piRNAs and PIWI proteins as potential biomarkers in Breast cancer

Mandana AmeliMojarad · Melika Amelimojarad

Received: 18 November 2021 / Accepted: 22 April 2022 / Published online: 25 May 2022
© The Author(s), under exclusive licence to Springer Nature B.V. 2022

Background PIWI interacting RNAs (piRNAs) are another subgroup of small non-coding RNAs, that can play different biological activity further to their capabilities in the germline such as regulating the gene and protein expression, epigenetic silencing of transposable elements, and regulating the spermatogenesis by interacting with PIWI proteins.

Methods We search online academic data bases including (Google Scholar, Web of Science and Pub Med), the relevant literature was extracted from the databases by using search terms of piRNAs and breast cancer as free-text words and also with the combination with OR /AND by may 2022.

Results Recently, with the help of next-generation sequencing abnormal piRNA expression has been observed to associate with the occurrence and development of human cancers, such as breast cancer (BC). Recent investigation proposing piRNA as a prognostic and diagnostic biomarker based on their cancer-related interaction in the treatment of BC.

Conclusion This review aims to focus on the role of piRNAs in the initiation, progression, and the occurrence of breast cancer in order to understand its function and provide a better therapeutic strategy.

Keywords PIWI-interacting RNA · piRNA · Small RNA · Breast cancer

Abbreviations

BC Breast cancer
HSF1 Heat shock factor 1
HSP Heat shock protein
lncRNA Long noncoding RNA
ncRNAs non-coding RNA
nt nucleotide
OS Overall survival
pi-RISC piRNAs-induced silencing complex
piRNA Piwi-interacting RNA
TE Transposable element
Zuc Zucchini

Mandana AmeliMojarad
Mandanalee13@gmail.com

Melika Amelimojarad
melikaamelimojarad@gmail.com

1 Faculty of biological science, University of Kharazmi, Tehran, Iran
2 Faculty of biological science, University of Kharazmi, Tehran, Iran

Background

Breast cancer (BC) is the first most diagnosed cancer and the major health concern among both women worldwide [1]. Different genetic alternations and lifestyle related risk factors can lead to BC initiation and proliferation [2]. Currently, Mammography screening is the gold standard techniques that can be used with other techniques such as MRI and PET scan, to diagnose BC patients at early stages however, there is still an urgent need to discover new anti-cancer markers for more specific and noninvasive therapeutic strategies [3, 4]. Unfortunately, based on Inadequate prognostic and diagnostic biomarkers most patients are diagnosed in advanced stages, losing their chance for early treatment, therefore finding sensitive and stable therapeutic markers is a crucial approach in controlling the BC [5, 6].

Recent discoveries on RNAs reported that noncoding RNAs contain 98% of the total human genome, involving different biological pathological activities [7–9]. PIWI-interacting RNAs (piRNAs) are a new class of recently discovered small noncoding RNAs with 24–31 nucleotides (nt) in length that are specially expressed in mammalian germ cells [7]. They were first discovered in 2001 in Drosophila melanogaster as small RNAs [7]. piRNAs can play a vital role in physiological processes both at the transcriptional or
post-transcriptional level [10]. piRNA binds to PIWI proteins to form a ribonucleoprotein silencing complex, RISC (RNA-induced silencing complex) to influence genome rearrangement, epigenetic regulation, transposon silencing, spermiogenesis, protein regulation, heterochromatin formation and, most importantly, preservation of genome integrity [11, 12]. A member of the Argonaute protein family encoded by the Drosophila piwi gene involved in DNA methylation, transposon silencing, germline development and fertility [13, 14]. Recently, studies have reported several abnormally expressed piRNA and PIWI proteins in different tumors including BC [15, 16]. It has been shown that high piRNA expression may be relevant for cancer tumorigenesis and cancer prognosis in various types of human tumors [7, 15, 16]. Therefore, in this review, we summarize recent studies on piRNAs and discuss their emerging roles in BC as potential biomarkers.

**piRNAs biogenesis**

Recent discoveries revealed that there are three subclasses of piRNAs based on their origin including transposon-derived, lncRNA-derived, and mRNA-derived piRNAs [17]. PiRNA biogenesis is initiated by Pol II copying RNA from its cluster [17]. piRNAs are primarily transcribed as large single-stranded transcripts resulting from single-stranded precursors in the nucleus. Nascent piRNAs (pre-piRNAs) require Dicer-independent post-transcriptional modification to become mature piRNAs. In both body and germ cells and a ‘ping-pong’ amplification mechanism that only forms in the germline [15, 18]. Primary piRNAs are cleaved by the Riboendonuclease zucchini (Zuc) with the help of the Minotaur (Mino) to produce piRNA intermediates with a five uracil. piRNA has a unique 2′-methylation structure at the 3′ end that is methylated by the Hen1 enzyme, the PIWI protein specifically binds to this structure at the 3′ end to create the piRNA/PIWI complex [19]. The PIWI complex migrates back to the nucleus, reaches its target transcript and represses transposons during transcription and after transcription, thus protecting the integrity of the germline. In a ping-pong mechanism, piRNAs bind the proprietary AGO3 or AUB proteins in the cytoplasm to form piRNA/AGO3 or piRNA/AUB complexes [20]. Ping pong structures have been identified in zebrafish, D. melanogaster, and several other species. However, recent data have reported that piRNA biogenesis during adult spermatogenesis in mice is independent of Ping-Pong mechanism [20]. This is in contrast to the common belief that the ping-pong pathway is a major mechanism for piRNA biogenesis during spermatogenesis therefore, the biogenesis of piRNA requires further studies in mammals yet [12, 21] Fig. 1.

**piRNAs and Piwi proteins in breast cancer**

PiRNAs and PIWIs dysregulation have been greatly studied in different cancers, including breast cancer in current years. The abnormal expression of piRNA and PIWIs has considered to be related with the carcinogenesis via accelerating the initiation, progression and metastasis of breast cancer. Based on the great capacity of piRNAs and PIwi proteins in regulating the epigenetic activities scientific consider them as a potential diagnostic tools and therapeutic targets in most cancers including BC [7]. Till now different abnormally expressed piRNAs has been reported in human breast cancer cells and tissues by new methods such as small RNA-Seq analysis including piR-823, piR-021285, piR-932, piR-016658 and piR-016975 piR-36712, among them piR-021285 was the first piRNA with the regulatory effect in breast tumor genesis by inducing the DNA methylation and increasing MCF-7 cells invasion [23–25]. The high expression of piR-651 was confirmed in breast cancer cell lines facilitating the cell progression, migration and invasion [7, 26]. The piR-651 overexpression can promote proliferation and invasion, and reduce cell apoptosis through promoting different oncogenes (CDK4, Cyclin D1 and MDM2) expression, whereas piR-651 inhibition showed the opposite function. In addition, piR-651 could promote phosphatase and tensin homolog (PTEN) methylation [26]. Additionally, a high expression of piR-4987 was reported in breast cancer associating with lymph node metastases [27]. piR-36712 is found to be significantly downregulated in BC compared to normal tissue [27]. piR-36712 can also amplify the chemotherapeutic drugs effect and was related to poor clinical prognosis. The lower expression of piR-36712 tends to inhibit the expression of SEPW1 via interacting with its pseudogene SEPW1P in breast cancer patients [28]. More interestingly, the piR-36712 is found to be a tumor suppressor and can be used as a prognostic marker or therapeutic target for breast cancer [28]. piR-932 is another over expressed piRNA in breast cancer with ability to form a piR-932/PIWIL2 complex to promotes epithelial–mesenchymal transition (EMT), proliferation and metastasis in BC [29]. The piR-823 is a regulatory piRNA in human breast cancer playing oncogenic function through modifying epigenetic mechanisms [30]. piR-823 expression has been found to be increased in malignant breast cancer with estrogen positive status [31]. Dysregulations of by piR-823 has been discovered in different cancers promoting cell proliferation and metastasis [32, 33]. DNA methyltransferase such as DNMT1, and DNMT3B, which promote DNA methylation in gene adenomatous polyposis coli (APC) also increased by overexpression of piR-823 [30]. Recently up regulation of piR-20365, piR-4987, piR-20485 and piR-20582 in 50 BC tissues compared with matched non-tumor tissues has
been revealed and among them piR-4987 has showed to be associated with positive lymph node [27]. Other study has suggested the diagnostic role of circulating, piR-36743 for monitoring the neoadjuvant chemotherapy (NACT) in triple negative breast cancer (TNBC) patients [34]. Further study has find piR-31143 had a higher expression in ERβ+ samples [35]. Another sequencing study of piRNAs, indicate the top five up regulated piRNA including piR-32745-21131, -23672, -1282, and top five down regulated including piR-30293-23662, 26527, -26526and -26528 in BC tumor tissues [36]. Another RNA sequencing analysis in 227 fresh-frozen breast tissue samples suggest the three up regulated piRNA(DQ596932, DQ570994, and DQ571955) all associating with high grade of tumors. Among them high expression of DQ571955 in estrogen receptor positive showed the shorter -free survival, among patents indicating it as

Fig. 1 The primary and ping-pong mechanism for piRNAs biogenesis [22]
a potential diagnostic marker for predicting radiotherapy response in positive estrogen receptor patients [37]. The PIWI protein is a member of the highly conserved family of Argonaute proteins found in mice, Drosophila, and humans. The PIWI protein in humans is made up of four proteins, including PIWIL1 (HIWI), PIWIL2 (similar to Miwi), PIWIL3 (HIWI3), and PIWIL4 (HIWI2) [23, 27]. Piwil1, Piwil2, Piwil3, and Piwil4 have been detected in different types of cancer such as breast cancer [38]. Among all four PIWI proteins, PIWIL1 is the most studied protein that can regulate gene expression, apoptosis, the cell cycle and cell proliferation [34, 39]. Piwil2 overexpression was mostly reported in BC functioning as oncogene [29]. The dysregulation of Piwil2 and Piwil4 plays an important role in the pathological process of breast cancers and, often associated with poor survival and aggressive clinicopathological properties of patients [40, 41]. High expression of Piwil4, was also reported in both breast cancer tissues and MDA-MB-231 breast cancer cell line. Piwil4 inhibition in MDA-MB-231 could significantly suppressed the cell proliferation and migration through regulating TGF-β and FGF signaling pathways [40]. More interestingly the PIWI proteins turned out to be a stem cell protein that plays a crucial role in cancer stem cell (CSC) differentiation, stem cell self-reproduction, DNA methylation, spermatogenesis playing gene regulation [7, 10]. In addition, piR-932 binds to PIWIL2 to promote latex methylation in breast cancer tumor cells and ultimately to promote breast cancer progression [29]. It was shown that both of these can be potential targets for blocking metastasis from. The expression of PIWIL2 was higher than that of the control group [42]. The mechanism of action of some piRNAs in BC progression is illustrated in Fig. 2 and all latest research on expression of piRNAs and PIWI proteins is listed in (Table 1).

### Discussion

Breast cancer (BC) is the most leading cancer in women worldwide [48, 49]. Several studies were carried out to find new biological markers for the early detection of BC. Recently, increased attention has been paid with the use of new sequencing technologies. Preclinical data in particular suggest that modulation of ncRNAs could have significant anti-cancer effects. There is great expectation that cancer therapy based on ncRNA will develop rapidly in early future [49]. To date, several piRNAs have been identified that are aberrantly expressed in breast cancer tissues and cells and that associate cell proliferation and metastasis, proposing that piRNAs are potential biomarkers and therapeutic targets in breast cancer [55]. piRNAs, which are similar in length to miRNAs, are very stable and resistant to degradation by ribonucleases in body fluids. As mentioned above, different piRNAs are expressed differently between paired tumor and normal tissues, which is associated with aggressive biological behavior [43]. Certain piRNAs are associating

| piRNA          | Cancer type       | Expression | Clinical correlation                                      | Reference |
|----------------|-------------------|------------|----------------------------------------------------------|-----------|
| PIR-021285     | Breast cancer     | Up         | Promoting migration, invasion inhibiting apoptosis       | [23]      |
| PIR-823        | Luminal Breast cancer | Up         | Promoting cancer cell stemness                           | [28]      |
| PIR-932        | Breast cancer     | Up         | Promoting the Breast cancer development                  | [44]      |
| PIR-651        | Breast cancer     | Up         | Promotes cell proliferation and migration Recurrence-free survival | [26, 45] |
| PIR-016658     | Breast cancer     | Up         | Promoting cancer cell stemness                           | [46]      |
| PIR-4987       | Breast cancer     | Up         | Associating with TNM stage and lymph node                 | [47]      |
| PIR-31106      | Breast cancer     | Up         | Associating with TNM stage                                | [48]      |
| PIR-36026      | Breast cancer     | Up         | Promoting cancer                                         | [49]      |
| PIR-36743      | Breast cancer     | Up         | Promoting cancer                                         | [34]      |
| PIR-20582      | Breast cancer     | Up         |                                                                 | [27]      |
| PIR-20365 PIR-20485 | Breast cancer | Up         |Associating with poor degree differentiation               | [50]      |
| PIR-36712      | Breast cancer     | Down       | Suppressing EMT                                           | [28]      |
| PIR-016975     | Breast cancer     | Down       |                                                                 | [38]      |
| PIR-FTH1       | Breast cancer     | Down       | Improving chemo sensitivity                               | [51]      |
| PIWI proteins  |                   |            |                                                           |           |
| PIWIL1         | Breast cancer     | Up         |                                                           | [52]      |
| PIWIL2         | Breast cancer     | Up         |                                                           | [53, 54]  |
| PIWIL4         | Breast cancer     | Up         |                                                           | [40]      |
with cancer hallmarks to promote proliferation and metastasis, including piR651, piR021285 [7, 23, 38], Fig. 3. Some piRNAs are known to be attractive diagnostic candidates and prognostic biomarkers especially due to their minimally invasive properties and high stability and abundance in tissue and plasma [27]. In addition, piRNAs have a great cancer-specific gene regulatory function both in the cytoplasm and in nucleus. Overall, based on the current evidences piRNA and Piwi proteins are considered as promising diagnostic tools, in cancer treatment. However, more research into their biosynthesis and function and is needed to discover their potential uses in the future.

**Conclusions and perspective**

piRNAs and PIWI proteins have been proven to be potential new biomarkers and therapeutic targets because of their tissue-specific role in the development of human cancers and their high levels of expression in tissue and blood. Abnormal expression of piRNAs and PIWI proteins have been demonstrated extensively in germline and stem cells and since the primary tumors contain different cells including deregulated somatic cells and cancer stem cells both with similarity in stemness ability and molecular mechanisms therefore, it can be proposed that piRNAs and PIWI proteins can play the crucial roles in tumor development and progression. Recent studies have shown the important role of piRNAs and PIWI proteins in cancers regulation and indicated that they could
be either suppressor or promotors to regulate cell proliferation and metastasis. Therefore, piRNAs and PIWI proteins can be considered as an ideal biomarkers or therapeutic targets. However, there are still majority of piRNAs and PIWI proteins and some unanswered questions remained unclear. For instance, is aberrantly expressed piRNAs the main cause for cancer initiation or this alternative expression is just a byproduct for other activities or interaction with different pathways or how to distinguish proper piRNAs thresholds between healthy and patients and how to target the predicted piRNAs and regulate their function. Therefore, answering these key challenges and further studies and clinical trials should help us to bring piRNAs sooner from bench to bed in the future.

Acknowledgments  Not applicable

Authors contributions  MAM and MAM contribute equally to drafting, editing, and approving the final

Funding  Not applicable

Data availability  Not applicable

Declarations

Conflict of interest  The authors declare no conflict of interest

Ethics approval and consent to participate  Not applicable

Consent for publication  Not applicable

References

1. Siegel RL, Miller KD, Jemal A (2017) Cancer statistics, 2017, CA. Cancer J Clin 67:7–30. https://doi.org/10.3322/caac.21387
2. McPherson K, Steel CM, Dixon JM (2000) ABC of breast diseases: breast cancer—Epidemiology, risk factors, and genetics. Br Med J 321:624–628. https://doi.org/10.1136/bmj.321.7261.624
3. Ronco AL, De Stéfani E, Stoll M (2010) Hormonal and metabolic modulation through nutrition: towards a primary prevention of breast cancer. Breast 19:322–332. https://doi.org/10.1016/j.breast.2010.05.005
4. Sell S (2006) Cancer stem cells and differentiation therapy. Tumor Biol 27:59–70. https://doi.org/10.1159/000092323
5. Mulrane L, McGee SF, Gallagher WM, O’Connor DP (2013) miRNA dysregulation in breast cancer.
Cancer Res 73:6554–6562. https://doi.org/10.1158/0008-5472.CAN-13-1841
6. Qian Y, Shi L, Luo Z (2020) Long non-coding RNAs in cancer: implications for diagnosis, prognosis, and therapy. Front Med 7:612393. https://doi.org/10.3389/fmed.2020.612393
7. Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, Li QN (2011) PiRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. Clin Chim Acta 412:1621–1625. https://doi.org/10.1016/j.cca.2011.05.015
8. Mattick JS, Makunin IV (2006) Non-coding RNA. Hum Mol Genet. https://doi.org/10.1093/hmg/ddi046
9. Ponting CP, Oliver PL, Reik W (2009) Evolution and functions of long noncoding RNAs. Cell 136:629–641. https://doi.org/10.1016/j.cell.2009.02.006
10. Guo B, Li D, Du L, Zhu X (2020) piRNAs: biogenesis and their potential roles in cancer. Cancer Metastasis Rev. 39:567–575. https://doi.org/10.1007/s10555-020-09863-0
11. Calcagno DQ, da Silva Mota ER, Moreira FC, de Sousa SBM, Burbano RR, Assumpção PP (2019) Role of PIWI-interacting RNA (piRNA) as epigenetic regulation. Handb Nutr Diet Epigenetics. https://doi.org/10.1007/978-3-319-55530-0_77
12. Thomson T, Lin H (2009) The biogenesis and function of PIWI proteins and piRNAs: progress and prospect. Annu Rev Cell Dev Biol. 24:110707.157327
13. Weng W, Liu N, Toiyama Y, Kusunoki M, Nagasaka T, Fuji -wara T, Wei Q, Qin H, Lin H, Ma Y, Goel A (2018) Novel evidence for a PIWI-interacting RNA (piRNA) as an oncogenic mediator of disease progression, and a potential prognostic biomarker in colorectal cancer. Mol Cancer. https://doi.org/10.1186/s12943-018-0767-3
14. Le Thomas A, Rogers AK, Webster A, Marinov GK, Liao SE, Calcagno DQ, da Silva Mota ER, Moreira FC, de Sousa SBM, Burbano RR, Assumpção PP (2019) Role of PIWI-interacting RNA (piRNA) as epigenetic regulation. Handb Nutr Diet Epigenetics. https://doi.org/10.1007/978-3-319-55530-0_77
15. Calcagno DQ, da Silva Mota ER, Moreira FC, de Sousa SBM, Burbano RR, Assumpção PP (2019) Role of PIWI-interacting RNA (piRNA) as epigenetic regulation. Handb Nutr Diet Epigenetics. https://doi.org/10.1007/978-3-319-55530-0_77
16. Thomson T, Lin H (2009) The biogenesis and function of PIWI proteins and piRNAs: progress and prospect. Annu Rev Cell Dev Biol. 24:110707.157327
17. Iwasaki YW, Siomi MC, Siomi H (2015) PIWI-interacting RNA: molecular biology and mechanisms. Adv Exp Med Biol. 831:4404–4421. https://doi.org/10.1007/978-3-319-311294-3
18. Yamashiro H, Siomi MC (2018) PIWI-interacting RNA in drosophila: biogenesis, transposon regulation, and beyond. Chem Rev 118:4404–4421. https://doi.org/10.1021/acs.chemrev.7b00393
19. Feng J, Yang M, Wei Q, Song F, Zhang Y, Wang X, Liu B, Li J (2020) Novel evidence for oncogenic piRNA-823 as a promising prognostic biomarker and a potential therapeutic target in colorectal cancer. J Cell Mol Med. https://doi.org/10.1111/jcmm.15537
20. Pan L, Su J, Zheng J, Zhao Q, Guo Y, Lu Z, Ma W, Liu P, Pestell RG, Liang C, Yu Z (2021) piRNA-823 is involved in cancer stem cell regulation through altering DNA methylation in association with luminal breast cancer. Front Cell Dev Biol. https://doi.org/10.3389/fcell.2021.641052
21. Öner Ç, Coşan DT, Çolak E (2016) Estrogen and androgen hormone levels modulate the expression of piwi interacting RNA in prostate and breast cancer. PLoS ONE. https://doi.org/10.1371/journal.pone.0159044
22. Cheng J, Deng H, Xiao B, Zhou H, Zhou F, Shen Z, Guo J (2012) PiR-823, a novel non-coding small RNA, demonstrates in vitro and in vivo tumor suppressive activity in human gastric cancer cells. Cancer Lett 315:563–568. https://doi.org/10.1016/j.canlet.2011.05.015
23. Beeyt E, Liu N, Lin H (2012) piRNA biogenesis during adult spermatogenesis in mice is independent of the ping-pong mechanism. Cell Res 22:1429–1439. https://doi.org/10.1038/cr.2012.120
24. Kodaru SV, Tiwari AK, Leberfinger A, Hazard SW (2017) A comprehensive NGS data analysis of differentially regulated miRNAs, piRNAs, IncRNAs and sn/snoRNAs in triple negative breast cancer. Cancer Res 84:5078–5096. https://doi.org/10.1158/0008-5472.CAN-17-0561
25. Kärkkäinen E, Heikkinen S, Tengström M, Kosma VM, Mannermaa A, Hartikainen JM (2021) The debatable presence of PIWI-interacting RNAs in invasive breast cancer. Cancer Med 10:3593–3603. https://doi.org/10.1002/cam4.3915
38. Qian L, Xie H, Zhang L, Zhao Q, Liu J, Yu Z (2021) Piwi-interacting RNAs: a new class of regulator in human breast cancer. Front Oncol. https://doi.org/10.3389/FONC.2021.695077

39. Wang QE, Han C, Milum K, Wani AA (2011) Stem cell protein Piwil2 modulates chromatin modifications upon cisplatin treatment. Mutat Res Fundam Mol Mech Mutagen 708:59–68. https://doi.org/10.1016/j.mrfmmm.2011.02.001

40. Wang Z, Liu N, Shi S, Liu S, Lin H (2016) The role of PIWIL4, an argonaute family protein, in breast cancer. J Biol Chem 291:10646–10658. https://doi.org/10.1074/jbc.M116.723239

41. Liu JJ, Shen R, Chen L, Ye Y, He G, Hua K, Jarijouma D, Nakano T, Ramesh GK, Shapiro CL, Barsky SH, Gao JX (2010) Piwil2 is expressed in various stages of breast cancers and has the potential to be used as a novel biomarker. Int J Clin Exp Pathol 3:328–337

42. Li D, Sun X, Yan D, Huang J, Luo Q, Tang H, Peng Z (2012) Piwil2 modulates the proliferation and metastasis of colon cancer via regulation of matrix metallopeptidase 9 transcriptional activity. Exp Biol Med 237:1231–1240. https://doi.org/10.1258/ebm.2012.011380

43. Yin J, Jiang XY, Qi W, Ji CG, Xie XL, Zhang DX, Cui ZJ, Wang CK, Bai Y, Wang J, Jiang HQ (2017) piR-823 contributes to colorectal tumorigenesis by enhancing the transcriptional activity of HSF1. Cancer Sci 108:1746–1756. https://doi.org/10.1111/cas.13300

44. Chu H, Xia L, Qiu X, Gu D, Zhu L, Jin J, Hui G, Hua Q, Du M, Tong N, Chen J, Zhang Z, Wang M (2015) Genetic variants in noncoding PIWI-interacting RNA and colorectal cancer risk. Cancer 121:2044–2052. https://doi.org/10.1002/cncr.29314

45. Martinez VD, Enfield KSS, Rowbotham DA, Lam WL (2016) An atlas of gastric PIWI-interacting RNA transcriptomes and their utility for identifying signatures of gastric cancer recurrence. Gastric Cancer 19:660–665. https://doi.org/10.1007/s10120-015-0487-y

46. Lu J, Zhao Q, Ding X, Guo Y, Li Y, Xu Z, Li S, Wang Z, Shen L, Chen HW, Yu Z, Pestell RG (2020) Cyclin D1 promotes secretion of pro-oncogenic immuno-miRNAs and piRNAs. Clin Sci (Lond) 134:791–805. https://doi.org/10.1042/CS20191318

47. Mai D, Ding P, Tan L, Zhang J, Pan Z, Bai R, Li C, Li M, Zhou Y, Tan W, Zhou Z, Li Y, Zhou A, Ye Y, Pan L, Zheng Y, Su J, Luo Z, Liu Z, Zhao Q, Li X, Huang X, Li W, Wu S, Jia W, Zou S, Wu C, Xu RH, Zheng J, Lin D (2018) PIWI-interacting RNA-54265 is oncogenic and a potential therapeutic target in colorectal adenocarcinoma. Theranostics 8:5213

48. Vychytilova-Faltejskova P, Stitkovcova K, Radova L, Sachlova M, Kosarova Z, Slaba K, Kala Z, Svoboda M, Kiss I, Vyzula R, Cho WC, Slaby O (2018) Circulating PIWI-interacting RNAs piR-5937 and piR-28876 are promising diagnostic biomarkers of colon cancer. Cancer Epidemiol Biomarkers Prev 27:1019–1028. https://doi.org/10.1158/1055-9965.EPI-18-0318

49. Romano G, Veneziano D, Acunzo M, Croce CM (2017) Small non-coding RNA and cancer. Carcinogenesis 38:485–491. https://doi.org/10.1093/carcin/bgx026

50. Yin J, Qi W, Ji C, Zhang D, Xie X, Ding Q, Jiang X, Han J, Jiang H (2019) Small RNA sequencing revealed aberrant piRNA expression profiles in colorectal cancer. Oncol Rep 42:263–272. https://doi.org/10.3892/or.2019.7158

51. Balaratnam S, West N, Basu SA (2018) piRNA utilizes HILI and HIWI2 mediated pathway to down-regulate ferritin heavy chain 1 mRNA in human somatic cells. Nucleic Acids Res. https://doi.org/10.1093/NAR/GKY728

52. Aberrant Expression of PIWIL1 and PIWIL2 and Their Clinical Significance in Ductal Breast Carcinoma | Anticancer Research, (n.d.). https://ar.iiarjournals.org/content/38/4/2021 (accessed November 6, 2021).

53. Liu JJ, Shen R, Chen L, Ye Y, He G, Hua K (2010) Piwil2 is expressed in various stages of breast cancers and has the potential to be used as a novel biomarker. Int J Clin Exp Pathol 3(4):328–337

54. Risner A, Nair-Menon J, Mcdowell C, Gangaaraju V, Kourtidis A, Furbish A, Woster P (2021) 34380 Cadherin complexes recruit PIWIL2 to suppress transposons and pro-tumorigenic transformation. J Clin Transl Sci 5:12. https://doi.org/10.1017/CSTS.2021.432

55. Mei Y, Clark D, Mao L (2013) Novel dimensions of piRNAs in cancer. Cancer Lett 336:46–52. https://doi.org/10.1016/j.canlet.2013.04.008

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.