PIWI-interacting RNA in cancer: Molecular mechanisms and possible clinical implications (Review)

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Abstract. PIWI-interacting RNA is a class of non-coding small RNA that is ~30 nt long and is primarily found in mammalian germ cells from mice and humans. In cooperation with the members of PIWI protein family, this macromolecule participates in germ cell development, inhibits DNA self-replication and maintains genomic stability. Increasing evidence has demonstrated that PIWI-interacting RNA (piRNAs) are abnormally expressed in various human cancers, such as liver cancer, stomach cancer, colorectal cancer, osteosarcoma, breast cancer, lung cancer, prostate cancer, etc. piRNAs abnormal expression is also associated with the occurrence and development of human cancers, such as liver cancer, stomach cancer, colorectal cancer, etc. Despite their unclear molecular mechanisms, piRNAs may act as oncogenes or tumor suppressors by interacting with multiple cancer-related signal pathways including STAT3/Bcl-xl or coding genes, such as heat shock transcription factor-1. Hence, piRNAs may be potential markers and targets and provide new opportunities for cancer diagnosis, treatment or prognosis monitoring. The current review mainly aims to highlight the latest research progress made in the biological functions and regulation of piRNAs in mammals, their involvement in various cancer forms and their potential clinical applications.

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Abbreviations: piRNAs, PIWI-interacting RNA; sncRNAs, small ncRNAs; PIWIL, PIWI-like; HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; GC, gastric cancer; CRC, cololectal cancer; NSCLC, non-small cell lung cancer; BC, breast cancer; EMT, epithelial-mesenchymal transition; PDAC, human pancreatic duct cancer; ccRCC, renal clear cell carcinoma; RCC, renal cell cancer; RASSF1C, Ras association domain family 1C; ER, estrogen receptor; BCR, biochemical recurrence; PCDH9, protocadherin family member 9

Key words: potential target, PIWI-interacting RNA, non-coding small RNA, carcinogenesis, molecular mechanism

Contents

1. Introduction

RNA in living organisms can be divided into 2 groups according to their coding potential for proteins: coding and non-coding RNAs (ncRNA) (1-3). NcRNAs account for ~98% of RNAs in mammals including humans (1-3). The discovery of small ncRNAs (sncRNAs) has created a new research field and caused an upsurge in RNA studies (1-3). SncRNAs are a large group of RNAs that do not code for proteins and are less than 200 nucleotides in length, usually ~20-30 nt (1,2). The role of sncRNAs in life goes far beyond previous cognition (4-7).

SncRNAs have various family members and form complex regulatory networks in cells (3-5). Among which the most studied are small nucleolar RNA (3,4), small interfering RNAs (5), microRNAs (6) and PIWI-interacting RNAs (piRNAs) (7) (Table I). SncRNAs are involved in the regulation of various biological functions, including organism immunity, growth, development, organ formation, cell proliferation, cell differentiation and cell death (1-7). Abnormalities in sncRNA expression and functions lead to numerous functional disorders and health problems including long-term memory disorder (2) and cancer (8-10). This review discusses the biological function of piRNAs and the current research progress made with regard to piRNAs in cancer.

Discovery and characteristics of piRNAs. piRNAs are a new and diverse group of sncRNAs and the human genome consists of >30,000 piRNA species (8). In 2006, scientists discovered a

new type of small ncRNA in the testes of mice (9). Such small ncRNAs could interact with the PIWI subfamily proteins of the AGO (Argonaut) family to serve important biological roles, hence they are named PIWI-interacting RNA (piRNA) (10).

piRNAs are generally derived from genomic sequences (11,12). These macromolecules originate from 3 main genome regions: the intergenic region containing a large number of transposition fragments and repetitive sequences, the long-chain non-coding gene region and the 3'-UTR region of the mRNA (11,12). PiRNAs produced from the intergenic region are distributed as clusters called piRNA clusters (11,12). Some piRNA clusters can be bidirectionally transcribed and consequently generate 2 piRNAs (13,14). Among which, the antisense piRNA is complementary to the DNA sequence template. The production of piRNA does not require the involvement of the Dicer enzyme in RNase III. The length of piRNA is ~24-32 nucleotides (13,14). In piRNAs the first base at the 5' end has a strong uracil bias and the 3' end is modified by methylation (13,14). piRNAs are tissue-specific and distributed mainly in mammalian germ cells and embryonic stem cells (11-14).

2. Biological functions of piRNAs

piRNAs are crucial for the maintainance of genomic integrity and stability. Transposons are a type of mobile DNA elements (15-17). Most of the active transposons in organisms are RNA transposons, which are also known as reverse transcriptional transposons that occupy a large proportion of the genome (15-17). During the development of germ cells and embryos, epigenetic reprogramming is activated and a large number of transcriptional transposon RNA and transposon activity is enhanced (15-17). Retrotransposons can move within the chromosomes or between different chromosomes, hence increasing the probability of structural and functional changes in the genome and leading to serious diseases, such as cancer (15-17). During germ cell development, piRNA combines with the PIWIL2 gene (member 2 of the PIWI-like subfamily also known as HILI) to form a piRNA-induced gene silencing complex (pi-RISC) (18). In piRNA generation, the primary production pathway enters the secondary generation pathway to form a piRNA generation cycle, a process also known as the 'ping-pong cycle' (19). The pi-RISC complex uses active transposon transcripts as precursors and amplifies piRNA in large quantities through the ping-pong cycle mechanism (Fig. 1). piRNA binds with transposons sequence by base complementation, hence completing transcriptome cutting and consuming a large number of transposon transcripts (20,21) (Fig. 1). This process directly silences the 'gene parasite' transposition element and protects germ cell genes from destruction (20,21). Thus, piRNAs maintain genomic integrity and stability.

piRNAs regulates the degradation of mRNA transcripts. PIWI/piRNA pathway mediates the degradation of a large number of mRNA transcripts during mouse sperm formation, particularly at the round spermatid stage (22,23). CAF1, a subunit of the CCR4-NOT complex, is a magnesium dependent deadenylase enzyme, which removes the poly(A) tail of mRNA (22). piRNA recognizes the 3'-UTR in mRNA sequences and its complementary sequence inhibits the activity of mRNA deadenylase CAF1 (22). As a result, the adenosine residues of mRNA become acidic and decay is initiated by the piRNA binding with the PIWI protein (22,23). Hence, piRNAs have an important regulatory role in the formation of mice germ cells (22-25). Similar mechanisms have also been observed in *Drosophila* germ cells (26).

piRNAs maintain germline and stem cell function. piRNAs maintain the DNA integrity of germline stem cells (24-28). Mouse PIWI homologs MIWI, MILI and MIWI2 are highly expressed in mouse testes (24). The piRNA-dependent clearance of MIWI via the anaphase-promoting complex/cyclosome (APC/C)-26S, mediated ubiquitin proteome pathway is essential for mRNA stabilization and proper sperm maturation during the late stages of sperm development, indicating that the stage-specific regulation of MIWI/piRNA is essential in male germ cell development (25). In model organisms, such as fruit flies, piRNA pathways are involved in the decay of maternal messenger RNA and the inhibition of translation in early embryos, implying their direct regulatory role for genes, development such as the embryonic posterior morphogen Nanos associated with embryo (26). In addition, human HIWI protein has 52% homology with *Drosophila* PIWI at the amino acid level (27). HIWI genes are expressed in developing fetal and adult tissues, including primitive hematopoietic cells that are negatively regulated by HIWI (27). The PIWI protein is a positive modulator of adult stem cell generation and is required for regeneration and tissue homeostasis during wound healing in lower organisms, such as the planarian *Schmidtea mediterranea* (28).

3. Progress of piRNAs in cancer research

piRNAs are associated with cancer development (29). Given the abnormal expression of piRNAs in different types of cancer, their functions cannot be ignored (29). A number of piRNAs with their binding partner, PIWI proteins, regulate the occurrence and development of cancer (30,31). piRNAs are differentially expressed in cancer and non-cancer tissues and hence, can be used to distinguish them and provide new cancer biomarkers (30,32). This section of the review mainly summarizes the abnormal expression and relationship of piRNAs in different human cancers including hepatocellular carcinoma (HCC), gastric cancer (GC), colorectal cancer (CRC), osteosarcoma, lung cancer, breast cancer (BC), prostate cancer, renal cell cancer (RCC) etc.

piRNA and PIWILs in HCC. HCC is one of the most common malignant tumors and among the top 5 cancers with the highest incidence and cancer-related deaths in China and worldwide, ~906,000 new cases and 830,000 deaths were reported worldwide in 2020 according to Global Cancer Statistics 2020 (33). In HCC, hundreds of piRNAs are differentially expressed according to small-RNA sequencing studies (34). Among which, piRNA-1/97 can promote the migration and metastasis of hepatoma cells (34) (Table II; Fig. 2). Several piRNAs including piR-Hep1 (30), piR-823 (35) and piR-651 (36) have been identified in the pathophysiology of HCC. piR-Hepl (30) is found to be upregulated in HCC tumors compared with

Table I. Classification of small non-coding RNA.

Classification	Length(nt)	Features
Small nucleolar RNAs	60-300	Biosynthesis of ribosomal RNA and guider of RNA modification
Small interfering RNAs	~21-22	Gene regulation, transposition and virus defense
microRNAs	~21-22	Transcriptional regulation
PIWI-interacting RNAs	~24-32	Gene silencing regulation; degradation of mRNA transcripts; maintenance of germline and stem cell function

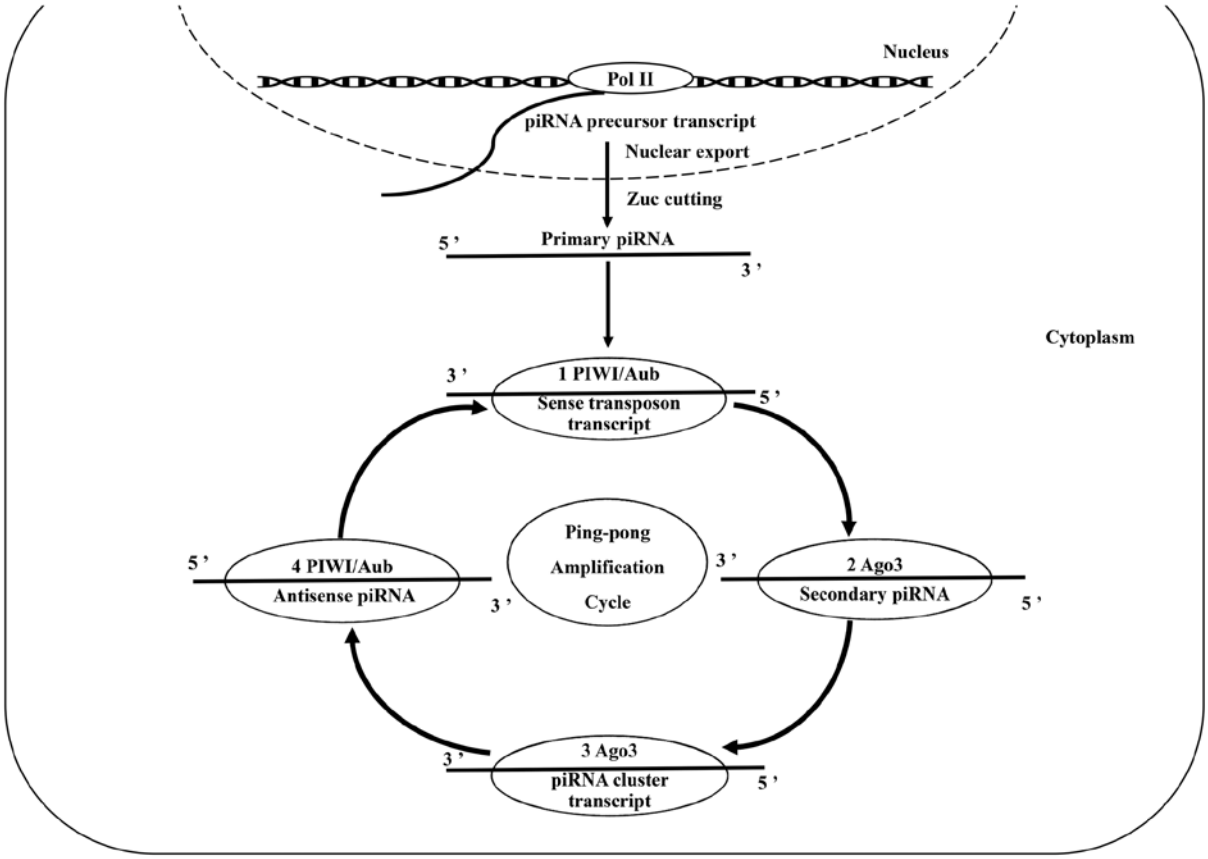

Figure 1. Ping-pong cycle pathway. Simultaneous production and the amplification of secondary piRNA; transposon mRNA is consumed as a substrate in large quantities resulting in suppression of transposition. piRNA, PIWI-interacting RNA; Pol, polymerase; Ago, Argonaut.

adjacent non-tumoral liver tissues and its silencing inhibits cell survival, motility and tumor invasiveness mainly through reducing the level of phosphorylated AKT (Table II; Fig. 2). In addition, the relative expression of PIWIL2 mRNA is higher in HCC tissues compared with adjacent normal liver tissues (37). A positive correlation was found between PIWIL2 expression and piR-Hep1 level according to Pearson's correlation analysis (30). PIWIL2 acts as an oncogene by activating the STAT3/Bcl-xl cell signaling pathway through endogenous RNAi mechanism, hence inhibiting cell apoptosis and promoting cell proliferation (31) (Table II; Fig. 2). AKT, the downstream target of the PIWIL2-activated signaling pathway, promotes the key carcinogenic pathway of liver cancer (30,31). Hence, the interaction between piR-Hep1 and PIWIL2 is crucial in the occurrence and development of tumors (30) (Table II). Rizzo *et al* (38) found the specific expression pattern of 24 piRNAs, including piR-823 in dysplastic nodules and HCC. The level of piR-823 is high during the progression from cirrhosis to low- and high-grade proliferative nodules in HCC and is upregulated in hepatic stellate cells (HSCs), which are responsible for liver fibrogenesis (35). piR-823 also activates HSCs and promotes extracellular matrix expression by binding with eukaryotic initiation factor 3B (EIF3B) and upregulating the expression of transforming growth factor β-1 (TGFβ-1) (35) (Table II; Fig. 2).

Given the crucial role of piRNA-1/97 in the migration and metastasis of liver cancer cells (34) (Table II; Fig. 2), further experimental studies may identify new pathways and molecular targets for the clinical diagnosis and treatment of HCC. The abnormal expression and involvement of piR-Hep1, PIWIL2, piRNA-1/97 and piR-823 in the occurrence of HCC (30,31,37) (Table II) and their close relationship with the

Table II. Summary of the abnormally expressed piRNA and PIWIL in cancers of digestive system.

Author(s), year	Cancer type	piRNA or PIWIL	Expression	Tumor promoter or suppressor	Molecular mechanisms	Possible applications	(Refs.)
Miao *et al*, 2018	HCC	piRNA1/97	Upregulated	Promoter	Promoted the migration and metastasis of hepatoma cells	Potential markers for monitoring metastasis	(34)
Law *et al*, 2013		piR-Hep1	Upregulated	Promoter	Promoted cell viability, motility and invasiveness by activating AKT signaling pathway	Potential diagnostic biomarker or therapeutic target	(30)
Lee *et al*, 2006		PIWIL2	Upregulated	Promoter	Acted as an oncogene by inhibition of apoptosis and promotion of proliferation via STAT3/Bcl-xl signaling pathway	Potential diagnostic biomarker or therapeutic target	(31)
Tang *et al*, 2018		piR-823	Upregulated	Promoter	Activated HSC and promoted ECM expression through binding with EIF3B and upregulation of TGF-β1 protein expression	Potential markers for monitoring the occurrence of HCC	(35)
Cheng *et al*, 2011		piR-651	Upregulated	Promoter	Acted as an oncogene diagnosis	Potential signs of cancer	(36)
Cheng *et al*, 2011	GC	piR-651	Upregulated	Promoter	Promoted cell cycle; associated with TNM stage	Diagnostic biomarkers or treatment target	(36)
Cheng *et al*, 2012		piR-823	Downregulated	Suppressor	Inhibited tumor growth in a dose-dependent manner	Diagnostic biomarkers or treatment target	(32)
Ge *et al*, 2020		piR-004918 and piR-019308 (serum exosomes)	Upregulated	-	Abnormal expression compared with unmetastatic GC	Potential markers for monitoring GC metastasis	(44)
Cheng *et al*, 2011	Colon cancer	piR-651	Upregulated	-	Acted as an oncogene	Diagnostic biomarkers	(36)
Vychytilova-Faltejskova *et al*, 2018		piR-5937 and piR-28876 (serum)	Downregulated	-	Abnormally low expression in the serum of patients	Prognostic molecular markers	(54)
Yin *et al*, 2017	CRC	piR-823	Upregulated	Promoter	Interacted with HSF-1 and increased phosphorylation of HSF-1 at Ser326	Diagnostic biomarkers or therapeutic target	(47)
Weng *et al*, 2018		piR-1245	Upregulated	Promoter	Promoted tumor progression by pi-RISC and its ability to repression of RNAs of several tumor suppressor genes including ATF3, BTG1, DUSP1, FAS, NFKBIA, UPP1, SESN2, TP53INP1 and MDX1	Prognostic molecular markers or therapeutic target	(48)

Table II. Continued.

Author(s), year	Cancer type	piRNA or PIWIL	Expression	Tumor promoter or suppressor	Molecular mechanisms	Possible applications	(Refs.)
Chu *et al*, 2015		piR-015551	Upregulated	-	Positively correlated with the expression level of lnc00964-3	Potential markers for monitoring development of CRC	(49)
Qu *et al*, 2019		piR-017724 (serum)	Downregulated	-	Associated with the poor overall survival and progression-free survival of patients	Prognostic molecular markers	(50)
Mai *et al*, 2018		piR-54265	Upregulated	Promoter	Promoted cell proliferation, metastasis and chemoresistance of CRC cells by binding to PIWIL2 and activation of the STAT3 signaling pathway	Prognostic molecular markers or therapeutic target	(51)
Tosar *et al*, 2021		piR-54265 (serum)	Upregulated	Promoter	Significantly elevated in serum of patients with primary and relapsed CRC	A valuable biomarker for CRC screening, early detection and clinical surveillance	(52)
Yin *et al*, 2019		piR-18849	Upregulated	Promoter	Positively correlated with lymph node metastasis potential and negatively correlated with tumor differentiation	Prognostic molecular markers	(53)
Yin *et al*, 2019		piR-19521	Upregulated	Promoter	Negatively correlated with the degree of tumor differentiation	Prognostic molecular markers	(53)
Wang *et al*, 2020		piR-020619 and piR-020450 (serum)	Upregulated	-	Abnormally high in the serum of patients with CRC	Early biomarkers of detection	(55)
Litwin *et al*, 2018		HIWI(PIWIL1)	Upregulated	-	Positively correlated with OCT4 mRNA levels	Prognostic molecular markers or treatment target	(56)
Litwin *et al*, 2018		HILI(PIWIL2)	Downregulated	-	Positively correlated with SOX2	Prognostic molecular markers or treatment target	(56)

HCC, hepatocellular carcinoma; HSC, hepatic stellate cell; ECM, extracellular matrix; EIF3B, eukaryotic initiation factor 3B; TGF-β1, transforming growth factor β1; GC, gastric cancer; TNM, tumor node metastasis; CRC, cololectal cancer; HSF-1, heat shock transcription factor-1; ATF3, activating transcription factor 3; BTG1, B-cell translocation gene 1; DUSP1, dual-specificity phosphatase-1; NFKBIA, nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α; UPP1, uridine phosphorylase1; SESN2, sestrin2, a highly conserved and stress-inducible protein; TP53INP1, tumor protein 53-induced nuclear protein 1; MDX1, MAX dimerization protein 1; Oct 4, a transcription factor of the POU protein family; SOX2, a marker of embryonic stem cell pluripotency; PIWIL, PIWI-like; -, not reported.

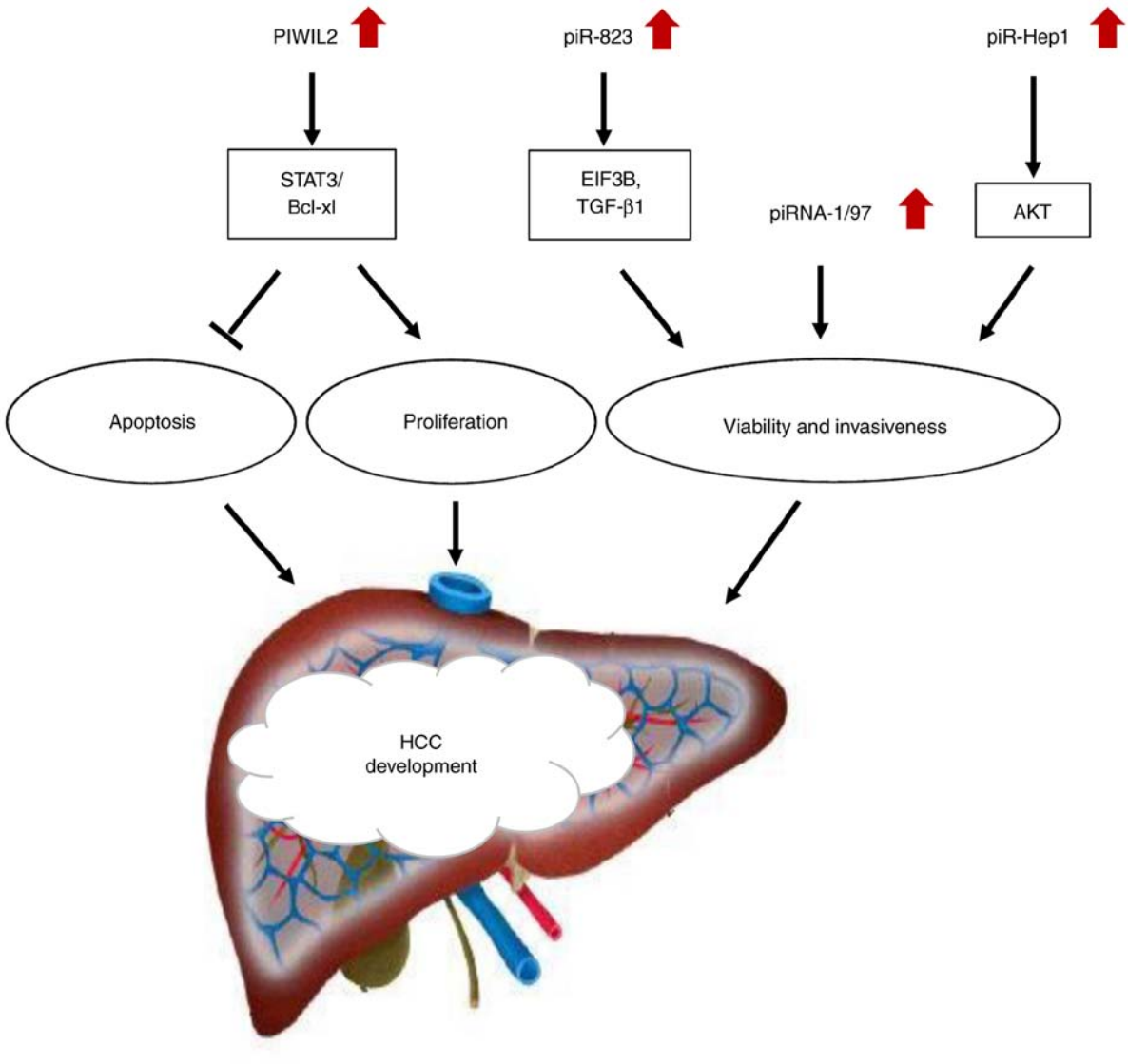

Figure 2. Abnormally expressed piRNAs in HCC and their mechanisms to promote tumor development. HCC, hepatocellular carcinoma; piRNA, PIWI-interacting RNA; TGF-β-1, transforming growth factor β-1; EIF3B, eukaryotic initiation factor 3B; PIWIL, PIWI-like.

key downstream carcinogenic pathway of HCC (Fig. 2) provide primary evidence for the implication of piRNAs/PIWIL in the clinical detection and treatment of liver cancer. Besides, abnormal piR-651 expression may be a potential indicator of the development and progression of HCC (36) and piR-823 accelerates oncogenic processes during HCC (38) (Table II). All the aforementioned studies suggest that piRNA/PIWIL may be potential markers for liver cancer detection.

piRNAs and GC. Although its incidence currently has a downward trend, GC is still the third leading cause of cancer-related deaths worldwide (39). In 2020, >1,000,000 new cases and an estimated 769,000 deaths were reported worldwide, with a substantial increase in Asian countries, such as Mongolia and Japan where the GC incidence is twice as high in men compared with women (33). GC is asymptomatic in the early stage. A number of patients are diagnosed at the middle or late stages of disease (39-42). piRNA expression is often closely related to the malignant degree of GC (40,41). In numerous GC cases, the expression levels of piRNAs in gastric carcinoma tissues are highly altered compared with those in normal gastric mucosa tissues (42).

piRNAs, such as piR-651 and piR-823 are differentially expressed in GC tissues (43). Among them, piR-651 is notably upregulated in several cancers including GC, CRC, lung cancer and BC and in cancer cell lines, such as HepG2 (liver cancer), HeLa (cervical cancer), BCAP-37 (BC), MSTO-211H (mesothelioma), NCI-H446 (lung cancer), MGC-803 and SGC-7901 (GC) (36). piR-651 inhibitor (antagonist) can inhibit cell cycle and growth in GC cells, including MGC-803 and SGC-7901 (36). In particular, piR-651 antagomir arrests MGC-803 cells in the G_2/M phase (36). The aforementioned studies suggested that piR-651 has an oncogenic role in development of GC (Table II). piR-823 is downregulated in GC tissues compared with non-cancerous tissues and its mimics can inhibit the growth of MGC-803 and SGC-7901 cells (32) (Table II). In addition, the levels of piR-651 and piR-823 in the circulation of patients with GC were lower compared with those in normal people (43). The positive detection rates of piR-651 (74.07%) and piR-823 (88.88%) are highly

sensitive (43) and therefore, can be used as biomarkers for GC diagnosis. Hence, the levels of piR-651 or piR-823 may be useful to detect GC incidence and therapeutic manipulation of these piRNAs could effectively inhibit the occurrence and development of GC.

The expression levels of piR-004918 and piR-019308 in the serum exosomes of patients with metastatic GC were significantly higher compared with patients with GC without metastasis (44). So, serum piR-004918 and piR-019308 could be used as potential markers to monitor GC metastasis (44) (Table II).

piRNAs and PIWILs in CRC and colon cancer. Early diagnosis of CRC is crucial for patient survival (45,46). Although the overall molecular mechanism of CRC has not been fully elucidated, piRNAs and PIWILs are crucial for the early diagnosis of this disease (45,46).

piR-651 expression is higher in colon cancer tissues compared with corresponding noncancerous normal tissues (36) (Table II). However, the role of piR-651 in the development of colon cancer remains largely unknown (36). piR-823 interacts with heat shock transcription factor-1 and increases its phosphorylation at Ser326, which in turn promotes its transcriptional activity and increases oncogene expression (47). The antagonist of piR-823 blocks the cell cycle at the G_1 phase and increases the apoptosis of CRC cells, such as HCT116 and DLD-1 (47) (Table II). These findings indicate that piR-823 may serve as a potential therapeutic target for CRC.

piR-1245 is also upregulated in CRC and its expression is associated with late-stage and metastatic CRC (48). However, an extremely high piR-1245 expression affects the prognosis of patients with CRC (48). Patients with a high expression of piR-1245 have shorter overall survival time compared with those with a low level of piR-1245 (48). Mechanistic studies found that a specific pi-RISC formed by piR-1245 induces tumor progression through its ability to repress the RNAs of several tumor suppressor genes including activating transcription factor 3, B-cell translocation gene 1, dual-specificity phosphatase-1, FAS, NFKBIA (encoding nuclear factor of κ-light polypeptide gene enhancer in B-cells inhibitor-α), uridine phosphorylase 1, sestrin2 (a highly conserved and stress-inducible protein), tumor protein 53-induced nuclear protein 1 and MAX dimerization protein 1, which are potential targets complementary to piR-1245 (48). In CRC, the expression levels of these targets are negatively associated with that of piR-1245 (48) (Table II). piR-1245 also exerts oncogenic function in CRC by promoting cell survival, migration and invasion and suppressing apoptosis (48). Hence, piR-1245 may be a potential diagnostic, prognostic, and/or therapeutic target for CRC.

piR-015551, generated from long non-coding RNA (lnc) 00964-3, is positively correlated with lnc00964-3 according to Pearson's correlation analysis and piR-015551 reduces the expression of lnc00964-3 in CRC tissues (49) (Table II). This finding suggests an interaction between lncRNAs and piRNAs during the development and progression of CRC.

A total of 5 piRNAs (piR-001311, piR-004153, piR-017723, piR-017724, and piR-020365) are differentially expressed in the circulation of patients with CRC (50). The reduction of serum level of piR-017724 is associated with patient survival rate and thus, may be an independent prognostic factor for CRC detection (50). However, further study is needed to increase its specificity (50) (Table II). In addition, piR-54265 expression is substantially higher in CRC and its expression level is associated with poor prognosis and poor overall survival time of patients (51,52). piR-54265 promotes CRC cell invasion and metastasis by binding to PIWIL2 and activating the STAT3 signaling pathway (51,52) (Table II). Thus, piRNA-54265 may be an oncogenic RNA in CRC and can be used as a therapeutic target.

In CRC tissues, piR-18849, piR-19521 and piR-17724 levels are increased (53). piR-18849 overexpression is positively correlated with lymph node metastasis potential, but negatively correlated with tumor differentiation degree, while piR-19521 expression is only negatively correlated with the degree of tumor differentiation according to Spearman's correlation analysis (53) (Table II). These findings revealed that targeting piR-18849 and piR-19521 may be effective in blocking the metastasis and differentiation of CRC. The differential expression of these piRNAs may be useful in CRC detection.

The serum levels of piR-5937 and piR-28876 may be applied to detect colon cancer with higher sensitivity and specificity compared with the biomarkers carcinoembryonic antigen and carbohydrate antigen 19-9 in patients with stage I colon cancer (54) (Table II). In addition, the combined monitoring of piR-020619 and piR-020450 can effectively distinguish colon cancer tissues from normal tissues and is highly specific for early colon cancer detection (55) (Table II).

Human PIWI proteins, such as HIWI (PIWIL1) and HILI (PIWIL2) act together in the occurrence of CRC (56). High HIWI and low HILI mRNA levels are detected in CRC tissues, which are positively correlated with CRC stem cell markers, OCT4 (a transcription factor of the POU protein family) and SOX2 (a marker of embryonic stem cell pluripotency), respectively, according to Spearman's correlation analysis (56). This finding suggests that the differential expression of HIWI, HILI and some cancer stem cell markers in CRC may have a prognostic value and could provide a new diagnostic and therapeutic approach for CRC treatment. This finding also indicates the complexity of CRC and provides new avenues for developing therapeutics against this disease.

piRNAs and osteosarcoma. Osteosarcoma is one of the most common primary osteoblastic tumors (bone tumors) and according to data from 1984-2013 in the SEER (Surveillance, Epidemiology and End Results) database of USA, the incidence of osteosarcoma between 0-29 years of age remained relatively stable for the past 30 years (57). The survival rate of osteosarcoma following surgery is only 15-20%, while its functional recovery after amputation is poor and its disability and metastasis rates are high (57,58). A total of 80-90% of patients with osteosarcoma die of distant metastasis, such as lung or bone metastases (58). Despite the unclear etiology and pathogenesis mechanisms of osteosarcoma, recent studies suggested that piRNAs serve an important role in the development of osteosarcoma (59).

piR-39980 overexpression with piR-39980 mimic in 2 human osteosarcoma cell lines (143B and HOS) promoted cell proliferation, migration and invasion via targeting serpin

family B member 1 (SERPINB1) and activating matrix metalloproteinase-2 (59). Inhibiting piRNA-39980 upregulated SERPINB1, promoted chromatin condensation and induced y-H2AX accumulation and cell death (59). This finding revealed that piRNAs can accelerate the metastatic potential of osteosarcoma by negatively regulating tumor suppressors, such as SERPINB1 (59) (Table III). Hence, piR-39980 may be a prognostic marker and therapeutic target for osteosarcoma.

piRNA and PIWILs in lung cancer. Lung cancer is one of the most common malignancies worldwide (33). With an estimated 2.2 million new cancer cases and 1.8 million new deaths, lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death in 2020 (33). piRNAs are associated with the progression of lung cancer (60-70).

In lung cancer, piRNAs, such as piR-010894-3 and piR-001168-4 are upregulated in non-smoking patients with lung tumors compared with patients who are smokers with lung tumors (60). These constitutive and differentially expressed piRNAs may be potential targets for improving the diagnosis and treatment of patients with lung cancer (60). A reduced piR-55490 expression is negatively correlated with patients' overall survival with lung cancer according to Spearman's correlation analysis (61). Restoring piR-55490 level inhibits the proliferation of lung cancer cells mainly by binding to the 3'-UTR of mTOR mRNA to induce its degradation and inactivate the mTOR/AKT pathway (61) (Table III).

Ras association domain family 1C (RASSF1C) is one of the two main subtypes of the RASSF1 gene, which has an anti-apoptotic effect and promotes cell proliferation in BC cells, such as breast cancer cell line T47D and lung cancer cells, such as A549 and NCI-H1299) (62,63). In stably overexpressing RASSF1C lung cancer cells, 4 piRNAs are differentially expressed (upregulated piR-34871 and piR-52200 and downregulated piR-35127 and piR-46545) (64). RASSF1C overexpression reduces p-AMPK, p21 and p27 protein levels, implying that RASSF1C mediates the regulation of piRNA expression by inhibiting the AMPK pathway and thereby modulating the level of its target genes (64). In tumor tissues, piR-35127 is negatively associated with RASSF1C (64). Silencing piR-34871 and piR-52200 or overexpressing piR-35127 and piR-46545 can block the proliferation of lung cancer cell lines (A549 and NCI-H1299) (64) (Table III), indicating that these piRNAs are involved in the regulation of lung cancer cells' transformation and tumorigenesis. In addition, RASSF1C promotes the expression of PIWIL1 through the MEK-ERK1/2 pathway and RASSF1C-PIWIL1 might be involved in the initiation and progression of lung cancer (65) (Table III). These studies revealed that RASSF1C is closely associated with piRNA- and PIWIL1-mediated oncogenic processes in lung cancer cells.

PIWIL1, a binding partner of piRNAs, is upregulated in lung adenocarcinoma and promotes the proliferation, invasion, and metastasis of lung adenocarcinoma cells (66). PIWIL1 expression is closely related to the shortened overall survival time of patients with lung adenocarcinoma (66) (Table III). Hence, the tumorigenic processes in patients with lung cancer can be determined by detecting the expression level of PIWIL1.

piR-651 is upregulated in numerous cancer tissues and cell lines including GC, osteosarcoma, lung cancer, HCC, GC and CRC (36,43,67). In a highly metastatic human lung cancer cell line named 95-D, piR-651 enhances the carcinogenic potential by promoting cell proliferation, migration, invasion and inhibiting apoptosis (67).

In non-small cell lung cancer (NSCLC), piR-651 promotes cell proliferation through the cyclin D1 and cyclin-dependent kinase 4 pathways (68) (Table III). Inhibiting piR-651 reduces cell proliferation and invasion and induces apoptosis in NSCLC (69) (Table III). These findings indicate that piR-651 may be a potential tool for the clinical diagnosis and treatment of lung cancer. The differential expression of piRNA/piRNA-L has been observed in NSCLC cell lines, such as H157, H226, H596, SK-MES-1, H522, H1437, H1792 and H1944 (70). piRNA/piRNA-L regulates lung carcinogenesis by directly interacting with proteins involved in the occurrence of lung tumors (70) and thus, may be a new tool for the diagnosis and treatment of lung cancer. However, potential applications of piRNAs in patients with lung cancer require further confirmation.

piRNAs and PIWILs in BC. BC has surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases and is the fifth leading cause of cancer mortality worldwide (33). piRNAs are involved in the occurrence of BC (71-81).

Compared with matched non-tumor tissues, a total of 4 piRNAs (piR-4987, piR-20365, piR-20485 and piR-20582) were upregulated in breast cancer tissues and the increased piR-4987 expression was substantially associated with lymph node metastasis (72) (Table III). The abnormal expression of these piRNAs and the association of piR-4987 with lymph node metastasis suggests their potential as important therapeutic targets for BC.

In BC cells, the expression levels of DQ596670, DQ598183, DQ597341, DQ598252, and DQ596311 are reduced, whereas those of DQ598677, DQ597960, and DQ570994 are increased (73). A search for mRNAs targeted by the BC piRNome revealed that these 8 piRNAs are involved in hormone signaling, cell transformation, growth inhibition, and/or cell cycle (73). These 8 piRNAs have specific expression patterns in breast tumors and target several key cancer cell pathways, such as Janus kinase-1, AKT3 etc. (73). These findings suggest that piRNAs may be a new class of primary regulators of BC development and may be useful for the detection of this disease.

The expression level of piR-651 and piR-823 are associated with hormone changes in gonadal development and BC (74). piR-651 and piR-823 overexpression promotes cell proliferation in BC and prostate cancer cell lines (74) (Table III). piRNAs, such as piR-021285 can epigenetically control cancer-related genes in BC cells (75). In MCF cells, piRNA-021285 alters the methylation status of several cancer-associated genes including the ARHGAP11A gene (75). piRNA-021285 inhibits the methylation of CpG sites at 5'-UTR of the first exon of ARHGAP11A mRNA, thus increasing ARHGAP11A level and the invasiveness of BC cells (75) (Table III). These studies reveal that these piRNAs regulate the expression of oncogenes in BC. Targeting piRNA-021285 may be therapeutically beneficial in BC treatment.

piR-36712 functions as a tumor suppressor and its low level is associated with poor clinical prognosis in patients

Table III. Summary of the abnormally expressed piRNA and PIWIL in other types of cancers.

Author(s), year	Cancer type	piRNA or PIWIL	Expression	Tumor promoter or suppressor	Molecular mechanisms	Possible applications	(Refs.)
Das *et al*, 2020	Osteosarcoma	piR-39980	Upregulated	Promoter	Promoted cell migration and invasion by negatively regulating tumor suppressors, such as SERPINB1	Potential diagnostic biomarker or therapeutic target	(59)
Peng *et al*, 2016	Lung cancer	piR-55490	Downregulated	Suppressor	Induced mTOR degradation by binding to the 3'-UTR of mTOR mRNA and resulted in inactivation of mTOR/AKT pathway	Potential diagnostic biomarker or therapeutic target	(61)
Reeves *et al*, 2017		piR-34871, piR-52200	Upregulated	Promoter	Promoted proliferation of lung cancer cell lines (A549 and H1299) by RASSF1C regulating piRNA expression and inhibiting the AMPK pathway	Potential mechanism molecules for future lung cancer research	(64)
Reeves *et al*, 2017		piR-35127, piR-46545	Downregulated	Suppressor	Blocked proliferation of lung cancer cell lines (A549 and H1299) by RASSF1C regulating piRNA expression and activating the AMPK pathway	Potential mechanism molecules for future lung cancer research	(64)
Reeves *et al*, 2012		PIWIL1	Upregulated	Promoter	Involved in the initiation and progression of lung cancer through the MEK-ERK1/2 pathway	Potential mechanism molecules for future lung cancer research	(65)
Xie *et al*, 2018	Lung adenocarcinoma	PIWIL1	Upregulated	Promoter	Promoted the proliferation, invasion and metastasis of lung adenocarcinoma cells	Potential markers for monitoring the development process	(66)
Li *et al*, 2016	NSCLC	piR-651	Upregulated	Promoter	Promoted cell proliferation through cyclin D1 and CDK4 pathways	Potential tool for the clinical diagnosis and treatment of NSCLC	(68)
Zhang *et al*, 2018		piR-651	Upregulated	Promoter	Promoted cell proliferation, migration and invasion and inhibited cell apoptosis	Potential biomarker for the clinical diagnosis and treatment of NSCLC	(69)
Huang *et al*, 2013	BC	piR-4987	Upregulated	Promoter	Associated with positive lymph nodes	Potential molecular targets	(72)
Huang *et al*, 2013		piR-20365, piR-20485, piR-20582	Upregulated	Promoter	Involved in the occurrence and development of breast cancer	Potential molecular targets	(72)
Oner *et al*, 2016		piR-651, piR-823	Upregulated	Promoter	Promoted malignant cell proliferation	Potential diagnostic biomarkers or therapeutic targets	(74)

Table III. Continued.

Author(s), year	Cancer type	piRNA or PIWIL	Expression	Tumor promoter or suppressor	Molecular mechanisms	Possible applications	(Refs.)
Fu *et al*, 2015		piR-021285	Upregulated	Promoter	Inhibited methylation of CpG sites at 5'-UTR of first exon of ARHGAP11A mRNA, which led to increased expression of ARHGAP11A and invasiveness of breast cancer cells	Potential diagnostic biomarkers or therapeutic targets	(75)
Maleki Dana P *et al*, 2020		piR-36712	Downregulated	Suppressor	Promotes the proliferation, invasion and migration of cancer cells; Downregulated piR-36712 which led to SEPW1 mediated suppression of P53, p21 and E-cadherin and upregulation of SLUG	Potential prognostic molecular markers	(77)
Lee *et al*, 2010		PIWIL2	Upregulated	Promoter	Promoted breast cancer cell survival by activating the STAT3/Bcl-xl pathway	Potential molecular target for the clinical prognostic treatment	(80)
Zhang *et al*, 2013		PIWIL2	Upregulated	Promoter	Acted as a positive modulator of EMT in breast cancer stem cells by methylating Latexin and suppressing its expression	Potential molecular target for the clinical treatment	(81)
Krishnan *et al*, 2016		PIWIL3	Upregulated	-	Related to overall survival periods and recurrence free survival periods	Potential independent prognostic marker	(78)
Heng *et al*, 2018		PIWIL4	Upregulated	Promoter	Triggered ER pathway by upregulating the canonical ER signaling molecules, such as Greb1, Tff1, Calcr and Ccnd1	New regulators and potential biological targets	(79)
Zuo *et al*, 2019	Prostate cancer	piR-000627, piR-005553, piR-019346	Upregulated	-	Associated with biochemical recurrence (BCR) of prostate cancer	Potential prognostic marker during treatment	(82)
Zhang *et al*, 2020		piR-001773, piR-017184	Downregulated	Suppressor	Bound to 3'-UTR site of PCDH9 and post-transcriptionally regulates PCDH9	Potential biological targets for future prostate cancer research	(83)
Chu *et al*, 2015	Bladder cancer	piRABC	Downregulated	Suppressor	Suppressed the development of bladder cancer by forming HIWI-piRABC complex and targeting 3'-UTR of tumor necrosis factor superfamily member 4 (TNFSF4) mRNA which increases cell death resistance	Potential mechanism molecules for future bladder cancer research	(84)
Ravo *et al*, 2015	Endometrial cancer	piR-020829, piR-019914, piR-016735	Upregulated	-	-	New biomarkers that can be used to study early endometrial cancer	(85)

Table III. Continued.

Author(s), year	Cancer type	piRNA or PIWIL	Expression	Tumor promoter or suppressor	Molecular mechanisms	Possible applications	(Refs.)
Ravo *et al*, 2015		piR-020496	Upregulated	Promoter	Targeted a transcriptional co-repressor known as TLE4 (Transduction-protein-like enhancers of fragment 4)	New biomarkers that can be used to study early endometrial cancer	(85)
Li *et al*, 2020	PDAC	PIWIL1	Upregulated	Promoter	Enhanced the metastatic potential of PDAC by functioning as a co-activator of anaphase-promoting complex/cyclosome (APC/C) E3 complex to facilitate the degradation of pinin	Potential target of PDAC	(86)
Lim *et al*, 2014	Ovarian cancer	PIWIL1	Upregulated	Suppressor	Reduced the aggression of SKOV3 (ovarian cancer cell lines)	Potential mechanism molecules for future ovarian cancer research	(87)
Busch *et al*, 2015	ccRCC	piR-30924, piR-38756	Upregulated	Promoter	Related to tumor recurrence and overall survival of clinical patients with ccRCC	Independent potential prognostic biomarker	(91)
Busch *et al*, 2015		piR-57125	Downregulated	Suppressor	Related to tumor recurrence and overall survival of clinical patients with ccRCC	Independent potential prognostic biomarker	(91)
Zhao *et al*, 2019		piR-34536, piR-51810	Downregulated	Suppressor	Found in ccRCC mitochondria	Potentially new prognostic biomarkers	(92)
Li *et al*, 2015		piR-32051, piR-39894, piR-43607	Upregulated	Promoter	Associated with metastasis	Potential mechanism molecules for future renal clear cell carcinoma research	(93)
Iliev *et al*, 2016	RCC	piR-823 (urine)	Upregulated	-	-	Potential diagnostic biomarker or therapeutic target for RCC	(94)
Stöhr *et al*, 2019		PIWI-like 1	-	Promoter	Associated with shorter cancer-specific survival	Potential indicators for the prognosis of patients with RCC	(96)

NSCLC, non-small cell lung cancer; BC, breast cancer; EMT, epithelial-mesenchymal transition; RASSF1C, Ras association domain family 1C; PCDH9, protocadherin family member 9; ER, estrogen receptor; TNFSF4, tumor necrosis factor superfamily member 4; Greb1, growth regulation by estrogen in breast cancer 1; Tff1, trefoil factor 1; Calcr, calcitonin receptor; Ccnd1, cyclin D1; TLE4, transduction-protein-like enhancers of fragment 4; PDAC, human pancreatic duct cancer; ccRCC, renal clear cell carcinoma; RCC, renal cell cancer; PIWIL, PIWI-like; -, not reported.

with BC. piRNA-36712 interacts with the RNAs generated by the pseudogene of SEPW1 (SEPW1P) and inhibits SEPW1 expression by competing with SEPW1P, microRNA-7 and microRNA-324 (77). In BC cells, downregulating piR-36712 leads to the SEPW1-mediated suppression of P53, p21 and E-cadherin and the upregulation of Snail family transcriptional repressor 2 (snail2 or SLUG) (77). This event promotes the proliferation, invasion, and migration of cancer cells (76,77) (Table III). Thus, by accelerating cancer development, SEPW1 may worsen the prognosis of patients with BC.

In addition to piRNAs, PIWI genes are promising prognostic markers for BC (78). In breast tumor tissues, PIWIL1 and PIWIL3 are upregulated, whereas PIWIL2 and PIWIL4 are downregulated. A total of 2 piRNAs (piR-009051 and piR-021032) and PIWIL3 in tumor tissues were found to be important for overall survival and recurrence free survival periods in patients with BC (78). A multivariate analysis confirmed that PIWIL3 is a potential independent prognostic marker for BC (78). Given that the PIWIL proteins are involved in piRNA biogenesis and the abnormal expression of these genes in BC could lead to abnormal piRNA expression, these proteins may be potential candidates for the prognosis of BC (78) (Table III). In human BC cells, the expression level of PIWIL4 is relatively high as it is required for cell growth, migration, and invasion (79) (Table III). Given that estrogen receptor (ER) signaling is involved in BC growth, an interaction occurs between PIWIL4 and ER signaling pathway (79). PIWIL4 expression can be induced by ER signaling, and PIWIL4 triggers ER pathway by upregulating the canonical ER signaling molecules, such as growth regulation by estrogen in breast cancer 1, trefoil factor 1, calcitonin receptor, and cyclin D1 (79). These findings suggest that PIWIL4 is a novel modulator of ER-dependent BC growth and targeting this protein can inhibit the growth and migration of these cancer cells (79) (Table III).

PIWIL2 is also abnormally expressed in BC cells and promotes cell survival by activating the STAT3/Bcl-xl pathway (80) (Table III). PIWIL2 specifically recognizes the 3' terminus of piR-932 and forms pi-RISC, which acts as a positive modulator of epithelial-mesenchymal transition in BC stem cells by methylating latexin and suppressing its expression (81) (Table III). All these studies reveal that the differentially expressed PIWIL genes in BC potentially influence the tumorigenic processes and thus, can be used as targets for the diagnosis and treatment of this disease.

piRNAs and prostate cancer. piRNAs serve an important role in numerous types of cancer such as BC, lung cancer, prostate cancer, etc. (61,72,82). In prostate cancer, the expression of certain piRNAs is associated with the biochemical recurrence (BCR) of prostate cancer and thus can be used to distinguish high-risk BCR patients from low-risk patients (82). A total of 3 piRNAs (hsa-piR-000627, hsa-piR-005553 and hsa-piR-019346) are associated with prostate cancer BCR (82). Among them, hsa-piR-000627 and hsa-piR-005553 have 343 common targeting genes, 2 of which are mainly related to nucleoplasm and intracellular transport (82) (Table III). These studies reveal that piRNAs regulate oncogenic processes during prostate cancer development.

PCDH9 (member 9 of the protocadherin family) is a tumor suppressor that is downregulated in prostate cancer and is a potential target of a number of piRNAs including piR-001773 and piR-017184. piR-001773/piR-017184 can directly bind to the 3'-UTR sites of PCDH9 and post-transcriptionally regulate the expression of PCDH9. The downregulation of piR-001773 and piR-017184 inhibits tumor growth *in vitro* and *in vivo* (83) (Table III). Given that piR-001773 and piR-017184 target PCDH9, therapeutically suppressing these piRNAs may block tumor growth in the prostate.

The targeted relationship between piRNA and tumor suppressors provides important clues for prostate cancer mechanisms and lays an important foundation for future prognosis monitoring and therapeutical strategies of prostate cancer (82,83).

piRNAs and bladder cancer. In bladder cancer, DQ585569 is highly upregulated and DQ594040 (piRABC) is downregulated. piRABC serves a tumor-suppressive function by regulating cell proliferation, colony formation and apoptosis in bladder cancer (84). piRABC can also suppress the development of bladder cancer by forming the HIWI-piRABC complex and targeting the 3'-UTR of tumor necrosis factor superfamily member 4 mRNA, which increases cell death resistance (84) (Table III).

piRNAs and endometrial cancer. Expression levels of has-piR-020829, hsa-piR-019914, and hsa-piR-016735 are increased in endometrial carcinoma and piR-020496 participates in endometrial cancer by targeting a transcriptional co-repressor known as transduction-protein-like enhancers of fragment 4 (85) (Table III). Hence, these newly identified piRNAs may be used as novel biomarkers for the early detection of endometrial cancer.

PIWIL and pancreatic duct cancer (PDAC). Without piRNA ligand, PIWIL1 activates anaphase by functioning as a co-activator of APC/C E3 complex in human PDAC (86). These complexes target and facilitate the degradation of pinin, a key cell adhesion-related protein and enhance the metastatic potential of PDAC (86) (Table III). This phenomenon is opposite to the APC/C-mediated removal of PIWIL1 during spermatogenesis (86). Hence, PIWILs could also function as co-activator in malignant cells and PIWIL1 has an oncogenic function in PDAC.

PIWIL and ovarian cancer. Abnormal expression of piRNA pathway genes, such as PIWIL1 is accompanied by the upregulation of Maelstrom, a known testis cancer gene in epithelial ovarian cancer and benign ovarian tumors (87). However, their expression reduces the aggressiveness and invasive potential of ovarian cancer cell line SKOV3 (87) (Table III). This study reveals that PIWIL has a differential function in ovarian cancer depending on the types of cells and tissues surrounding the cancer cells.

piRNAs and PIWILs in RCC. RCC is one of the deadliest malignancies of the urinary system and represented 2.4% of all adult malignancies worldwide in 2012 (88). Early detection of kidney cancer is difficult due to its asymptomatic

nature and setting the early diagnostic markers and treatment in patients with RCC remains challenging (89,90). piRNAs, PIWIs and PIWILs serve important roles in the pathogenesis of RCC (91-96).

The most common pathological and histological subtype of RCC is renal clear cell carcinoma (ccRCC), which accounts for ~70-80% of RCC cases (91). Numerous piRNAs including piR-30924, piR-57125 and piR-38756 are abnormally expressed in primary non-metastatic and metastatic ccRCC tissues (91). Metastatic primary tumors have higher expression of piR-30924 and piR-38756 and lower piR-57125 expression compared with non-metastatic tumors (91). Hence, piR-30924 and piR-57125 can be independent potential prognostic biomarkers (91) (Table III). In addition, all these piRNAs are associated with tumor recurrence and overall survival time and are likely to improve prognostic information in patients with ccRCC (92). A total of 2 mitochondrial-derived piRNAs, namely piR-34536 and piR-51810, have downregulated expression in ccRCC tissues, but not in the serum (92). Hence, their levels could serve as independent predictive markers to detect ccRCC progression, cancer specificity and overall survival span of patients with ccRCC, thus providing new ways to optimize individualized treatment specific to RCC stages and ultimately improve patient survival (92) (Table III). In addition, the abnormal expression levels of piR-32051, piR-39894, and piR-43607 originating from the same piRNA cluster on chromosome 17 are highly associated with ccRCC metastasis (93) (Table III). In serum and urine, piR-823 expression is high in patients with RCC and its level is positively associated with adverse cancer outcomes (94). Hence, urinary piR-823 may have an important diagnostic value in patients with RCC (94) (Table III).

PIWIL1, PIWIL2, and PIWIL4 are downregulated in RCC and their levels are associated with the clinical stage of tumor and associated with poor survival in patients with RCC (95). These studies indicate that PIWIL1, PIWIL2, and PIWIL4 may be useful prognostic biomarkers in patients with RCC; however, due to their complex functioning mechanisms, further confirmation studies are required (95). In addition, PIWI-like proteins serve an important role in the pathogenesis of RCC (96). PIWI-like 1 expression is associated with tumor staging and distant metastasis. The positivity of PIWI-like 1 is associated with shorter cancer-specific survival. Hence, the role and expression levels of PIWI-like proteins render them as potential prognostic markers in patients with RCC (96) (Table III).

4. Conclusion and future perspective

Knowledge about PIWIL and piRNA-associated pathways and their biological functions has progressively increased (15-28). Despite their highly altered levels in numerous types of cancer, such as liver cancer, GC, CRC, osteosarcoma, BC, lung cancer, prostate cancer, etc, the mechanisms of PIWIL/piRNAs dependent regulation of cancer development are largely unknown (44,50,54,55,85,94). The differential expression of piRNAs in an organ-specific manner in cancer tissues highlights that PIWIL/piRNAs may be useful in specific diagnosis, prognosis, and molecular targeted therapy based on the specific type and stage of cancer (34-36,48-53,80-85). Therapeutic manipulation for some piRNAs can block/halt tumor progression. For example, the antagonists of piRNAs such as piR-651 (36) and piR-823 (47) (Table II) can inhibit cell cycle progression and thereby increase tumor apoptosis and suppress tumor growth. Similarly, PIWIL2 inhibits tumor apoptosis and promotes cell proliferation by activating the STAT3/Bcl-xl cell signaling pathway (36,80) (Tables II and III). piR-651 promotes tumor cell proliferation through the cyclin D1 and cyclin-dependent 4 pathways (68) (Table III). Inhibiting PIWIL2 and piRNA-651 using siRNA/antagonists effectively attenuates cancer cell growth (36,80). In addition, pi-RISC formed by piRNA accelerates oncogenic processes by inhibiting the expression of multiple tumor-suppressive genes (48) (Table II). piRNA-021285 induces the methylation of cancer-associated genes in BC cells. In particular, piR-021285 can modulate the invasiveness of BC cells by methylating CpG sites at the first exon of 5'-UTR on ARHGAP11A mRNA (75). However, the variation of SNPs in piR-021285 leads to the increased expression of ARHGAP11A and the enhancement of migration and invasion of breast tumor cells (75) (Table II). Similarly, piR-55490 binding to 3'-UTR of mTOR mRNA induces the degradation and inactivation of the mTOR/AKT pathway, thus suppressing lung cancer cell proliferation (61) (Table III). In addition, the oncogenic piRNAs, piR-001773 and piR-017184 inhibit the expression of a tumor suppressor PCDH9 in prostate cancer (83). piR-001773 and piR-017184 mediate the post-transcriptional suppression of PCDH9 to accelerate prostate tumor growth (83) (Table III). In contrast, oncogenic genes such as RASSF1C can regulate the expression of piRNAs including piR-35127 by inhibiting the AMPK pathway, which participates in cancer progression (64) (Table III). RASSFIC promotes PIWIL1 expression through the MEK-ERK1/2 pathway, which participates in lung cancer development (65) (Table III). Although the functions of PIWIL/piRNAs and associated pathways in various forms of cancer are largely unknown, currently available reports provide a vital clue that piRNAs and PIWIL are important contributors to the development and regulation of various cancers. Interestingly, PIWILs and numerous piRNAs have malignant cell type- and tumor-specific functions, implying that they could be efficient markers and effective/promising targets for the treatment of a particular type of cancer.

piRNAs are abnormally expressed in tumors and may represent potentially relevant tumor biomarkers (30-32,34,35). This article reviews the importance of piRNAs in tumorigenesis, proliferation, migration and metastasis of various tumors (30,34). However, mechanisms for abnormal piRNAs/PIWI expression in various cancers have not been clarified in most studies and applications of piRNAs/PIWI in targeted therapy are only mentioned in a few studies (47,53,83).

An in-depth understanding of the carcinogenic/tumor suppressive mechanisms of PIWIL/piRNAs would provide a new avenue in the therapeutic approach for cancer diagnosis and treatment. The present review will provide new research ideas for future piRNAs/PIWI research and more research will reveal in detail the specific mechanisms between piRNAs and cancer and their potential as cancer biomarkers and therapeutic agents.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

CY and HQ wrote the manuscript. YC and MP were responsible for figures and tables. ZL designed and edited the manuscript. MP edited the tables and critically revised the manuscript. Data authentication is not applicable. All authors have read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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