Histol Histopathol (2021) 36: 807-816

http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW **Open Access**

The function and regulation mechanism of piRNAs in human cancers

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Summary. Piwi-interacting RNAs (piRNAs) are mainly expressed in mammalian germ cells, playing an important role in maintaining germtable line DNA integrity, inhibiting transposon transcription and translation, participating in heterochromatin formation, epigenetic regulation, and germ cell genesis. They combine with P-element induced wimpy testis (PIWI) proteins to form effector complexes known as piRNA-induced silencing complexes (pi-RISC) to regulate the gene silencing pathway. Recent evidence suggests that numerous piRNAs, with tumor-promoting and tumor-suppressing functions in cancer development, are dysregulated in tumor tissues, and are related to clinical prognosis. In the present review, we summarize the current state of knowledge on the function and regulatory mechanisms of piRNAs in the tumorigenesis and progression of cancer, providing evidence for the potential use of piRNAs in the diagnosis and clinical treatment of cancer.

Key words: PIWI protein, PIWI-interacting RNA, piRNA clusters, Posttranscriptional gene silencing, Genome defense, Neoplasm

Introduction

Piwi-interacting RNAs (piRNAs) are a class of small non-coding regulatory RNAs mainly found in mammalian germline stem cells. Mature piRNAs are about 26-32 nt in length. In contrast to the production mechanism of small interfering RNAs (siRNAs) and microRNAs (miRNAs), piRNAs are not synthesized from a dsRNA precursor. They are produced from the initial transcripts of clustered piRNA, followed by the formation of mature piRNAs (Simon et al., 2011). PiRNAs specifically interact with PIWI subfamily proteins, and regulate the gene silencing pathway by binding to PIWI subfamily proteins to form a piRNA complex (piRC), which plays an important role in silencing gene transcription, maintaining germline and stem cell function, and regulating translation and mRNA stability (Izumi et al., 2016). Increasing numbers of studies have shown that the expression of piRNAs is dysregulated in various cancers (Siddiqi and Matushansky, 2012). The high expression of PIWI also leads to increased tumor growth and development in stomach, endometrium, gastrointestinal tract, and breast cancer cells (Lee et al., 2010; Cheng et al., 2011, 2012).

P-element induced wimpy testis (PIWI) proteins belong to the Argonaute family, members of which are highly conserved among species and play a central role in small non-coding RNA regulation pathways. The PIWI subfamily proteins include four subtypes of Piwi, like RNA-mediated gene silencing 1 (PIWIL1)/HIWI, PIWIL2/HILI, PIWIL3, and PIWIL4/HIWI2 in humans (Sasaki et al., 2003; Gunawardane et al., 2007; Tan et al., 2015; Kim, 2019). The function of PIWI is mainly realized by interactions with Piwi-interacting RNAs (piRNAs).

This review focuses on the function and the possible regulatory mechanisms of piRNAs in human tumors.

The molecular mechanisms of piRNAs

Generation and modification of piRNAs

Previous studies analyzed piRNA sequences of Drosophila, mice, and other species, and speculated that piRNAs might be produced in two ways: the primary processing pathway and the Ping-Pong amplification loop (Gunawardane et al., 2007; Han et al., 2015; Mohn et al., 2015). There is evidence that most piRNA sequences correspond to smaller genomic regions, which

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DOI: 10.14670/HH-18-323

are called piRNA clusters (Aravin et al., 2006; Girard et al., 2006). Each piRNA cluster can generate multiple sequences of a piRNA. These piRNA clusters are transcribed to produce long single-stranded piRNA precursors. The long single-stranded RNA precursors, or two non-overlapping reverse transcriptional precursors formed by piRNA clusters, are independent of Dicer, and their 5' ends are uracil biased, while the 3' ends are characterized by 2'-O-methylation (2'-O-Me) structure catalyzed by miRNA methyltransferase (Kawaoka et al., 2011; Simon et al., 2011). Studies have shown that the single strand specific endonuclease Zuc (Zucchini or MitoPLD) is involved in the processing and maturation of the 5' end of primary piRNAs (Nishimasu et al., 2012; Mohn et al., 2015; Izumi et al., 2016, 2020). Formation of piRNA 3' ends is poorly understood. A team from the University of Tokyo in Japan identified an enzyme called Trimmer. Trimmer does not work alone, but requires the combination of Papi-, a PIWI-related protein, to cut the 3' end of pre piRNAs. Furthermore, they confirmed that shearing the 3' ends of these pre-piRNA plays an important role in the function of piRNA, and might occur on the surface of the mitochondria. The 3' end of a piRNA is also modified by 2'-O-Me, which might protect it from degradation by exonucleases. In addition, the 3' ends of small RNA molecules modified by 2'-O-Me are more likely to be recognized and bound by the PAZ domain of PIWI proteins (Izumi et al., 2016).

piRNA pathway inhibits transposon expression

Transposons are DNA sequences that can be replicated and shifted on chromosomal DNA, which can "jump" from one position of the genome to another (Leslie, 2013). They can insert themselves into other sites of the genome by jumping frequently, thus changing the structure and expression of genes, which is of great significance to species evolution. PiRNAs and PIWI proteins constitute the core of the piRNA pathway. In gonadal cells, this conserved pathway is essential for genomic defense, and its main function is to silence transposons, to maintain the stability and integrity of the germ cell genome. This is achieved through post-transcriptional and transcriptional gene silencing (Czech et al., 2018). The PIWI-piRNA pathway depends on the specificity provided by the piRNA sequence that uses base pairing complementarity to recognize its RNA target, while the PIWI protein plays an effector role (Tolia and Joshua-Tor, 2007; Rouget et al., 2010; Gou et al., 2015; Shen et al., 2018a). The PIWI-piRNA complex silences its target genes at the transcriptional and post-transcriptional levels. Gene silencing at the transcriptional level is usually achieved by suppressing chromatin modification and *de novo* DNA methylation at the target site of the genome. Post transcriptional gene silencing usually occurs through the cleavage of target mRNA by the endonuclease activity of PIWI (Kuramochi-Miyagawa et al., 2008; De Fazio et al., 2011; Ashe et al., 2012; Shirayama et al., 2012; Di Giacomo et al., 2013; Toth et al., 2016; Kim et al., 2019). In Drosophila germline cells, piRNAs silence transposable elements and maintain genomic stability by interacting with members of the PIWI protein family, which may play a major role in inhibiting transposable elements at the epigenetic level. In mouse male germ cells, MIWI2 and MILI proteins mainly bind to transposons, retrotransposons, and other pre-pachytene piRNAs, thereby inhibiting transposon activity at epigenetic and post-transcriptional levels, which maintains the normal development and differentiation of spermatogenic cells. Studies have shown that the PIWI-piRNA pathway in mice also acts as a silent transposable element at the epigenetic level (Kuramochi-Miyagawa et al., 2008; Guzzardo et al., 2013).

piRNA and the regulation of gene expression

Experimental evidence shows that in addition to acting on mobile genetic elements such as silencing transposons, piRNAs can also exert their biological function by regulating the expression of protein-coding genes. In the cytoplasm, PIWI can cleave the transposon RNA that is complementary to a piRNA, dependent on its splicing enzyme activity, which leads to transposon gene post-transcriptional silencing, which is related to piRNA biosynthesis (Iwasaki et al., 2015). For example, mutations in MILI and MIWI proteins in mice can reduce the level of mature piRNAs. In addition, PIWI and piRNA can bind to polysomes and participate in the control of gene translation. At the same time, MIWI can bind to eukaryotic translation initiation factor 4e, and MILI can form a complex with eukaryotic translation initiation factor 3 subunit A (EIF3A) and participates in the regulation of protein synthesis (Girard et al., 2006; Rouget et al., 2010). In the nucleus, PIWI can be used as an epigenetic regulator to regulate gene expression. In Drosophila, Piwi can guide a piRNA to recognize the transposon sequence that binds to it, and then recruits the heterochromatin protein 1a dimer (HP1a), or other epigenetic modification factors such as histone methylase. In this process, Piwi can directly interact with HP1a without its shearing enzyme activity, which leads to epigenetic modification of the transposon gene and its adjacent genes. In mice, the MILI and MIWI proteins are enriched in the nucleus and can form complexes with piRNAs, which can cause *de novo* methylation of the transposon gene, eventually leading to the formation of heterochromatin, which transcriptionally inhibits the transposon gene and its adjacent genes, i.e., epigenetic modification rather than post-transcriptional silencing (Kuramochi-Miyagawa et al., 2008).

piRNA and sperm development

PIWI is mainly expressed in germline stem cells in different species. The piRNA induced silencing complex leads to homologous transposon gene silencing, which

protects the stability and integrity of the genome of reproductive stem cells, and plays an important role in the self-renewal of germ cells and the development of gametes and embryos (Cox et al., 2000; Lingel et al., 2004). In mice, MILI and MIWI are expressed at different stages of sperm development. MILI is expressed in spermatogonia and round sperm cells, whereas MIWI is expressed during the formation of long spermatocytes from pachytene spermatocytes. MILI is mainly related to self renewal and meiosis of germ stem cells, while MIWI is related to the regulation of spermatocyte differentiation (Unhavaithaya et al., 2009). In humans, HIWI is specifically expressed in testicular tissue, and its overexpression is related to the formation of a seminoma, which is a kind of tumor that mainly originates from malignant primitive reproductive stem cells, thus fully illustrating the different functions of PIWI proteins in germline stem cells.

Liu Mofang's group found that in mouse elongated spermatozoa, the pachytene piRNA, its binding protein MIWI and deadenylate enzyme CAF1 form the pi-RISC complex. The sequence elements of target mRNA 3' untranslated regions are identified by base incomplete pairing, and target mRNA deadenylation and degradation are induced. Depending on the different sequences of millions of piRNAs, pi-RISC mediates the degradation of thousands of different mRNAs in the later stage of sperm cell development. This research not only identified the molecular mechanism of large-scale degradation of mRNA in the late stage of spermatogenesis, but also revealed the important function of pachytene piRNAs in sperm development, proving that piRNAs are involved in the regulation of coding genes in addition to silencing transposons (Unhavaithaya et al., 2009).

PiRNAs and ovarian germline stem cell

PiRNAs in female Drosophila has biological functions such as ensuring normal fertility of female Drosophila, preventing DNA damage, ensuring the formation and release of normal eggs, and ensuring the normal adhesion between germ cells and somatic cells in the ovary (Akkouche et al., 2017). Sexually mature female Drosophila can produce piRNAs targeting Parasitic-DNA, transposons released by Parasitic-DNA fall into piRNA clusters, and piRNA clusters produce reverse piRNAs to regulate Parasitic-DNA, to prevent jumping and ensure the formation and release of normal eggs (Leslie, 2013). In mice, studies have shown that piRNAs play an important role in mammalian oogenesis. Astrin protein paticipates in mouse oocyte mitosis and meiosis, and especially plays a key role in spindle assembly and maturation during oocyte meiosis. PiRNAs can cause Astrin function loss, and lead to oocyte spindle disintegration (Yuan et al., 2009). In human, the piRNAs of human fetal ovary can mediate cleavage. Gametocyte-specific factor 1(GTSF1) is an important factor in retrotransposon silencing in the piRNA pathway. Researchers found that GTSF1 was highly expressed in oocytes during sexual maturation and gestation, suggesting the existence of piRNAs in female gametes and silencing retrotransposons during gamete development (Huntriss et al., 2017). The above research shows that piRNAs promote the normal development and release of oocytes, the normal adhesion of ovarian germ cells and somatic cells, and ensure normal fertility in female animals.

PiRNAs and stemness features

PiRNAs have recognized functions in stemness, in primitive animals with high regeneration ability, and in germline and somatic stem cells in other animals (Rojas-Rios and Simonelig, 2018). PIWI can also be expressed outside germline cells, mainly in stem cells and progenitor cells. This was observed in human hematopoietic stem cells, mouse mesenchymal stem cells (MSCs), and somatic stem cells in cnidarians. Hydra is a simple multicellular organism that belongs to the cnidarians. It was reported that Hydra PIWI proteins accumulate in the cytoplasm of stem/progenitor cells, which are essential for these animals. These data reveal the important function of PIWI beyond transposon silencing and strongly suggest that the main function of PIWI-piRNA pathway in Hydra stem cells is post transcriptional regulation. PIWI expression in stem cells and/or progenitor cells indicates that PIWI plays an important role in stem cell regulation. A study provided a comprehensive analysis of PIWI proteins and piRNAs in cnidarians and strongly suggested that the PIWI-piRNA pathway has ancient conserved stem cell functions beyond the germline (Juliano et al., 2014).

The function of piRNAs in cancer

There is a lack of PIWI expression in normal tissues, while in tumor cells, PIWI often shows abnormally high expression. This results in tumor stem cells having abnormal epigenetic characteristics, which is beneficial to tumor formation (Chen et al., 2007). The expression of piRNAs is dysregulated in various cancers, such as human papillary thyroid cancer (Liu et al., 2019), ovarian cancer, kidney cancer, and colorectal cancer (Lee et al., 2010; Siddiqi and Matushansky, 2012; Li et al., 2015; Yin et al., 2017; Mai et al., 2018; Singh et al., 2018). In endometrial, gastrointestinal tract, and breast cancer cells, high expression of PIWI also leads to increased tumor growth and development compared with that of normal cells (Lee et al., 2010; Cheng et al., 2011; Cheng et al., 2012; Han et al., 2017) . Here, we detail the roles of piRNAs and PIWI in several common cancers (Figs. 1, 2).

PiRNAs in gastric cancer

Using piRNA microarray analysis, piR-651 was observed to be highly expressed in gastric cancer tissues

compared with that in adjacent normal tissues, and the downregulation of piR-651 was able to inhibit the proliferation of tumor cells (Cheng et al., 2011; Cui et al., 2011), thus it is suggested that piR-651 might be involved in gastric cancer development. PIWIL1 is overexpressed in gastric cancer cells, which correlates with poor prognosis of patients with gastric cancer. In PIWIL1 knockout gastric cells, the expression levels of most oncogenes were decreased and those of tumor suppressor genes were increased (Wang et al., 2012; Araujo et al., 2018; Gao et al., 2018). This suggested that PIWIL1 is involved in gastric cancer tumorigenesis and progression by regulating the expression of oncogenes and anti-oncogenes. However, the specific mechanism of piR-651's involvement in gastric cancer invasion and metastasis remains unclear.

Cheng et al. found that compared with non-cancer tissues, piR-823 expression in gastric cancer tissues was significantly lower. In addition, piR-823 overexpression in gastric cancer cells might inhibit their growth *in vivo* and *in vitro*. This suggested that piR-823 is an attractive therapeutic target for gastric cancer. The abnormal expression of piRNAs in gastric cancer provides a good prospect for future research (Cheng et al., 2012).

PiRNAs in lung cancer

Cheng et al. found that piR-651 is overexpressed in liver cancer, lung cancer, colon cancer, stomach cancer, breast cancer, and gastric cancer cell lines (Cheng et al., 2011). The high expression of piR-651 in non-small cell lung cancer cell lines was also confirmed by Yao et al. They found that downregulation of piR-651 inhibited the migration of lung cancer cells and increased cell apoptosis (Yao et al., 2016). Another study showed that piR-651 regulates cell proliferation and metastasis by inducing cyclinD-1 and CDK4 expression (Li et al., 2016). Ras association domain family member 1 (RASSF1C) was observed to upregulate piR-34871 and piR 52200, downregulate piR-35127 and piR-46545, and promote lung cancer cell proliferation and epithelial-mesenchymal transition (EMT) (Reeves et al., 2017). Peng et al. found that the expression of piR-55490 in lung cancer tissue was lower than that in normal lung tissue. Overexpression of piR-55490 inhibited cell proliferation, whereas silencing of piR-55490 led to proliferation *in vitro* and *in vivo*. The inhibition of piR-55490 could promote lung cancer cell proliferation by inhibiting the activation of the mammalian target of rapamycin (mTOR) pathway. This suggested that piR-55490 plays an anti-cancer role in the occurrence and development of lung cancer (Peng et al., 2016).

PiRNA in breast cancer

It has been reported that piRNAs play an important role in the occurrence of breast cancer. In breast cancer

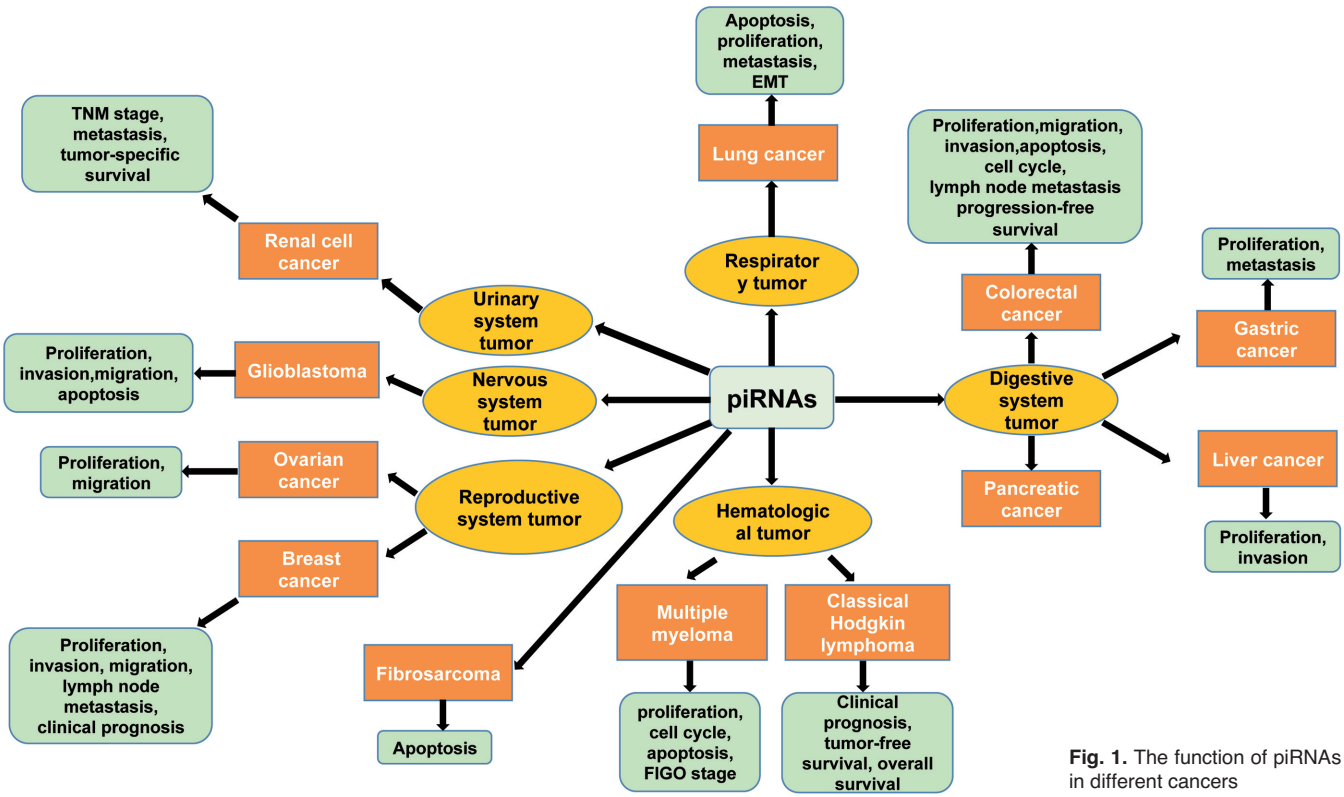

Fig. 1. The function of piRNAs in different cancers

cells, piR-651 is overexpressed (Cheng et al., 2011). In addition, the expression level of piR-4987 is related to lymph node metastasis (Huang et al., 2013). It was found that compared with normal breast tissues, the level of piRNA-36712 was significantly lower in breast cancer tissues, and was related to poor clinical prognosis. Other studies showed that piRNA-36712 interacts with RNA produced by *SEPW1P*, a reverse transcriptional pseudogene of *SEPW1* (encoding Selenoprotein W), which might function as a long non-coding RNA to regulate its protein-coding counterpart (SEPW1) by acting as a competitive endogenous RNA (ceRNA). Higher expression of piRNA-36712 in breast cancer might lead to the inhibition of SEPW1, increased P53, P21, and E-cadherin levels, and the promotion of cancer cell proliferation, invasion, and migration. Moreover, increased piR-36712 levels played synergistic roles with doxorubicin and paclitaxel in inhibiting the cell proliferation, invasion, and migration. The above-mentioned studies suggest that piRNAs are involved in breast cancer. However, their detailed role in breast cancer remains to be examined (Wu et al., 2017; Tan et al., 2019).

PiRNA in colorectal cancer (CRC)

In CRC, piR-1245 plays a tumor-promoting role, in which its high expression promotes the growth of CRC cells, cell migration, and invasion, and inhibits cell apoptosis. It binds to the intron regions of the targeted mRNA and participates in key tumor inhibition pathways. In CRC, the expression of piR-1245 was markedly increased in the cases of poor differentiation, T stage, lymph node metastasis, and distant metastasis (Weng et al., 2018). Another study showed that piR-54265 expression was increased in CRC tissues. The formation of PIWIL2/STAT3/p-SRC complexes promoted CRC cell proliferation and metastasis, in which STAT3 was activated by p-SRC phosphorylation, and then the expression levels of BCL-XL, MMP2 and MMP9 was upregulated. In addition, high piR-54265 levels correlated with shorter progression-free survival (Mai et al., 2018). Furthermore, piR-823 can upregulate the proliferation of CRC cells and inhibit apoptosis in CRC tissues. PiR-823 interacts with HSF-1, a common transcription factor that regulates the expression of heat shock proteins (HSPs), to promote its phosphorylation at

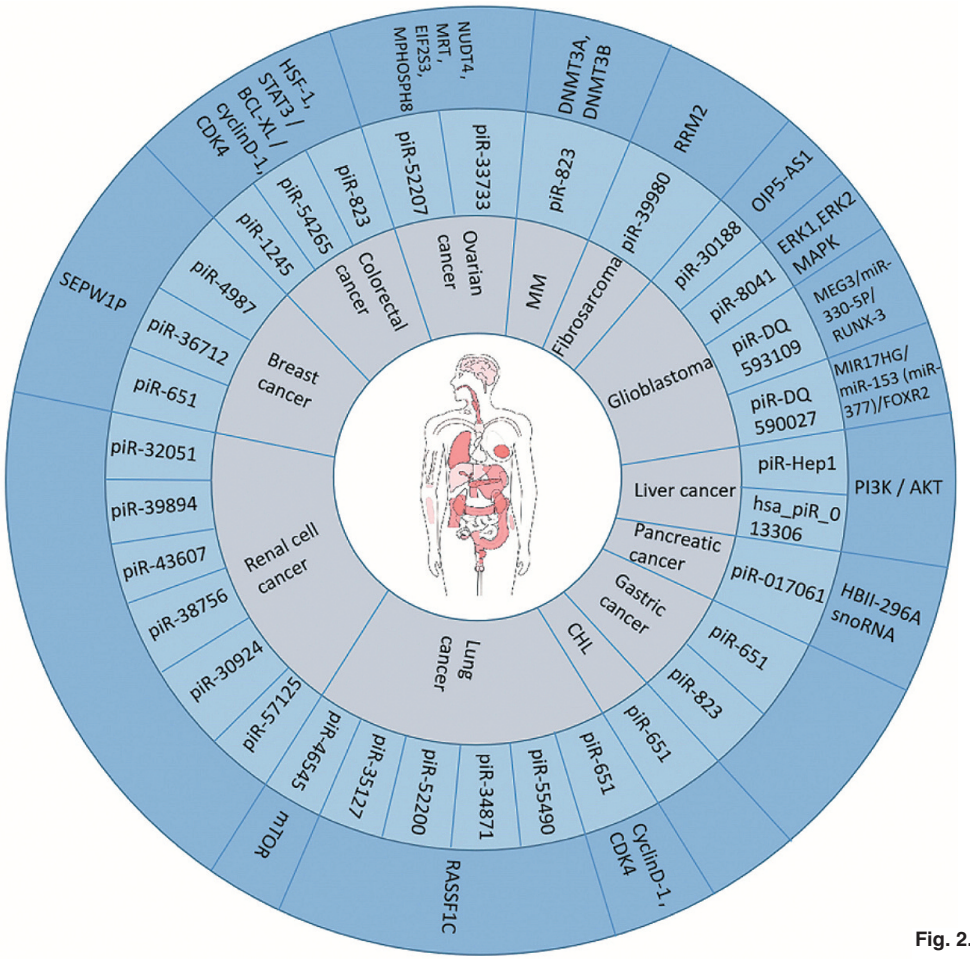

Fig. 2. The mechanisms of piRNAs in tumors

Ser326 and induce HSF-1 activation. The phosphorylation of STAT3 mediated by the piR-823/PIWIL2 complex and the activation of STAT3/BCL-XL/cyclinD-1 signaling pathway can induce the expression of CDK inhibitors and regulate the progression of the G1 phase. Inhibitors of piR-823 can induce G1 phase arrest and reduce the expression of cyclinD-1 and CDK-4, thus inhibiting the proliferation of CRC cells and promoting apoptosis, which suggested that piR-823 could be developed as a therapeutic target (Yin et al., 2017).

PiRNAs in liver cancer

The upregulation of piR-Hep1 in hepatocellular carcinoma (HCC) might promote cell proliferation and invasion by binding to PIWIL2 and upregulating the phosphorylation of AKT in the PI3K/AKT signaling pathway (Law et al., 2013). In addition, the expression of piRNAs increased in HCC, such as hsa_piR_020498, hsa_piR_013306, piR_LLi_30552, and hsa_piR_00823, and functional analysis suggested that piRNAs might target p53, PI3K/ Akt, PTEN, and tumor necrosis factor (TNF) receptor signaling pathways, which participate in hepatocellular carcinoma occurrence and HCC development (Rizzo et al., 2016).

PiRNA in renal cell cancer

A study showed that the high expression of piR-32051, piR-39894, and piR-43607 on chromosome 17 is relevant to the advanced tumor stage, metastasis, and tumor-specific survival of renal cell carcinoma (Li et al., 2015). Besides, Busch et al. reported that the high expression of piR-38756 and piR-30924, and the low expression of piR-57125, in metastatic primary tumors correlated significantly with tumor recurrence (Busch et al., 2015), suggesting that they might be biomarkers for the diagnosis, treatment, and prognosis of renal cell cancer; however, the mechanism of action of these piRNAs in renal cell carcinoma requires further study.

PiRNA in multiple myeloma (MM)

The expression of piR-823 was increased in cells from patients with multiple myeloma, and correlated positively with the FIGO stage. In addition, piR-823 is directly related to *de novo* DNA methyltransferases DNMT3A and 3B in primary CD138+ MM cells. Thus, piR-823 might regulate cell proliferation, the cell cycle, and apoptosis of MM cells by regulating DNA methylation and angiogenesis (Yan et al., 2015). Moreover, myelosuppressive cells derived from granulocytes might enhance the stem cell properties of MM stem cells by promoting the production of more piR-823 and DNMT3B to improve the survival of MM cells and maintain their stem cell properties (Ai et al., 2019). The accumulation of piR-823 in MM-derived extracellular vesicle (EVS), which effectively transports piR-823 to endothelial cells (ECs), promotes the secretion of VEGF, IL-6, ICAM-1, and CXCR-4, leading to malignant transformation. Thus, piR 823 is necessary to re-educate ECs to adapt to the environment in which MM cells grow by changing the biological characteristics of ECs. Therefore, piR-823 is regarded as an ideal target for MM therapy (Li et al., 2019).

PiRNAs in classical Hodgkin lymphoma (CHL)

High expression of piR-651 was observed in lymph nodes of patients with CHL, which is closely associated with clinical prognosis. Low expression of piR-651 is related to shorter tumor-free survival and shorter overall survival, and is thus an independent prognostic factor for these indicators (Cordeiro et al., 2016).

PiRNAs in glioblastoma

The expression of piR-30188 and PIWIL3 correlated negatively with the pathological grade of glioma. Glioblastoma cell proliferation, invasion, and migration was inhibited, and cell apoptosis was promoted by piR-30188 binding to OIP5-AS1 (Liu et al., 2018), a prominent tumor associated lncRNA that contributes to complex cellular mechanisms during malignant tumor evolution (Li and Han et al., 2019). Jacobs et al. found that piR-8041 was downregulated in glioblastoma multiforme and might inhibit cell proliferation by interacting with ERK1 and ERK2 MAPK. In addition, piR-8041 was able to inhibit cell proliferation and promote cell death through downregulating several members of the HSP and DNAJ protein families. PiR-8041 can reduce the expression of glioma stem cell marker ALCAM/CD166 and inhibit the proliferation of the A172 glioma cell line rather than normal human astrocytes, suggesting its clinical value in targeted therapy for glioma (Jacobs et al., 2018). PiRNA-DQ 593109/PIWIL1 binds to the long noncoding RNA (lncRNA) MEG3 via MEG3/miR-330-5p/RUNX-3 axis, which increases the permeability of the blood-tumor barrier (BTB) (Shen et al., 2018b). In addition, the expression of piR DQ 590027 was low in ECs under glioma conditions, while overexpression of piR DQ 590027 might reduce the expression of ococin, claudin-5, and zonula occludens 1(ZO-1) through the piR-DQ 590027/MIR17HG/miR-153 (miR-377)/FOXR2 pathway, and further increases the permeability of the BTB under glioma conditions. Therefore, piR-DQ 590027 is an ideal target for glioma therapy (Leng et al., 2018).

PiRNAs in ovarian cancer

A study observed that piR-52207 was upregulated in endometrioid ovarian cancer, and piR-52207 and piR-33733 were also overexpressed in serous ovarian cancer. Upregulated piR-52207 binds to the 3'-UTR of *NUDT4, MRT, EIF2S3,* and *MPHOSPH8*, and promotes the proliferation, migration, and tumorigenesis of endometrioid ovarian cancer cells. In serous ovarian

cancer, piR-33733 and piR-52207 combine with their corresponding targets, resulting in an enhanced anti-apoptotic effect and decreased levels of pro-apoptotic proteins. Therefore, piR-33733 and piR-52207 are involved in the genesis of ovarian cancer by participating in a variety of cellular signaling pathways at the post-transcriptional level, suggesting them as potential therapeutic targets for such malignant tumors (Singh et al., 2018).

PiRNA in pancreatic cancer

A study has shown that piR-017061 is located within the HBII-296A snoRNA, and is markedly downregulated in pancreatic ductal adenocarcinoma (PADC); however, the mechanism is not clear (Muller et al., 2015).

PiRNAs in fibrosarcoma

PiR-39980 is a tumor suppressor gene in fibrosarcoma. It inhibits the expression of ribonucleoside-diphosphate reductase subunit M2 (RRM2) by binding to its 3'-UTR, catalyzes the formation of dNTPs, the precursor of DNA synthesis, and regulates the anti-apoptotic protein BCL2 (Das et

Table 1. The involvement of piRNAs in various Cancers.

Cancer type/Name of piRNA	Function/Expression in cancer	Reference
Gastric cancer		
piR-651	Oncogene	Cheng et al., 2011; Cui et al., 2011; Wang et al., 2012; Araujo et al., 2018; Gao et al., 2018
piR-823	Tumor suppressor	Cheng et al., 2012
Lung cancer		
piR-651	Oncogene	Cheng et al., 2011; Li et al., 2016; Yao et al., 2016
piR-55490	Tumor suppressor	Peng et al., 2016
piR-34871	Upregulated	Reeves et al., 2017
piR-52200	Upregulated	Reeves et al., 2017
piR-35127	Downregulated	Reeves et al., 2017
piR-46545	Downregulated	Reeves et al., 2017
Breast cancer		
piR-651	Oncogene	Cheng et al., 2011
piR-36712	Tumor suppressor	Wu et al., 2017; Tan et al., 2019
piR-4987	Associated with lymph node metastasis	Huang et al., 2013
Colorectal cancer		
piR-1245	Oncogene	Weng et al., 2018
piR-54265	Oncogene	Mai et al., 2018
piR-823	Oncogene	Yin et al., 2017
Liver cancer		
piR-Hep1	Oncogene	Law et al., 2013
hsa_piR_013306	Related to hepatic carcinogenesis	Rizzo et al., 2016
Renal cell cancer		
piR-32051	Upregulated	Li et al., 2015
piR-39894	Upregulated	Li et al., 2015
piR-43607	Upregulated	Li et al., 2015
piR-38756	Associated with the metastasis of the cancer	Busch et al., 2015
piR-30924	Associated with the metastasis of the cancer	Busch et al., 2015
piR-57125	Tumor suppressor	Busch et al., 2015
Multiple myeloma		
piR-823	Oncogene	Yan et al., 2015; Ai et al., 2019; Li et al., 2019
Classical Hodgkin lymphoma (CHL)		
piR-651	Upregulated, related to clinical prognosis	Cordeiro et al., 2016
Glioblastoma		
piR-30188	Tumor suppressor	Liu et al., 2018
piR-8041	Downregulated, promoted proliferation, inhibited apoptosis	Jacobs et al., 2018
piR-DQ 593109	Downregulated	Shen et al., 2018b
piR-DQ 590027	Downregulated	Leng et al., 2018
Ovarian cancer		
piR-52207	Oncogene	Singh et al., 2018
piR-33733	Upregulated, inhibited cells apoptosis	Singh et al., 2018
Pancreatic cancer		
piR-017061	Downregulated	Muller et al., 2015
Fibrosarcoma		
piR-39980	Downregulated, inhibited cell proliferation	Das et al., 2019

al., 2019) (Table 1).

Conclusion

PiRNAs combine with PIWI to form pi-RISC, which silences transposon genes and resists the invasion and destruction of genomes by transposable elements. It also participates in regulating the expression of protein-coding genes and maintaining germline cell development, differentiation, and gametogenesis. Numerous piRNAs are upregulated or downregulated in tumor tissues, playing both oncogenic and tumor suppressor roles during tumor development. However, their specific roles in tumors are not clear. With further research, piRNAs might emerge as novel biomarkers and therapeutic targets, providing a new strategy for the diagnosis and treatment of tumors.

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Accepted March 2, 2021