BP2) and insulin like growth factor 1 receptor (IGF1R) to stabilize IGF1R mRNA and activate the downstream signaling pathways, including PI3K/Akt signaling and NF-κB signaling, which ultimately facilitate tumor growth and BM (Figure 2) [53].

6. The Diagnostic and Prognostic Value of PCAT6 Overexpression

Various studies have shown that high expression of PCAT6 in multiple cancers is associated with various clinicopathologic features, mainly including larger tumor size, high tumor differentiation, advanced tumor stage, more tissues metastasis, and so on (Table 2). Some researchers have estimated the diagnostic and prognostic values of upregulated PCAT6 in cancers (Table 3). Zhang et al. found that the area under the curve (AUC) of the serum PCAT6 level was greater than 0.8, which could distinguish BC patients from the normal controls. It has been further demonstrated that the serum PCAT6 level is suitable as a BC diagnosis biomarker [24]. Wan et al. revealed that the tissue PCAT6 level had great diagnostic values, including AUC greater than 0.9, with higher sensitivity (86.67–100%) and higher specificity (78.57–96%) in 349 cases of NSCLC from five GEO datasets (GSE19804, GSE18842, GSE30219, GSE19188, and GSE27262). Meanwhile, they also had noticed that the AUCs of plasma PCAT6 were 0.9213 (sensitivity, 87.67%; specificity, 97.44%) in lung adenocarcinoma (LUAD) and 0.9583 (sensitivity, 94.12%; specificity, 100%) in lung squamous cell carcinoma (LUSC), respectively [41]. These results suggest that PCAT6 may be a promising diagnostic biomarker for BC and LC.

In addition, more studies have found that the accumulation of PCAT6 is closely related to the prognosis of various tumor patients. It has been illustrated that the PCAT6 level is negatively correlated to the overall survival (OS) of patients with CRC [30], GC [34], LC [20,40,43], and PDAC [51]. Furthermore, increased expression of PCAT6 reduces OS and progression-free survival (PFS) in BC [21,24] and Osa [44,45] patients. Lv et al. conducted Kaplan–Meier survival analysis to investigate the association between PCAT6 level and postoperative survival in patients with CC. They found that a high level of PCAT6 predicts poor OS and disease-free survival (DFS) in patients. Subsequently, univariate analysis and multivariate analysis also have revealed that high expression of PCAT6 is an independent poor prognostic factor for both OS and DFS in CC [28]. For HCC, many reports have revealed that upregulated PCAT6 is associated with shorter OS, PFS, and DFS [36–38,132]. Similarly, Kaplan–Meier Plotter analyses have demonstrated that high expression of PCAT6 can be used as a prognostic biomarker for OS, PFS, and post-progression survival (PPS) in OvCa patients [48]. In PCa patients with BM, patients with higher PCAT6 expression have poorer overall and BM-free survivals and shorter DFS [53]. These results have indicated that PCAT6 may be a clinical prognostic factor.
### Table 2. Clinicopathologic features of **PCAT6** in multiple human cancers.

| Tumor Types          | Clinicopathologic Features                                                                 | Ref.       |
|----------------------|---------------------------------------------------------------------------------------------|------------|
| Bladder cancer       | Larger tumor size, high tumor differentiation, advanced TNM stage, more lymph nodes         | [24]       |
|                      | metastasis, more distant metastasis                                                        |            |
|                      | Pathological stage                                                                          | [21]       |
| Breast cancer        | More tissues metastasis, higher tumor stages                                                | [26]       |
|                      | More lymph nodes metastasis, advanced tumor stages                                          | [27]       |
| Cervical cancer      | Advanced FIGO stage, more lymph nodes metastasis, depth of cervical invasion                | [28]       |
| Colorectal cancer    | Tumor subtype, N classification, metastasis, poorer clinical stage                         | [30]       |
|                      | Larger tumor size, advanced TNM stage, lymph node metastasis                              | [31]       |
| Gastric cancer       | Larger tumor size, advanced TNM stage, more metastasis                                     | [34]       |
| Hepatocellular       | Moderated or poorly differentiation, advanced TNM stage                                     | [37]       |
| carcinoma            |                                                                                             |            |
| Lung cancer          | Advanced TNM stage, more metastasis                                                        | [41]       |
|                      | Larger tumor size, more lymph nodes metastasis, advanced TNM stage                          | [39]       |
|                      | Larger tumor size, more lymph node metastasis, advanced TNM stage                           | [40]       |
| Osteosarcoma         | Larger tumor size, more metastasis, advanced TNM stage                                     | [41]       |
|                      | Larger tumor size, more metastasis, advanced TNM stage                                     | [45]       |
| Ovarian cancer       | More lymph node metastasis, more distant metastasis                                        | [47]       |
|                      | Advanced TNM stage                                                                          | [48]       |
| Cholangiocarcinoma   | Advanced TNM stage                                                                          | [49]       |
| Pancreatic ductal    | Advanced TNM stage, more lymph node invasion                                                | [51]       |
| adenocarcinoma       |                                                                                             |            |
| Prostate cancer      | Poor differentiation, higher serum PSA, advanced gleason grade, more BM                     | [53]       |

TNM, tumor node metastasis; FIGO, Federation of Gynecology and Obstetrics; PSA, prostate specific antigen; BM, bone metastasis.

### Table 3. Diagnostic or prognostic value of **PCAT6**.

| Tumor Types          | Expression | Diagnostic or Prognostic Value                                                      | Ref.       |
|----------------------|------------|-------------------------------------------------------------------------------------|------------|
| Bladder cancer       | Up         | Poor OS, and poor PFS, AUC > 0.8                                                    | [24]       |
|                      | Up         | Poor OS                                                                              | [21]       |
| Cervical cancer      | Up         | Shorter OS and DFS                                                                   | [28]       |
| Colorectal cancer    | Up         | Worse OS                                                                              | [30]       |
|                      | Up         | Poor OS                                                                              | [31]       |
| Gastric cancer       | Up         | Worse prognosis                                                                      | [34]       |
|                      | Up         | Poor OS                                                                              | [36]       |
|                      | Up         | Poor OS and DFS                                                                      | [37]       |
|                      | Up         | Shorter OS                                                                           | [38]       |
|                      | Up         | Poor PFS                                                                             | [132]      |
| Hepatocellular       | Up         | Tissue **PCAT6**: AUC > 0.9, sensitivity 86.67–100%, specificity 78.57–96%. Plasma **PCAT6**: a. LUAD: AUC = 0.9213, sensitivity 87.67%, specificity 97.44; b. LUSC: AUC = 0.9583, sensitivity 94.12%, specificity 100% | [41]       |
| carcinoma            | Up         | Poor OS                                                                              | [40]       |
|                      | Up         | Poor OS                                                                              | [20]       |
| Lung cancer          | Up         | Poor OS                                                                              | [40]       |


Table 3. Cont.

| Tumor Types                        | Expression | Diagnostic or Prognostic Value       | Ref.  |
|------------------------------------|------------|--------------------------------------|-------|
| Osteosarcoma                       | Up         | Poor OS                              | [43]  |
|                                    | Up         | Shorter OS and PFS                   | [44]  |
|                                    | Up         | Shorter OS and PFS                   | [45]  |
| Ovarian cancer                     | Up         | Poor OS, PFS and PPS                 | [48]  |
| Pancreatic ductal adenocarcinoma   | Up         | Worse OS                             | [51]  |
| Prostate cancer                    | Up         | Shorter overall and BM-free survival, shorter DFS | [53]  |

OS, overall survival; PFS, progression-free survival; AUC, area under curve; DFS, disease-free survival; PPS, post progression survival.

7. Discussion and Perspectives

In conclusion, LncRNA PCAT6, a vital oncogene, is first found overexpressed in lung cancer [20], and subsequently verified in multiple human cancers. It has been proven to be a promising diagnostic biomarker and clinical prognostic factor in different diseases (Table 3). The accumulation of PCAT6 is closely related to many clinicopathological features (Table 2). Furthermore, PCAT6 overexpression promotes tumor cell proliferation [21], migration [44], invasion [45], chemoresistance [29,31], and radioresistance [27]. These processes involve various signaling pathways, including PI3K/Akt/mTOR signaling, Wnt/β-catenin signaling, and RhoA-ROCK signaling. It has been confirmed that these pathways play indispensable roles in tumorigenesis and disease progression [133–136]. However, PCAT6 can regulate the signaling pathways through ceRNA [26] and other mechanisms [28]. Hence, PCAT6, as a promising diagnostic biomarker, may be a checkpoint target for precision therapy in human cancers.

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