piRNAs and PIWI proteins as potential biomarkers in Breast cancer

MANDANA Amelimojarad

Kharazmi University

Melika Amelimojarad (✉ melikaamelimojarad@gmail.com)

Kharazmi University <https://orcid.org/0000-0003-0515-7835>

Research Article

Keywords: PIWI-interacting RNA, piRNA, Small RNA, breast cancer

Posted Date: November 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1063012/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

PIWI-interacting RNAs (piRNAs) are another subgroup of small non-coding RNAs, that can play different biological activities 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. Recently, with the help of next-generation sequencing, abnormal expression of piRNAs have been observed in different types of cancer such as breast cancer (BC). A new investigation proposes piRNA as a prognostic and diagnostic biomarker in the treatment of BC. Therefore, this review aims to focus on the role of piRNAs in the initiation, progression, and metastasis of BC and its molecular mechanisms to understand its function and provide a better therapeutic strategy.

Background

Breast cancer (BC) is the first most diagnosed cancer and the major health concern among women worldwide (1). Different genetic alternations and life-style related risk factors can lead to BC initiation and proliferation (2). Currently, Mammography screening is the gold standard technique 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 in different biological pathological activities (7–9).PIWI-interacting RNAs (piRNAs) are a new class of recently discovered small non-coding RNAs with 24–31 nucleotides (nt) in length that are especially expressed in mammalian germ cells (10). piRNAs were first discovered in 2001 in *Drosophila melanogaster* as small RNAs(10).piRNAs can play a vital role in physiological processes both at the transcriptional or post-transcriptional level(11). 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 (12, 13). A member of the argonaute protein family encoded by the *Drosophila piwi* gene is involved in DNA methylation, transposon silencing, germline development, and fertility (14, 15). Recently several studies have reported several abnormally expressed piRNA and PIWI proteins in different tumors including BC, it has been shown that high expression of piRNAs and PIWI proteins may be relevant for cancer tumorigenesis and cancer prognosis in various types of human tumors (7, 16, 17). 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 transposons-derived, lncRNA-derived, and mRNA-derived piRNAs(18). piRNA biogenesis is initiated by Pol II copying RNA from its cluster(19). 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 (16, 20). Primary piRNAs are cleaved by the ribonuclease Zucchini (Zuc) with the help of the Minotaur (Mino) to produce piRNA intermediates with a 5' uracil in the cytoplasm(18). piRNA has a unique 2'-O-methyl 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 form the piRNA / PIWI complex (21). 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(22). In a ping-pong mechanism, piRNAs bind the proprietary AGO3 or AUB proteins in the cytoplasm to form piRNA / Ago3 or piRNA / AUB complexes. (21). Ping pong structures have been identified in zebrafish, *D. melanogaster*, and several other species. However, recent studies have reported that piRNA biogenesis in mice is independent of the ping-pong mechanism; (24).

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 been considered to be related to carcinogenesis via accelerating the initiation, progression, and metastasis of breast cancer(25). Based on the great capacity of piRNAs and Piwi proteins in regulating the epigenetic activities, scientists consider them as potential diagnostic tools and therapeutic targets in most cancers including BC (26).

Till now different abnormally expressed piRNAs have been reported in breast cancer cells and tissues by new methods such as small RNA-Seq analysis, 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(27).

The high expression of piR651 was confirmed in breast cancer cell lines facilitating the cell progression, migration, and invasion(28, 29). Additionally, a high expression of piR-4987 was reported in breast cancer associated with lymph node metastases (30). piR-36712 is found to be significantly downregulated in BC compared to normal tissue. piRNA-36,712 can also amplify the effect of the chemotherapeutic drug. The lower expression of piR-36712 tends to increase the expression of SEPW1 and predict a poorer prognosis in breast cancer patients(31). More interestingly, the piR36712 is found to be a tumor suppressor and can be used as a prognostic marker or therapeutic target for breast cancer(31). piR-932 is another over-expressed piRNA in breast cancer with the ability to form a piR-932/PIWIL2 complex to promote epithelial-mesenchymal transition (EMT), proliferation, and metastasis in BC(32).

piR823 is a regulatory piRNA in human breast cancer playing an oncogenic function through modifying epigenetic mechanisms(33). piR823 expression is increased in malignant breast cancer with estrogen-

positive status(34). Dysregulation of piR-823 has been discovered in different cancers promoting cell proliferation and metastasis(35, 36).

Recently up-regulation of piR-20365, piR-4987, piR-20485, and piR-20582 in 50 BC tissues compared with matched non-tumor tissues have been revealed and among them, piR-4987 has shown to be associated with positive lymph node(37). Another study has suggested the diagnostic role of circulating, piR-36743 for monitoring neoadjuvant chemotherapy (NACT) In triple-negative breast cancer (TNBC) patients(38). Further study has to find piR-31143 had a higher expression in ER β + samples (39).

Another sequencing study of piRNAs indicates the top five upregulated piRNA including piR-32745, 21131 -21131, -23672, -1282, and top five down-regulated including piR-30293 -23662, 26527, -26526and -26528 in BC tumor tissues (40). Another RNA sequencing analysis in 227 breast tissue samples discovered three upregulated piRNAs, associating with high grade of tumors including (DQ570994, DQ596932, and DQ571955). Among them, high expression of DQ571955 in estrogen receptor-positive showed the shorter-free survival, among patients indicating it as a potential diagnostic marker for predicting radiotherapy response in positive estrogen receptor patients (41).

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) (37, 42)Among all four PIWI proteins, PIWIL1 is the most studied protein that can regulate gene expression, apoptosis, the cell cycle and cell proliferation (38)(43). The dysregulation of Piwil2and Piwil4 plays an important role in the pathological process of breast cancers and, often associated with poor survival and aggressive clinicopathological properties of patients(44, 45).

The PIWI protein 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 (11, 46).

In addition, piR932 binds to PIWIL2 to promote latex methylation in breast cancer tumor cells and ultimately to promote breast cancer progression (32). It was shown that both of these can be potential targets for blocking metastasis. The expression of PIWIL2 was higher than that of the control group (47).

In addition, expression of the three different PIWI including (PIWIL1, PIWIL2, and PIWIL4).

Were studied in six different BC cell lines indicating that PIWIL1level was significantly evaluated among other PIWIS in four cell lines compared to the normal cell lines while PIWIL 4 was evaluated in five cell lines in advance.

The mechanism of action for piRNAs in CRC is listed in (Table 1).

Table 1
The Role of piRNAs in different Cancer

piRNA	Cancer type	Expression	Clinical correlation	Reference
piR-021285	Breast cancer	up	Promoting migration, invasion inhibiting apoptosis	(48)
piR-823	Colorectal Cancer	up	Promoting proliferation and suppressing apoptosis via HSF1 activation	(49)
piR-932	Breast cancer	up	Promoting the Breast cancer development	(50)
piR-651	Breast cancer	up	Recurrence-free survival	(51)
piR-4987	Breast cancer	up	Associating with TNM stage/lymph metastasis	(52)
PiR-31106	Breast cancer	up	associating with TNM stage	(53)
PiR-36026	Breast cancer	up	Promoting cancer proliferation	(54)
PiR-36743	Breast cancer	up	Promoting cancer proliferation	(38)
PiR-20582	Breast cancer	up		(55)
piR-20365 piR-20485 piR-20582	Breast cancer	up	associating with poor degree differentiation /tumor marker	(56)
piR-36712	Breast cancer	down	Promoting the Breast cancer development	(31)
piR-016975	Breast cancer	down	Promoting cancer proliferation	(57)
piR-FTH1	Breast cancer	down	Promoting cancer proliferation	(58)
PIWI proteins				
PIWIL1	Breast cancer	up	Promoting cancer proliferation	(59)

piRNA	Cancer type	Expression	Clinical correlation	Reference
PIWIL2	Breast cancer	up	Promoting cancer proliferation	(60)
PIWIL4	Breast cancer	up	Promoting cancer proliferation	(61)

Discussion

Breast cancer (BC) is leading cancer in women worldwide (59, 60). Several studies were carried out to find new biological markers for the early detection of BC. Recently, increased attention has been paid to 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 the early future (54). To date, several piRNAs have been identified that are aberrantly expressed in breast cancer tissues and cells and that associate cell proliferation and metastasis, suggesting that piRNAs are potential biomarkers and therapeutic targets in breast cancer (62). 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 (54), certain piRNAs are associated with cancer proliferation and metastasis, including piR651, piR021285 (46, 57). piRNA also has great potential as a minimally invasive biomarker in British Columbia due to its stability and abundance of tissue. In addition, some piRNAs are known to be attractive diagnostic candidates and prognostic biomarkers (61). piRNA with gene Regulatory function both in the cytoplasm and in the cell nucleus and its role in the cancer-specific development of human cancers has proven to be a very promising area of cancer research, although there is still a need to investigate the oncogenic or tumor-suppressive function of piRNAs. The expression has now been extensively described in a variety of tumor types.

Conclusions

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. Although piRNA / PIWI has become a hot topic in cancer development, research into its function and biosynthesis is not fully understood and further research is needed to discover their potential uses in the development of different cancers as well as BC.

Abbreviations

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

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors declare no conflict of interest

Funding

Not applicable

Authors' contributions

M.A and M.A contribute equally to drafting, editing, and approving the final

Acknowledgments

Not applicable

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017 Jan;67(1):7–30.
2. McPherson K, Steel CM, Dixon JM. ABC of breast diseases: Breast cancer - Epidemiology, risk factors, and genetics [Internet]. Vol. 321, *British Medical Journal*. BMJ Publishing Group; 2000 [cited 2021 May 24]. p. 624–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/10977847/>
3. Ronco AL, De Stéfani E, Stoll M. Hormonal and metabolic modulation through nutrition: Towards a primary prevention of breast cancer [Internet]. Vol. 19, *Breast*. Churchill Livingstone; 2010 [cited 2021 May 24]. p. 322–32. Available from: <https://pubmed.ncbi.nlm.nih.gov/20542695/>
4. Sell S. Cancer stem cells and differentiation therapy [Internet]. Vol. 27, *Tumor Biology*. Tumour Biol; 2006 [cited 2021 Jun 19]. p. 59–70. Available from: <https://pubmed.ncbi.nlm.nih.gov/16557043/>
5. Mulrane L, McGee SF, Gallagher WM, O'Connor DP. miRNA dysregulation in breast cancer [Internet]. Vol. 73, *Cancer Research*. Cancer Res; 2013 [cited 2021 Apr 11]. p. 6554–62. Available from: <https://pubmed.ncbi.nlm.nih.gov/24204025/>
6. Qian Y, Shi L, Luo Z. Long Non-coding RNAs in Cancer: Implications for Diagnosis, Prognosis, and Therapy [Internet]. Vol. 7, *Frontiers in Medicine*. Frontiers Media S.A.; 2020 [cited 2021 Jun 2]. p. 612393. Available from: [/pmc/articles/PMC7734181/](https://pmc/articles/PMC7734181/)
7. Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, et al. PiRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. *Clin Chim Acta* [Internet]. 2011 Aug 17 [cited 2021 Jun 4];412(17–18):1621–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/21616063/>
8. Mattick JS, Makunin I V. Non-coding RNA. Vol. 15 *Spec No, Human molecular genetics*. Hum Mol Genet; 2006.

9. Ponting CP, Oliver PL, Reik W. Evolution and Functions of Long Noncoding RNAs [Internet]. Vol. 136, Cell. Elsevier B.V.; 2009 [cited 2021 Jun 4]. p. 629–41. Available from: <https://pubmed.ncbi.nlm.nih.gov/19239885/>
10. Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, et al. PiRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. Clin Chim Acta [Internet]. 2011 Aug 17 [cited 2021 May 18];412(17–18):1621–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/21616063/>
11. Guo B, Li D, Du L, Zhu X. piRNAs: biogenesis and their potential roles in cancer [Internet]. Vol. 39, Cancer and Metastasis Reviews. Springer; 2020 [cited 2021 May 17]. p. 567–75. Available from: <https://pubmed.ncbi.nlm.nih.gov/31960205/>
12. Calcagno DQ, Mota ER da S, Moreira FC, de Sousa SBM, Burbano RR, Assumpção PP. Role of PIWI-interacting RNA (piRNA) as epigenetic regulation. In: Handbook of Nutrition, Diet, and Epigenetics [Internet]. Springer International Publishing; 2019 [cited 2021 Jun 19]. p. 187–209. Available from: https://link.springer.com/referenceworkentry/10.1007/978-3-319-55530-0_77
13. T T, H L. The biogenesis and function of PIWI proteins and piRNAs: progress and prospect. Annu Rev Cell Dev Biol [Internet]. 2009 Nov [cited 2021 Jul 31];25:355–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/19575643/>
14. Weng W, Liu N, Toiyama Y, Kusunoki M, Nagasaka T, Fujiwara T, et al. 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 [Internet]. 2018 Jan 30 [cited 2021 May 17];17(1). Available from: <https://pubmed.ncbi.nlm.nih.gov/29382334/>
15. Le Thomas A, Rogers AK, Webster A, Marinov GK, Liao SE, Perkins EM, et al. Piwi induces piRNA-guided transcriptional silencing and establishment of a repressive chromatin state. Genes Dev [Internet]. 2013 Feb 15 [cited 2021 May 17];27(4):390–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/23392610/>
16. Ishizu H, Siomi H, Siomi MC. Biology of Piwi-interacting RNAs: New insights into biogenesis and function inside and outside of germlines [Internet]. Vol. 26, Genes and Development. Genes Dev; 2012 [cited 2021 Jun 19]. p. 2361–73. Available from: <https://pubmed.ncbi.nlm.nih.gov/23124062/>
17. Yamashiro H, Siomi MC. PIWI-Interacting RNA in Drosophila: Biogenesis, Transposon Regulation, and beyond. Chem Rev. 2018 Apr 25;118(8):4404–21.
18. Ku HY, Lin H. PIWI proteins and their interactors in piRNA biogenesis, germline development and gene expression [Internet]. Vol. 1, National Science Review. Oxford University Press; 2014 [cited 2021 May 17]. p. 205–18. Available from: <https://pubmed.ncbi.nlm.nih.gov/25512877/>
19. Iwasaki YW, Siomi MC, Siomi H. PIWI-interacting RNA: Its biogenesis and functions. Annu Rev Biochem. 2015 Jun 2;84:405–33.
20. Weick EM, Miska EA. piRNAs: From biogenesis to function [Internet]. Vol. 141, Development (Cambridge). Company of Biologists Ltd; 2014 [cited 2021 Jun 19]. p. 3458–71. Available from: <https://pubmed.ncbi.nlm.nih.gov/25183868/>

21. Ku HY, Lin H. PIWI proteins and their interactors in piRNA biogenesis, germline development and gene expression [Internet]. Vol. 1, National Science Review. Oxford University Press; 2014 [cited 2021 Jun 19]. p. 205–18. Available from: [/pmc/articles/PMC4265212/](https://pubmed.ncbi.nlm.nih.gov/24265212/)
22. Luteijn MJ, Ketting RF. PIWI-interacting RNAs: From generation to transgenerational epigenetics [Internet]. Vol. 14, Nature Reviews Genetics. Nat Rev Genet; 2013 [cited 2021 Jun 19]. p. 523–34. Available from: <https://pubmed.ncbi.nlm.nih.gov/23797853/>
23. E B, N L, H L. piRNA biogenesis during adult spermatogenesis in mice is independent of the ping-pong mechanism. Cell Res [Internet]. 2012 Oct [cited 2021 Jul 31];22(10):1429–39. Available from: <https://pubmed.ncbi.nlm.nih.gov/22907665/>
24. Thomson T, Lin H. The biogenesis and function of PIWI proteins and piRNAs: Progress and prospect [Internet]. Vol. 25, Annual Review of Cell and Developmental Biology. Annu Rev Cell Dev Biol; 2009 [cited 2021 Jun 19]. p. 355–76. Available from: <https://pubmed.ncbi.nlm.nih.gov/19575643/>
25. Ross RJ, Weiner MM, Lin H. PIWI proteins and PIWI-interacting RNAs in the soma [Internet]. Vol. 505, Nature. Nature; 2014 [cited 2021 Jun 19]. p. 353–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/24429634/>
26. Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, et al. piRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. Clin Chim Acta. 2011 Aug 17;412(17–18):1621–5.
27. A F, DI J, AE H, T Z, Y Z. PIWI-interacting RNA 021285 is involved in breast tumorigenesis possibly by remodeling the cancer epigenome. Carcinogenesis [Internet]. 2015 Aug 16 [cited 2021 Nov 6];36(10):1094–102. Available from: <https://pubmed.ncbi.nlm.nih.gov/26210741/>
28. J C, JM G, BX X, Y M, Z J, H Z, et al. piRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. Clin Chim Acta [Internet]. 2011 Aug 17 [cited 2021 Nov 4];412(17–18):1621–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/21616063/>
29. T L, J W, L S, M L, X H, J J, et al. Piwi-interacting RNA-651 promotes cell proliferation and migration and inhibits apoptosis in breast cancer by facilitating DNMT1-mediated PTEN promoter methylation. Cell Cycle [Internet]. 2021 [cited 2021 Nov 6];20(16):1603–16. Available from: <https://pubmed.ncbi.nlm.nih.gov/34313525/>
30. G H, H H, X X, S S, E G, G G, et al. Altered expression of piRNAs and their relation with clinicopathologic features of breast cancer. Clin Transl Oncol [Internet]. 2013 Jul [cited 2021 Nov 4];15(7):563–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/23229900/>
31. Tan L, Mai D, Zhang B, Jiang X, Zhang J, Bai R, et al. PIWI-interacting RNA-36712 restrains breast cancer progression and chemoresistance by interaction with SEPW1 pseudogene SEPW1P RNA. Mol Cancer 2019 181 [Internet]. 2019 Jan 12 [cited 2021 Nov 4];18(1):1–15. Available from: <https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-019-0940-3>
32. Zhang H, Ren Y, Xu H, Pang D, Duan C, Liu C. The expression of stem cell protein Piwil2 and piR-932 in breast cancer [Internet]. Vol. 22, Surgical Oncology. Surg Oncol; 2013 [cited 2021 May 18]. p. 217–23. Available from: <https://pubmed.ncbi.nlm.nih.gov/23992744/>

33. X D, Y L, J L, Q Z, Y G, Z L, et al. piRNA-823 Is Involved in Cancer Stem Cell Regulation Through Altering DNA Methylation in Association With Luminal Breast Cancer. *Front cell Dev Biol* [Internet]. 2021 Mar 15 [cited 2021 Nov 6];9. Available from: <https://pubmed.ncbi.nlm.nih.gov/33791297/>
34. Öner Ç, Coşan DT, Çolak E. Estrogen and androgen hormone levels modulate the expression of piwi interacting RNA in prostate and breast cancer. *PLoS One*. 2016 Jul 1;11(7).
35. Cheng J, Deng H, Xiao B, Zhou H, Zhou F, Shen Z, et al. PiR-823, a novel non-coding small RNA, demonstrates in vitro and in vivo tumor suppressive activity in human gastric cancer cells. *Cancer Lett*. 2012 Feb 1;315(1):12–7.
36. J F, M Y, Q W, F S, Y Z, X W, et al. Novel evidence for oncogenic piRNA-823 as a promising prognostic biomarker and a potential therapeutic target in colorectal cancer. *J Cell Mol Med* [Internet]. 2020 [cited 2021 Nov 6];24(16). Available from: <https://pubmed.ncbi.nlm.nih.gov/32596991/>
37. Huang G, Hu H, Xue X, Shen S, Gao E, Guo G, et al. Altered expression of piRNAs and their relation with clinicopathologic features of breast cancer. *Clin Transl Oncol*. 2013 Jul;15(7):563–8.
38. Ritter A, Hirschfeld M, Berner K, Rücker G, Jäger M, Weiss D, et al. Circulating non-coding RNA-biomarker potential in neoadjuvant chemotherapy of triple negative breast cancer? *Int J Oncol*. 2020;56(1):47–68.
39. Alexandrova E, Lamberti J, Saggese P, Cells GP-, 2020 undefined. Small non-coding RNA profiling identifies miR-181a-5p as a mediator of estrogen receptor beta-induced inhibition of cholesterol biosynthesis in triple. *mdpi.com* [Internet]. [cited 2021 Nov 6]; Available from: <https://www.mdpi.com/681922>
40. <https://www.ncbi.nlm.nih.gov/pmc/articles/pmc5370502/>
41. Kärkkäinen E, Heikkinen S, Tengström M, Kosma VM, Mannermaa A, Hartikainen JM. The debatable presence of PIWI-interacting RNAs in invasive breast cancer. *Cancer Med*. 2021 Jun 1;10(11):3593–603.
42. A F, DI J, AE H, T Z, Y Z. PIWI-interacting RNA 021285 is involved in breast tumorigenesis possibly by remodeling the cancer epigenome. *Carcinogenesis* [Internet]. 2015 Aug 16 [cited 2021 Nov 4];36(10):1094–102. Available from: <https://pubmed.ncbi.nlm.nih.gov/26210741/>
43. Wang QE, Han C, Milum K, Wani AA. Stem cell protein Piwil2 modulates chromatin modifications upon cisplatin treatment. *Mutat Res - Fundam Mol Mech Mutagen* [Internet]. 2011 Mar 15 [cited 2021 Jun 21];708(1–2):59–68. Available from: [/pmc/articles/PMC3091508/](https://pubmed.ncbi.nlm.nih.gov/21616063/)
44. Wang Z, Liu N, Shi S, Liu S, Lin H. The role of PIWIL4, an argonaute family protein, in breast cancer. *J Biol Chem*. 2016 May 13;291(20):10646–58.
45. JJ L, R S, L C, Y Y, G H, K H, et al. 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* [Internet]. 2010 [cited 2021 Jul 26];3(4):328–37. Available from: <https://pubmed.ncbi.nlm.nih.gov/20490325/>
46. Cheng J, Guo JM, Xiao BX, Miao Y, Jiang Z, Zhou H, et al. PiRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. *Clin Chim Acta* [Internet]. 2011 Aug 17 [cited 2021 Jun 22];412(17–18):1621–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/21616063/>

47. Li D, Sun X, Yan D, Huang J, Luo Q, Tang H, et al. Piwi2 modulates the proliferation and metastasis of colon cancer via regulation of matrix metalloproteinase 9 transcriptional activity. *Exp Biol Med* [Internet]. 2012 Oct 1 [cited 2021 Jun 21];237(10):1231–40. Available from: <https://journals.sagepub.com/doi/abs/10.1258/ebm.2012.011380>
48. Weng W, Liu N, Toiyama Y, Kusunoki M, Nagasaka T, Fujiwara T, et al. 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*. 2018 Jan 30;17(1).
49. Yin J, Jiang XY, Qi W, Ji CG, Xie XL, Zhang DX, et al. piR-823 contributes to colorectal tumorigenesis by enhancing the transcriptional activity of HSF1. *Cancer Sci* [Internet]. 2017 Sep 1 [cited 2021 May 18];108(9):1746–56. Available from: <https://pubmed.ncbi.nlm.nih.gov/28618124/>
50. Chu H, Xia L, Qiu X, Gu D, Zhu L, Jin J, et al. Genetic variants in noncoding PIWI-interacting RNA and colorectal cancer risk. *Cancer* [Internet]. 2015 Jun 1 [cited 2021 May 18];121(12):2044–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/25740697/>
51. Martinez VD, Enfield KSS, Rowbotham DA, Lam WL. An atlas of gastric PIWI-interacting RNA transcriptomes and their utility for identifying signatures of gastric cancer recurrence. *Gastric Cancer* [Internet]. 2016 Apr 1 [cited 2021 May 17];19(2):660–5. Available from: <https://pubmed.ncbi.nlm.nih.gov/25779424/>
52. Mai D, Ding P, Tan L, Zhang J, Pan Z, Bai R, et al. PIWI-interacting RNA-54265 is oncogenic and a potential therapeutic target in colorectal adenocarcinoma. *Theranostics*. 2018;8(19):5213–30.
53. Vychytilova-Faltejskova P, Stitkovcova K, Radova L, Sachlova M, Kosarova Z, Slaba K, et al. Circulating PIWI-interacting RNAs piR-5937 and piR-28876 are promising diagnostic biomarkers of colon cancer. *Cancer Epidemiol Biomarkers Prev* [Internet]. 2018 Sep 1 [cited 2021 May 17];27(9):1019–28. Available from: <https://pubmed.ncbi.nlm.nih.gov/29976566/>
54. Romano G, Veneziano D, Acunzo M, Croce CM. Small non-coding RNA and cancer [Internet]. Vol. 38, *Carcinogenesis*. Oxford University Press; 2017 [cited 2021 Apr 11]. p. 485–91. Available from: <https://pubmed.ncbi.nlm.nih.gov/28449079/>
55. G H, H H, X X, S S, E G, G G, et al. Altered expression of piRNAs and their relation with clinicopathologic features of breast cancer. *Clin Transl Oncol* [Internet]. 2013 Jul [cited 2021 Jul 10];15(7):563–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/23229900/>
56. Yin J, Qi W, Ji C, Zhang D, Xie X, Ding Q, et al. Small RNA sequencing revealed aberrant piRNA expression profiles in colorectal cancer. *Oncol Rep* [Internet]. 2019 Jul 1 [cited 2021 Aug 1];42(1):263–72. Available from: <http://www.spandidos-publications.com/10.3892/or.2019.7158/abstract>
57. Qian L, Xie H, Zhang L, Zhao Q, Lü J, Yu Z. Piwi-Interacting RNAs: A New Class of Regulator in Human Breast Cancer. *Front Oncol*. 2021 Jul 6;0:2525.
58. S B, N W, S B. A piRNA utilizes HILI and HIWI2 mediated pathway to down-regulate ferritin heavy chain 1 mRNA in human somatic cells. *Nucleic Acids Res* [Internet]. 2018 [cited 2021 Nov 6];46(20). Available from: <https://pubmed.ncbi.nlm.nih.gov/30102404/>

59. Aberrant Expression of PIWIL1 and PIWIL2 and Their Clinical Significance in Ductal Breast Carcinoma | Anticancer Research [Internet]. [cited 2021 Nov 6]. Available from: <https://ar.iijournals.org/content/38/4/2021>
60. <https://www.ncbi.nlm.nih.gov/pmc/articles/pmc2872741/>
61. Wang Z, Liu N, Shi S, Liu S, Lin H. The Role of PIWIL4, an Argonaute Family Protein, in Breast Cancer. J Biol Chem [Internet]. 2016 May 13 [cited 2021 Nov 8];291(20):10646–58. Available from: <https://pubmed.ncbi.nlm.nih.gov/26957540/>
62. Mei Y, Clark D, Mao L. Novel dimensions of piRNAs in cancer [Internet]. Vol. 336, Cancer Letters. Elsevier Ireland Ltd; 2013 [cited 2021 May 19]. p. 46–52. Available from: <https://pubmed.ncbi.nlm.nih.gov/23603435/>

Figures

Tumor marker

PiR20365

PiR20485

Tumor progression

PiR615

PiR36712

lymphnode metastasis

PiR4987

Figure 1

Figure legend not provided with this version.