Send Orders for Reprints to reprints@benthamscience.net

Current Medicinal Chemistry, 2024, *31*, 453-463

REVIEW ARTICLE

Novel Perspectives for the Diagnosis and Treatment of Gynecological Cancers using Dysregulation of PIWI Protein and PiRNAs as Biomarkers

Bahman Yousefi[1,2], Fatemeh Sadoughi[3,*], Zatollah Asemi[3], Mohammad Ali Mansournia[4] and Jamal Hallajzadeh[5,*]

[1]Molecular Medicine Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; [2]Department of Biochemistry, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran; [3]Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, I.R. Iran; [4]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [5]Department of Biochemistry and Nutrition, Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran

ARTICLE HISTORY

Received: May 24, 2022
Revised: November 23, 2022
Accepted: December 23, 2022

DOI:
10.2174/0929867330666230214101837

Abstract: The term "gynecological cancer" is used for a group of cancers occurring in the female reproductive system. Some of these cancers are ranked as the leading causes of death in developed and developing countries. The lack of proper diagnostic strategies is one of the most important reasons that make them lethal. PIWI-interacting RNAs or piRNAs are a class of small non-coding RNAs, which contain 24-32 nucleotides. These RNAs take part in some cellular mechanisms, and their role in diverse kinds of cancer is confirmed by accumulative evidence. In this review, we gather some information on the roles of these RNAs and members of the PIWI protein family to provide new insight into accurate diagnostic biomarkers and more effective anti-cancer drugs with fewer side effects.

Keywords: PIWI protein, piRNA, PIWIL2, ovarian cancer, cervical cancer, anti-cancer drug.

1. INTRODUCTION

For years, the main known function for RNAs was the production of proteins [1], and thus, because only 1-2% of DNA can encode proteins, the other 98% of DNA was considered useless. The discovery of microRNAs as the first RNAs, which were transcribed from the non-coding parts of DNA, was a turning point regarding RNAs' capabilities [2-4]. Considering the functional activities of non-coding RNAs or ncRNAs, we can classify them into three groups: housekeeping, transferring, and regulatory [5-8].

Regulatory ncRNAs, which influence many cellular processes, such as gene expression, cell cycle, and apoptosis, are classified into two subgroups: long and small ncRNAs [7, 9, 10]. P-Element induced wimpy testis (PIWI) - interacting RNAs known as piRNAs are a kind of small non-coding RNAs (sncRNAs) that are longer than miRNAs and siRNAs (two other members of sncRNAs) and contain 24-32 nucleotides [11]. These ncRNAs were primarily discovered in Drosophila melanogaster testis by Aravin and colleagues [12-14]. PiRNAs influence numerous cellular functions, including the silencing of retrotransposons at the post-transcriptional and epigenetic levels, maintaining DNA integrity, and other genetic elements in germ lines by means of binding to PIWI proteins [4, 11]. Regarding the functions of piRNAs, it has been observed that they can be involved in the pathogenesis of a few diseases, including cancer. Recent studies have found dysregulated piRNAs in gastric [15, 16], breast [17], and kidney cancers [18].

Gynecological cancer is a general term for a group of cancers affecting the organs of the female reproductive system. These organs include the uterine corpus, cervix, ovary, vulva, and vagina. According to cancer

*Address correspondence to these authors at the Research Center for Biochemistry and Nutrition in Metabolic Diseases, Institute for Basic Sciences, Kashan University of Medical Sciences, Kashan, I.R. Iran; E-mail: rahasadoughi@gmail.com (Fatemeh Sadoughi)
Department of Biochemistry and Nutrition, Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran;
E-mail: j.hallajzadeh@mrgums.ac.ir (Jamal Hallajzadeh)

1875-533X/24 $65.00+.00

statistics, gynecological cancers are the eighth most common cancers in the United States, and 33100 women died from these cancers in 2019 [19]. Demography of the World Cancer Research Fund demonstrates that cervical, endometrial, ovarian, vulvar, and vaginal cancers are the eighth, fifteenth, eighteenth, thirtieth, and thirty-fourth common cancers among the people of the world, respectively [20]. Therefore, the noticeable number of newly diagnosed cases and the extensive mortality rate of these cancers are representative of their importance and the need for novel diagnostic and/or therapeutic procedures. This paper is an attempt to pave the way for the diagnosis of gynecological cancers by designing novel biomarkers through the medium of piRNAs. Considerable potentials of these RNAs might be a solution for an earlier diagnosis or prognosis of these lethal cancers.

2. GYNECOLOGICAL CANCERS: PREVALENCE, PATHOGENESIS, AND IAGNOSIS

Of all the cancers occurring in the female reproductive system, cervical, uterine corpus, and ovarian cancers are more common and are respectively ranked as the fourth, sixth, and eighth most frequent cancers among women worldwide [20]. In this section, we examine the pathogenesis of each gynecological cancer and recent diagnostic tools used for women that are suspected of having one of these cancers.

2.1. Cervical Cancer

A mortality rate of 311365 in 2018 has made cervical cancer a serious challenge in both developed and developing countries [21]. Commonly, this cancer is acknowledged as being a result of the human papillomavirus infection. The oncogenic feature of types 16 and 18 of this virus is the most important risk factor for transforming normal cervical cells into cancerous ones [22]. Visual examination, biopsy, colposcopy, Papanicolaou smear, and some other tests for the detection of HPV infection are the common screening tests that are practical for cervical cancer diagnosis [23-25].

2.2. Tumors of the Uterine Corpus

This kind of tumor can originate from the epithelial cells (endometrial carcinoma or EC), the stromal cells (endometrial stromal tumors or EST), and the smooth muscles (Uterine smooth muscle tumors or USMT) of the uterine. Endometrial carcinoma is the most common form of uterine cancer [26]. Imaging techniques, such as transvaginal ultrasonography, MRI, biopsy, and Pap smear, are some methods commonly utilized for the diagnosis of endometrial cancer [27, 28].

2.3. Ovarian Cancer

Annually, 23,9000 new women are diagnosed with ovarian cancer, and 15,2000 women are estimated to die due to this lethal cancer [29, 30]. Ovarian cancer is fatal cancer in comparison to other gynecological cancers, and women of all ages are prone to be affected by this disease [31]. The 5-year survival rate of this cancer has a wide range and depends on the stage of the disease and the country in which the patients are being diagnosed [32]. Overall, due to the late diagnosis of this cancer, the survival rate for most of the patients is only 29% [33]. Common procedures known for the diagnosis of ovarian cancer are physical examination, transvaginal ultrasonography, and detecting serum biomarkers, such as cancer antigen 125 (CA 125) and human epididymis protein 4 (HE4) [30, 33, 34]. Furthermore, some new methods with more sensitivity and specificity have been revealed recently for the diagnosis of this cancer, including serum proteomics and immunohistochemistry screening [34].

2.4. Other Less Common Gynecological Cancers

Among all organs of the female reproductive system, the vagina and vulva are the least common organs affected by cancer. Both of these cancers, the same as cervical cancer, are results of HPV infection; however, vulvar cancer can also have a non-HPV origin [35]. Vulvar cancer is a rare condition mostly observed in postmenopausal women and represents only 2-5% of all gynecological malignancies [36, 37]. According to evidence, mostly symptoms, direct examination, biopsy, and imaging techniques are adopted for diagnosis of this disease due to the lack of a specific diagnostic method [38-40]. Vaginal cancer is another rare cancer in women (2-3% of all gynecological cancers) that involves the vaginal wall and can spread into paravaginal tissues, pelvic sidewall, bladder, and rectal mucosa in its advanced stages [35]. Similar to vulvar cancer, direct examination, biopsy, and imaging techniques are utilized for vaginal cancer diagnosis [35, 40, 41].

3. PiRNAs AND PIWI PROTEINS: CELLULAR MECHANISMS

There are some roles defined for piRNAs that are specific to germ cells. These roles include the death of the germ cell, spermatogenesis, phenotypic variations, genome rearrangement, and atrophy of the gonades, and they can also cause sterility in invertebrates and vertebrates [8, 42-51]. Besides these functions, it has been reported that they are involved in some functioning of somatic cells. Gene regulation through transposon silencing is among such functions. Transposons

are some DNA fragments with mobility properties, and their activities lead to genomic instability [52-54], gene dysregulation, DNA mutations that can be harmful, and the rearranging of cell chromosomes [55]. Generally, RNA interference is a primary pathway that enables cells to regulate their gene expression rapidly. RNA interference, or RNAi, is conducted by small non-coding RNAs, such as piRNAs [56]. In the case of piRNAs, RNAi impacts gene expression by suppressing piRNA/PIWI complexes. These complexes must migrate back to the nucleus and epigenetically silence transposons [56]. According to some evidence, these complexes can bind to euchromatin from one side and bind to heterochromatin protein 1 from the other side. This binding leads to the accumulation of heterochromatin protein 1, which is related to decreasing the binding of euchromatin and RNA polymerase [57]. This means that the piRNA/PIWI complex regulates gene expression by two mechanisms: indirectly by silencing TEs and directly by conducting epigenetic alterations on a specific gene. These are reasons why the role of recognizing sequence is attributed to the piRNA/PIWI complex [58].

4. PiRNAs AND PIWI PROTEINS: ONCOGENIC MECHANISMS

Up to now, a great number of piRNAs have been discovered, and each of them affects a different gene. Due to the diversity of genes, piRNAs are engaged in many mechanisms, including processes leading to cancer. However, this does not mean that they cannot function as tumor-suppressor agents [59, 60]. As mentioned before, piRNAs are only functional when they are linked to PIWI proteins. Therefore, any alteration in the expression of piRNAs and PIWI proteins is responsible for producing a cancerous cell. Generally, the PIWI protein family has four members in humans: PIWIL1 or Hiwi, PIWIL2 or Hili, PIWIL3, and PIWIL4 or Hiwi2 [61]. PiRNA/PIWI complexes perform their tasks by DNA hypomethylation, regulating diverse genes, and histone hypoacetylation [44]. Currently, investigations on different cancers have helped us to understand more about genes that can be affected by these RNAs. In this section, we explore some reasons other than DNA hypomethylation for the oncogenic roles of these complexes.

Influencing apoptosis is one of the tasks of these complexes; the piRNA/PIWI pathway can affect apoptosis directly and indirectly. The indirect mechanism is recognized in murine and zebrafish, which impacts some proteins, such as MAEL [62], but the direct mechanism occurs in humans by disturbing apoptotic genes, such as Bcl-X_L [56]. Overexpression of PIWI proteins is associated with the up-regulation of a group of proteins known as signal transducers and activators of transcription (STATs), which cause an induction in amounts of Bcl-XL expression [63]. Furthermore, some other genes and pathways in the apoptosis process that are prone to be affected by PIWI proteins are p14ARF/p53 and NF-κB pathway, Bcl-2, and c-Myc genes. Therefore, PIWI/piRNA complexes can impact apoptosis, cell cycle, cell growth, and cell division [63-66]. Besides, new research works have shown that these complexes are also involved in repairing damaged DNA. They modulate histone acetylation and thereby cause chromatin relaxation. This process is the main reason why the piRNA/PIWI pathway is implicated in repairing DNA [67]. Moreover, chromosome dynamics is another important factor impacted by the piRNA/PIWI pathway [63].

5. GYNECOLOGICAL CANCERS AND PIWI-INTERACTING RNAs

In this section, we explain the role of PIWI proteins and piRNAs in cervical, ovarian, and endometrial cancers. We did not find any reliable evidence regarding the role of PIWI-interacting RNAs in vulvar and vaginal cancers. Thus, we suggest investigating PIWI proteins and piRNAs in these cancers might help provide more diagnostic approaches.

5.1. Cervical Cancer

Cheng and colleagues explored the expression of piR-651 in some cancer cells and found that this piRNA was overexpressed in a cervical cancer cell line (HeLa). Hence, they suggested that these piRNAs might not only be involved in the pathogenesis of many cancers, including cervical cancer but they can also be utilized as a biomarker for this cancer [15]. Besides piRNAs, evidence demonstrates that all of the PIWI proteins except for PIWI3 are also involved in cervical cancer.

Some trials have investigated the expression of PIWI1 or HIWI in cervical cancer cells and discovered significant results. Liu *et al.* [68] declared that HIWI might be one of the related factors in the pathogenesis of cervical cancer by increasing stem cell-related transcription factors, OCT4, NANOG, KLF4, and BMI1. They suggested this hypothesis because of the role of this protein in self-renewal, gametogenesis, RNA silencing, and translational regulation of stem cells and its dysregulation in other types of cancer [69]. Therefore, new anti-cancer drugs targeting PIWIL1 can be useful for cervical cancer therapy. In another study,

Table 1. Empirical studies on piRNAs and PIWI proteins that are involved in cervical cancer.

Name of piRNA or PIWI Protein	Expression	Model	Function	Application	References
piR-651	Overexpression	*In vitro*	Involved in cervical cancer pathogenesis	Diagnosis	[15]
PIWIL1	Overexpression	*In vitro and Ex-vivo*	Affecting cancer stem cells and increasing resistance to chemo and radiotherapy	Diagnosis and treatment	[68]
PIWIL1	Overexpression	*In vitro*	Involve in HPV infection	Diagnosis and treatment	[70]
PIWIL2	Overexpression	*Ex-vivo*	To be used complementary with p16 as a biomarker	Diagnosis	[71]
PIWIL2	Overexpression	*In vitro*	Increasing binding of NME2 to G-quadruplex to increase c-Myc expression	Diagnosis and treatment	[65]
PIWIL4	Overexpression	*In vitro*	Affecting p14ARF/p53 pathway	Diagnosis and treatment	[74]
PL2L	Overexpression	*In vitro*	Affecting Bcl/STATS pathway	Diagnosis and treatment	[64]

another dimension of the HIWI contribution to cervical cancer was investigated. It was demonstrated that the overexpression of HIWI is related to HPV16 infection. In addition, due to the variable expression of this protein in different levels of cancer, HIWI can be used as a biomarker for determining the extent of cancer progression [70].

He *et al.* [71] examined the expression of the PIWIL2 gene in 91 specimens of patients with various types of cervical lesions. They observed that this gene was expressed in all cervical lesions ranging from benign to malignant. Therefore, it can be used complementary with HR-HVP, Pap test, and p16 for designing a more specific and sensitive biomarker. He *et al.* [71] also conducted similar research on using PIWIL2 complementary to p16 for providing a more effective biomarker. Ye *et al.* [64] also worked on PIWIL2 and found some variants of this gene in humans, like Piwil2-like (PL2L) genes. Explorations on PL2L revealed that it affects cell survival and proliferation by regulating BCL-2 and STATS-3 and affecting NF-κB. Eventually, their results proposed that Piwil2 and PL2L proteins might have two applications: being applied as biomarkers and two targets for designing new anticancer drugs for cervical cancer. Another research perusing the mechanisms by which PIWIL2 affects cell proliferation in tumors defines how PIWIL2 simplifies the binding of nucleoside diphosphate kinase 2 (NME2) to G-quadruplex to increase c-Myc expression [65]. C-Myc is one of the important genes in cell growth and apoptosis, and its overexpression in various cancers has been proven [72, 73]. PIWIL4 is the last member of this family. Su *et al.* [74] illustrated its role in cervical cancer pathogenesis. They expressed that PIWIL4 causes augmentation in cell growth and invasion of HeLa cells and may increase apoptosis through the p14ARF/p53 pathway. In other words, this protein also has the potential to be used as a biomarker or therapeutic target (Table **1**).

5.2. Ovarian Cancer

In ovarian cancer, several investigations also support the role of PIWI proteins in cancer pathogenesis. In a human study, Chen *et al.* [75] examined all forms of PIWI proteins in patients with ovarian cancer and observed that all four types of PIWI proteins were overexpressed in these patients. They noticed a meaningful relationship between the overexpression of these proteins and the primary and metastatic stages of this cancer. As a result, PIWI proteins can be used for both diagnostic and therapeutic purposes in ovarian cancer.

Lim *et al.* [62] conducted an *in vitro* research on the first member of the PIWI protein family, PIWIL1, and another protein named Maelstrom (MAEL), which is engaged in the piRNA pathway. They identified that both of these proteins are considerably up-regulated in the ovarian cancer cell line. However, no association with cancer invasiveness was reported for these two proteins. They also found that PIWI2 and 4 were expressed in both normal and cancerous cells of ovaries with no significant difference.

Lee *et al.* [63] attempted to find the mechanisms through which PIWIL2 works. They noticed that the overexpression of this protein is related to apoptosis and cell proliferation in cancer stem cells with the help of the STATS/Bcl-X_L signaling pathway. Wang *et al.* [67] investigated another role of PIWIL2 in ovarian cancer. They declared that this protein takes part in acetylating cellular chromatin, and after the exposure of DNA to a damaging agent, it causes a relaxation in the genome. Considering this function of PIWIL2, they concluded that the overexpression of PIWIL2 is responsible for making ovarian tumors resistant to cisplatin (one of the common chemotherapeutic drugs). Another article inquired about the expression of one of the

Table 2. Empirical studies on the role of piRNAs and PIWI proteins that are involved in ovarian cancer.

Name of piRNA or PIWI Protein	Expression	Model	Function	Application	References
piR-33733	Overexpression	*Ex-vivo*	Affecting the expression of ACTR10 and PLEKHA5 genes	Diagnosis and treatment	[77]
piR-52207	Overexpression	*Ex-vivo*	Disturbing Lipoate biosynthesis pathway by the LIAS gene	Diagnosis and treatment	[77]
piR-n4_chr11_122017273	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[78]
PIWIL1	Overexpression	*Ex-vivo*	Causing metastasis	Diagnosis and treatment	[76]
PIWIL1	Overexpression	*Ex-vivo and In vitro*	Co-expression with MAEL and L1	Diagnosis	[62]
PIWIL1	Overexpression	*Ex-vivo*	Causing metastasis	Diagnosis and treatment	[75]
PIWIL2	Overexpression	*Ex-vivo and In vitro*	Co-expression with MAEL and L1	Diagnosis	[62]
PIWIL2	Overexpression	*In vitro*	Inhibiting apoptosis through activation of STAT3/Bcl-XL pathway	Diagnosis and treatment	[63]
PIWIL2	Overexpression	*Ex-vivo*	Modulating chromatin modifications upon cisplatin treatment	Diagnosis and treatment	[67]
PIWIL2	Overexpression	*Ex-vivo*	STATS/Bcl-X_L signaling pathway, resistance to cisplatin	Diagnosis and treatment	[76]
PIWIL2	Overexpression	*Ex-vivo*	Causing metastasis	Diagnosis and treatment	[75]
PIWIL3	Overexpression	*Ex-vivo*	Causing metastasis	Diagnosis and treatment	[75]
PIWIL3	Overexpression	*In vitro*	Causing metastasis	Diagnosis	[76]
PIWIL4	Overexpression	*Ex-vivo*	Causing metastasis	Diagnosis and treatment	[75]
PIWIL4	Overexpression	*In vitro*	Affecting p14ARF/p53 pathway	Diagnosis and treatment	[76]
PL2L	Overexpression	*In vitro*	Affecting Bcl/STATS pathway	Diagnosis and treatment	[64]

PIWIL2 variants called PL2L genes and found that this gene is not only overexpressed in ovarian and cervical cancer but is also widely expressed in a great number of other cancers. Considering the oncogenic roles of this gene in ovarian cells and cervical cells, it is a candidate for being used as a biomarker and a therapeutic target [64].

Another research conducted by Chen *et al.* demonstrated an association between the PIWI proteins and ovarian cancer metastasis. They demonstrated that all of the members of PIWI proteins are overexpressed in advanced and metastatic stages of ovarian cancer, and therefore, they attributed these proteins to ovarian cancer metastasis [6]. Singh and colleagues [76, 77] conducted a genome-wide piRNA profiling trial and observed 111 dysregulated piRNAs in endometrioid ovarian cancer and serous ovarian cancer. They introduced up-regulated piR-33733 as an involved factor in the pathogenesis of this cancer by influencing lipoic acid synthetase or LIAS gene, thereby disturbing the lipoate biosynthesis pathway. Likewise, they introduced piR-52207, which affects ACTR10 (actin-related protein 10 homolog, also known as Arp11) and PLEKHA5 (Pleckstrin homology domain-containing family A member 5) genes in cervical cancer cells, thereby helping the cancer progression. Another study examined the role of piRNAs and miRNAs in tumor spread and identified 13 small RNAs, including piR-n4_chr11_122017273, involved in this cancer [78] (Table **2**).

5.3. Endometrial Cancer

Ravo *et al.* [79] inspected the role of entire small non-coding RNAs on endometrial cancer. After smallRNA-Seq analysis, they found 10 piRNAs, including hsa_piR_016658_DQ59293, hsa_piR_001152_DQ57-1500, hsa_piR_019354_DQ596587, hsa_piR_019825_DQ597218, hsa_piR_001170_DQ571526, hsa_piR_017791_DQ594556, hsa_piR_019168_DQ596311, hsa_piR_020009_DQ597484, hsa_piR_020496_DQ5-98175, and hsa_piR_020815_DQ598651 in significant levels.

Considering the PIWIL1, Chen *et al.* [80] recognized a meaningful difference in the amounts of this

Table 3. Experimental studies conducted on piRNAs and PIWI proteins that are involved in endometrial cancer.

Name of piRNA or PIWI Protein	Expression	Model	Function	Application	References
hsa_piR_001152_DQ571500	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_001170_DQ571526	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_016658_DQ59293	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_017791_DQ594556	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_020009_DQ597484	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_019168_DQ596311	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_019354_DQ596587	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_019825_DQ597218	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_020496_DQ598175	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
hsa_piR_020815_DQ598651	Overexpression	*Ex-vivo*	Unknown	Diagnosis	[79]
PIWIL1	Overexpression	*Ex-vivo*	Increases invasion, growth, and metastasis of cancer cells by inducing the epithelial-mesenchymal transition (EMT) process	Diagnosis and treatment	[81]
PIWIL2	Overexpression	*Ex-vivo*	Inactivate a tumor suppressor gene, PTEN, by the DNA methylation mean	Diagnosis and treatment	[80]

gene's expression. They clarified that PIWIL1 increases the invasion, growth, and metastasis of cancer cells by inducing the epithelial-mesenchymal transition (EMT) process. Moreover, PIWIL1 causes augmentation in some markers, which are known for endometrial cancer, such as CD44 and ALDH1. Another study also represents another mechanism for PIWIL2, *i.e.*, epigenetic functions. It was revealed that PIWIL1 could inactivate a tumor suppressor gene, PTEN, by DNA methylation. PIWIL1 participates in DNA methylation by affecting an enzyme known as DNA methyltransferase 1 in type 1 endometrial cancer [81]. Liu and colleagues also confirmed the overexpression of this protein in endometrial cancer [82] (Table **3**).

CONCLUSION

Enhancing the therapeutic strategies and designing more specific and sensitive biomarkers have saved a great number of individuals from suffering from different types of cancer. These advancements have improved 5-year survival rate of many cancers to a significant level. However, there is still room for more diagnostic and therapeutic procedures to achieve an earlier diagnosis and a less risky therapy with fewer side effects. Gynecological cancers are causing numerous deaths each year. For instance, cervical cancer, which has the fourth rank among all the cancers occurring in both men and women, affected approximately 569,847 new cases in 2018 [20]. Poor prognosis, late diagnosis due to being asymptomatic in early stages, and resistance to the common therapies are some factors that have made some of these cancers, like ovarian cancer, an important global challenge. Studying PIWI proteins and their interacting RNAs, piRNAs, in cancer is still in its infancy, and yet, extensive research is required to determine their exact roles in different stages of cancer, such as pathogenesis, prognosis, diagnosis, and treatment. Recently, an increasing number of papers have been published to define the role of PIWI proteins and piRNAs in gynecological cancers, which have successfully revealed their expressions in these cancers. Nevertheless, there is an intense need for reliable evidence on the effect of PIWI proteins and piRNAs in vaginal and vulvar cancers. In this paper, we reviewed several pieces of evidence and noticed that the overexpression of intended proteins and RNAs had been confirmed in ovarian, cervical, and endometrial cancers. This fact has not only widened our knowledge about the pathogenesis of these cancers but has also paved the way to provide some novel biomarkers and anti-cancer drugs. For instance, the detection of overexpression of PIWIL2 in ovarian cancer can have two results:

1. Fabricating a sensitive and specific biomarker for early and asymptomatic stages of ovarian cancer.

2. Providing a novel drug with the ability to target this protein to induce apoptosis, specifically in cancerous cells of ovaries (Figs. **1** and **2**). This drug will not only increase cancer cell death with a low amount of

side effects but also increase the response of this cancer to cisplatin.

All taken together, identifying the dysregulation of PIWI proteins and their interacting RNAs in gynecological cancers will help us to fully understand some mechanisms by which these cancers work and will make an evolution in diagnostic and therapeutic procedures of these cancers in the coming years.

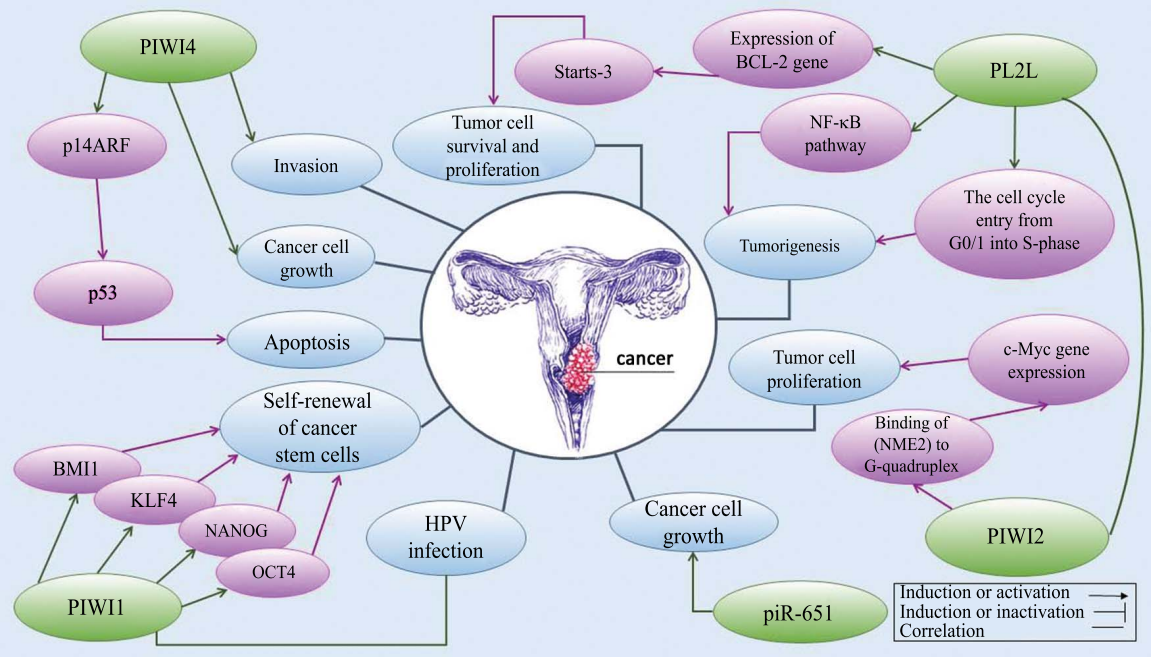

Fig. (1). Functions of PIWI proteins and their interacting RNAs in cervical cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

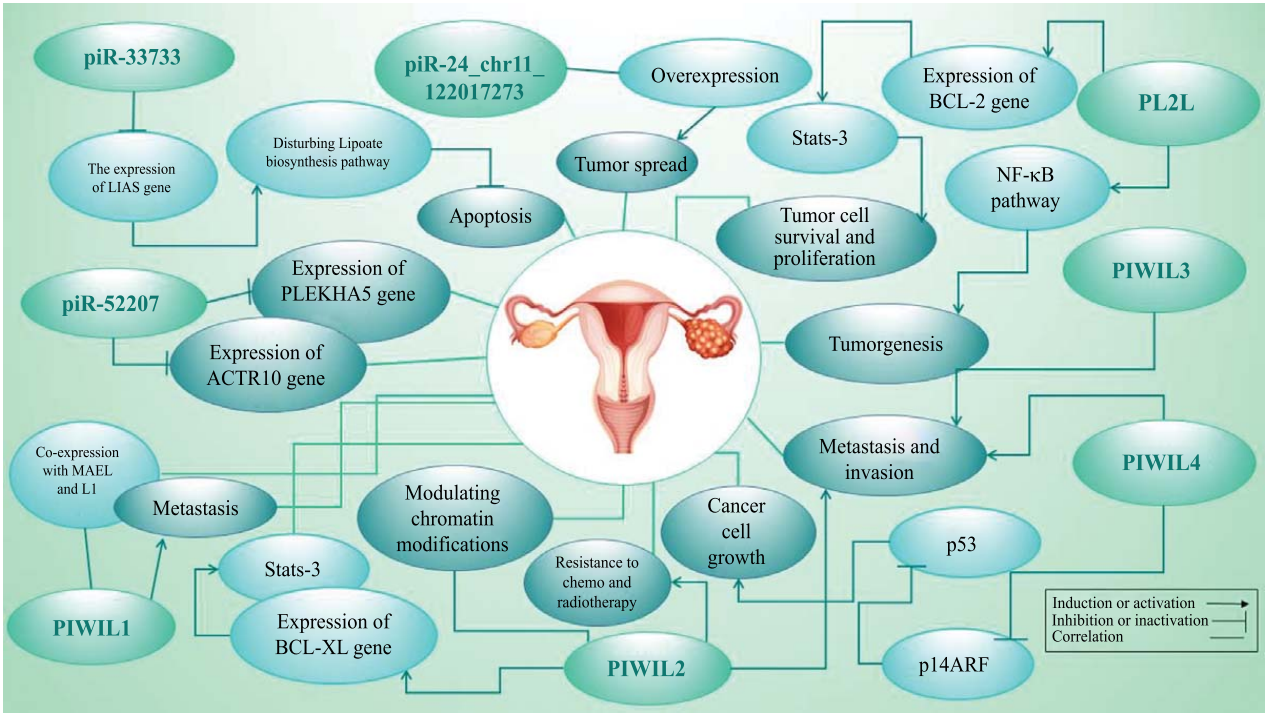

Fig. (2). Functions of PIWI proteins and their interacting RNAs in ovarian cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

ACKNOWLEDGMENTS

The authors would like to thank Shohada Clinical Research Development Unit, Shohada Hospital, Tabriz University of Medical Science, Tabriz, Iran.

LIST OF ABBREVIATIONS

PIWI	=P-Element Induced Wimpy Testis
sncRNAs	=Small Non-coding RNAs EC
	=Endometrial Carcinoma
EST	=Endometrial Stromal Tumors
USMT	=Uterine Smooth Muscle Tumors
EEC	=Endometrioid Endometrial Carcinoma
NEEC	=Non-endometrioid Endometrial Carci noma
CA 125	=Cancer Antigen 125
HE4	=Human Epididymis Protein 4
Zuc	=Zucchini
AGO3	=Argonaute 3
Aub	=Aubergine
STATs	=Signal Transducer and Activator of Transcription
HeLa	= Cervical Cancer Cell Line
PL2L	= Piwil2-like
NME2	= Nucleoside Diphosphate Kinase 2
MAEL	= Maelstrom
ACTR10	= Actin-related Protein 10 Homolog
PLEKHA5	= Pleckstrin Homology Domain-containing Family A Member 5
EMT	= Epithelial-mesenchymal Transition

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

[1] Crick, F. Central dogma of molecular biology. *Nature,* **1970**, *227*(5258), 561-563. http://dx.doi.org/10.1038/227561a0 PMID: 4913914

[2] Yang, J.X.; Rastetter, R.H.; Wilhelm, D. Non-coding RNAs: An introduction. *Adv. Exp. Med. Biol.,* **2016**, *886*, 13-32. http://dx.doi.org/10.1007/978-94-017-7417-8_2 PMID: 26659485

[3] Elgar, G.; Vavouri, T. Tuning in to the signals: Noncoding sequence conservation in vertebrate genomes. *Trends Genet.,* **2008**, *24*(7), 344-352. http://dx.doi.org/10.1016/j.tig.2008.04.005 PMID: 18514361

[4] Romano, G.; Veneziano, D.; Acunzo, M.; Croce, C.M. Small non-coding RNA and cancer. *Carcinogenesis,* **2017**, *38*(5), 485-491. http://dx.doi.org/10.1093/carcin/bgx026 PMID: 28449079

[5] Palazzo, A.F.; Lee, E.S. Non-coding RNA: What is functional and what is junk? *Front. Genet.,* **2015**, *6*, 2. http://dx.doi.org/10.3389/fgene.2015.00002 PMID: 25674102 [6] Siomi, M.C.; Sato, K.; Pezic, D.; Aravin, A.A. PIWI-interacting small RNAs: The vanguard of genome defence. *Nat. Rev. Mol. Cell Biol.,* **2011**, *12*(4), 246-258. http://dx.doi.org/10.1038/nrm3089 PMID: 21427766

[7] Ghildiyal, M.; Zamore, P.D. Small silencing RNAs: An expanding universe. *Nat. Rev. Genet.,* **2009**, *10*(2), 94-108. http://dx.doi.org/10.1038/nrg2504 PMID: 19148191

[8] Han, Y.N.; Li, Y.; Xia, S.Q.; Zhang, Y.Y.; Zheng, J.H.; Li, W. PIWI proteins and PIWI-interacting RNA: Emerging roles in cancer. *Cell. Physiol. Biochem.,* **2017**, *44*(1), 1-20. http://dx.doi.org/10.1159/000484541 PMID: 29130960

[9] Bartel, DP MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell,* **2004**, *116*(2), 281-97.

[10] Mercer, T.R.; Dinger, M.E.; Mattick, J.S. Long non-coding RNAs: Insights into functions. *Nat. Rev. Genet.,* **2009**, *10*(3), 155-159. http://dx.doi.org/10.1038/nrg2521 PMID: 19188922

[11] Iwasaki, Y.W.; Siomi, M.C.; Siomi, H. PIWI-Interacting RNA: Its Biogenesis and Functions. *Annu. Rev. Biochem.,* **2015**, *84*(1), 405-433. http://dx.doi.org/10.1146/annurev-biochem-060614-03425 8 PMID: 25747396

[12] Aravin, A.A.; Naumova, N.M.; Tulin, A.V.; Vagin, V.V.; Rozovsky, Y.M.; Gvozdev, V.A. Double-stranded RNA--mediated silencing of genomic tandem repeats and transposable elements in the *D. melanogaster* germline. *Curr. Biol.,* **2001**, *11*(13), 1017-1027. http://dx.doi.org/10.1016/S0960-9822(01)00299-8 PMID:11470406

[13] Ozata, D.M.; Gainetdinov, I.; Zoch, A.; O'Carroll, D.; Zamore, P.D. PIWI-interacting RNAs: Small RNAs with big functions. *Nat. Rev. Genet.,* **2019**, *20*(2), 89-108. http://dx.doi.org/10.1038/s41576-018-0073-3 PMID: 30446728

[14] Aravin, A.; Gaidatzis, D.; Pfeffer, S.; Lagos-Quintana, M.; Landgraf, P.; Iovino, N.; Morris, P.; Brownstein, M.J.; Kuramochi-Miyagawa, S.; Nakano, T.; Chien, M.; Russo, J.J.; Ju, J.; Sheridan, R.; Sander, C.; Zavolan, M.; Tuschl, T. A novel class of small RNAs bind to MILI protein in mouse testes. *Nature,* **2006**, *442*(7099), 203-207. http://dx.doi.org/10.1038/nature04916 PMID: 16751777

[15] Cheng, J.; Guo, J.M.; Xiao, B.X.; Miao, Y.; Jiang, Z.;

Zhou, H.; Li, Q.N. piRNA, the new non-coding RNA, is aberrantly expressed in human cancer cells. *Clin. Chim. Acta,* **2011**, *412*(17-18), 1621-1625. http://dx.doi.org/10.1016/j.cca.2011.05.015 PMID: 21616063

[16] Cheng, J.; Deng, H.; Xiao, B.; Zhou, H.; Zhou, F.; Shen, Z.; Guo, J. 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**, *315*(1), 12-17. http://dx.doi.org/10.1016/j.canlet.2011.10.004 PMID: 22047710

[17] Hashim, A.; Rizzo, F.; Marchese, G.; Ravo, M.; Tarallo, R.; Nassa, G.; Giurato, G.; Santamaria, G.; Cordella, A.; Cantarella, C.; Weisz, A. RNA sequencing identifies specific PIWI-interacting small non-coding RNA expression patterns in breast cancer. *Oncotarget,* **2014**, *5*(20), 9901-9910. http://dx.doi.org/10.18632/oncotarget.2476 PMID: 25313140

[18] Li, Y.; Wu, X.; Gao, H.; Jin, J.M.; Li, A.X.; Kim, Y.S.; Pal, S.K.; Nelson, R.A.; Lau, C.M.; Guo, C.; Mu, B.; Wang, J.; Wang, F.; Wang, J.; Zhao, Y.; Chen, W.; Rossi, J.J.; Weiss, L.M.; Wu, H. Piwi-interacting RNAs (piRNAs)are dysregulated in renal cell carcinoma and associated with tumor metastasis and cancer-specific survival. *Mol. Med.,* **2015**, *21*(1), 381-388. http://dx.doi.org/10.2119/molmed.2014.00203 PMID: 25998508

[19] Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2019. *CA Cancer J. Clin.,* **2019**, *69*(1), 7-34. http://dx.doi.org/10.3322/caac.21551 PMID: 30620402

[20] World cancer research fund. Global cancer incidence: Both sexes. **2018**. Available from: https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data

[21] Cohen, P.A.; Jhingran, A.; Oaknin, A.; Denny, L. Cervical cancer. *Lancet,* **2019**, *393*(10167), 169-182. http://dx.doi.org/10.1016/S0140-6736(18)32470-X PMID: 30638582

[22] Crosbie, E.J.; Einstein, M.H.; Franceschi, S.; Kitchener, H.C. Human papillomavirus and cervical cancer. *Lancet,* **2013**, *382*(9895), 889-899. http://dx.doi.org/10.1016/S0140-6736(13)60022-7 PMID: 23618600

[23] Hosseini, E.S.; Meryet-Figuiere, M.; Sabzalipoor, H.; Kashani, H.H.; Nikzad, H.; Asemi, Z. Dysregulated expression of long noncoding RNAs in gynecologic cancers. *Mol Cancer.,* **2017**, *16*(1), 107. http://dx.doi.org/10.1186/s12943-017-0671-2

[24] Goodman, A. HPV testing as a screen for cervical cancer. *BMJ,* **2015**, *350*, h2372. http://dx.doi.org/10.1136/bmj.h2372 PMID: 26126623

[25] Tsikouras, P.; Zervoudis, S.; Manav, B.; Tomara, E.; Iatrakis, G.; Romanidis, C.; Bothou, A.; Galazios, G. Cervical cancer: Screening, diagnosis and staging. *J. BUON,* **2016**, *21*(2), 320-325. PMID: 27273940

[26] Hanley, K.Z.; Birdsong, G.G.; Mosunjac, M.B. Recent developments in surgical pathology of the uterine corpus. *Arch. Pathol. Lab. Med.,* **2017**, *141*(4), 528-541. http://dx.doi.org/10.5858/arpa.2016-0284-SA PMID: 28353387

[27] Braun, M.M.; Overbeek-Wager, E.A.; Grumbo, R.J. Diagnosis and management of endometrial cancer. *Am. Fam. Physician,* **2016**, *93*(6), 468-474. PMID: 26977831

[28] Rizzo, S.; Femia, M.; Buscarino, V.; Franchi, D.; Garbi, A.; Zanagnolo, V.; Del Grande, M.; Manganaro, L.; Alessi, S.; Giannitto, C.; Ruju, F.; Bellomi, M. Endometrial cancer: An overview of novelties in treatment and related imaging keypoints for local staging. *Cancer Imaging,* **2018**, *18*(1), 45. http://dx.doi.org/10.1186/s40644-018-0180-6 PMID: 30514387

[29] Kossaï, M.; Leary, A.; Scoazec, J.Y.; Genestie, C. Ovarian cancer: A heterogeneous disease. *Pathobiology,* **2018**, *85*(1-2), 41-49. http://dx.doi.org/10.1159/000479006 PMID: 29020678

[30] Scaletta, G.; Plotti, F.; Luvero, D.; Capriglione, S.; Montera, R.; Miranda, A.; Lopez, S.; Terranova, C.; De Cicco Nardone, C.; Angioli, R. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: A systematic review. *Expert Rev. Anticancer Ther.,* **2017**, *17*(9), 827-839. http://dx.doi.org/10.1080/14737140.2017.1360138 PMID: 28756722

[31] Doubeni, C.A.; Doubeni, A.R.; Myers, A.E. Diagnosis and management of ovarian cancer. *Am. Fam. Physician,* **2016**, *93*(11), 937-944. PMID: 27281838

[32] Brett M, R.; Brett M, R.; Jennifer B, P.; Thomas A, S.; Jennifer B, P.; Thomas A, S. Epidemiology of ovarian cancer: A review. *Cancer Biol. Med.,* **2017**, *14*(1), 9-32. http://dx.doi.org/10.20892/j.issn.2095-3941.2016.0084 PMID: 28443200

[33] Allemani, C.; Weir, H.K.; Carreira, H.; Harewood, R.; Spika, D.; Wang, X.S.; Bannon, F.; Ahn, J.V.; Johnson, C.J.; Bonaventure, A.; Marcos-Gragera, R.; Stiller, C.; Azevedo e Silva, G.; Chen, W.Q.; Ogunbiyi, O.J.; Rachet, B.; Soeberg, M.J.; You, H.; Matsuda, T.; Bielska-Lasota, M.; Storm, H.; Tucker, T.C.; Coleman, M.P. Global surveillance of cancer survival 1995-2009: Analysis of individual data for 25,676,887 patients from 279 population-based registries in 67 countries (CONCORD-2). *Lancet,* **2015**, *385*(9972), 977-1010. http://dx.doi.org/10.1016/S0140-6736(14)62038-9 PMID: 25467588

[34] Zhang, W.; Lei, P.; Dong, X.; Men, X. Advances in tumor markers of ovarian cancer for early diagnosis. *Indian J. Cancer,* **2014**, *51*(7)(Suppl. 3), 72. http://dx.doi.org/10.4103/0019-509X.154049 PMID: 25818738

[35] Shetty, A.S.; Menias, C.O. MR imaging of vulvar and vaginal cancer. *Magn. Reson. Imaging Clin. N. Am.,* **2017**, *25*(3), 481-502. http://dx.doi.org/10.1016/j.mric.2017.03.013 PMID: 28668156

[36] Rajaram, S.; Gupta, B. Management of vulvar cancer. *Rev. Recent Clin. Trials,* **2015**, *10*(4), 282-288. http://dx.doi.org/10.2174/1574887110666150923112723 PMID: 26411953

[37] Rogers, L.J.; Cuello, M.A. Cancer of the vulva. *Int. J. Gynaecol. Obstet.,* **2018**, *143*(Suppl. 2), 4-13. http://dx.doi.org/10.1002/ijgo.12609 PMID: 30306583

[38] Hacker, N.F.; Barlow, E.L. Staging for vulvar cancer. *Best Pract. Res. Clin. Obstet. Gynaecol.,* **2015**, *29*(6), 802-811. http://dx.doi.org/10.1016/j.bpobgyn.2015.01.004 PMID: 25842047

[39] Weinberg, D.; Gomez-Martinez, R.A. Vulvar cancer. *Obstet. Gynecol. Clin. North Am.,* **2019**, *46*(1), 125-135.

http://dx.doi.org/10.1016/j.ogc.2018.09.008 PMID: 30683259

[40] Queiroz, M.A.; Kubik-Huch, R.A.; Hauser, N.; Freiwald-Chilla, B.; von Schulthess, G.; Froehlich, J.M.; Veit-Haibach, P. PET/MRI and PET/CT in advanced gynaecological tumours: Initial experience and comparison. *Eur. Radiol.,* **2015**, *25*(8), 2222-2230. http://dx.doi.org/10.1007/s00330-015-3657-8 PMID: 26017734

[41] Adams, T.S.; Cuello, M.A. Cancer of the vagina. *Int. J. Gynaecol. Obstet.,* **2018**, *143*(Suppl. 2), 14-21. http://dx.doi.org/10.1002/ijgo.12610 PMID: 30306589

[42] Huang, X.; Fejes Tóth, K.; Aravin, A.A. piRNA Biogenesis in *Drosophila melanogaster*. *Trends Genet.,* **2017**, *33*(11), 882-894. http://dx.doi.org/10.1016/j.tig.2017.09.002 PMID: 28964526

[43] Brennecke, J.; Aravin, A.A.; Stark, A.; Dus, M.; Kellis, M.; Sachidanandam, R.; Hannon, G.J. Discrete small RNA-generating loci as master regulators of transposon activity in Drosophila. *Cell,* **2007**, *128*(6), 1089-1103. http://dx.doi.org/10.1016/j.cell.2007.01.043 PMID: 17346786

[44] Yu, Y.; Xiao, J.; Hann, S.S. The emerging roles of PIWI-interacting RNA in human cancers. *Cancer Manag. Res.,* **2019**, *11*, 5895-5909. http://dx.doi.org/10.2147/CMAR.S209300 PMID: 31303794

[45] Clark, J.P.; Lau, N.C. Piwi Proteins and piRNAs step onto the systems biology stage. *Adv. Exp. Med. Biol.,* **2014**, *825*, 159-197. http://dx.doi.org/10.1007/978-1-4939-1221-6_5 PMID: 25201106

[46] Hirakata, S.; Siomi, M.C. piRNA biogenesis in the germline: From transcription of piRNA genomic sources to piRNA maturation. *Biochim. Biophys. Acta. Gene Regul. Mech.,* **2016**, *1859*(1), 82-92. http://dx.doi.org/10.1016/j.bbagrm.2015.09.002 PMID: 26348412

[47] Nishida, K.M.; Sakakibara, K.; Iwasaki, Y.W.; Yamada, H.; Murakami, R.; Murota, Y.; Kawamura, T.; Kodama, T.; Siomi, H.; Siomi, M.C. Hierarchical roles of mitochondrial Papi and Zucchini in *Bombyx germline* piRNA biogenesis. *Nature,* **2018**, *555*(7695), 260-264. http://dx.doi.org/10.1038/nature25788 PMID: 29489748

[48] Gunawardane, L.S.; Saito, K.; Nishida, K.M.; Miyoshi, K.; Kawamura, Y.; Nagami, T. A slicer-mediated mechanism for repeat-associated siRNA 5'end formation in *Drosophila*. *Science,* **2007**, *315*(5818), 1587-90.

[49] Ross, R.J.; Weiner, M.M.; Lin, H. PIWI proteins and PIWI-interacting RNAs in the soma. *Nature,* **2014**, *505*(7483), 353-359. http://dx.doi.org/10.1038/nature12987 PMID: 24429634

[50] Czech, B.; Munafò, M.; Ciabrelli, F.; Eastwood, E.L.; Fabry, M.H.; Kneuss, E.; Hannon, G.J. piRNA-guided genome defense: From biogenesis to silencing. *Annu. Rev. Genet.,* **2018**, *52*(1), 131-157. http://dx.doi.org/10.1146/annurev-genet-120417-031441 PMID: 30476449

[51] Schoeberl, U.E.; Mochizuki, K. Keeping the soma free of transposons: Programmed DNA elimination in ciliates. *J. Biol. Chem.,* **2011**, *286*(43), 37045-37052. http://dx.doi.org/10.1074/jbc.R111.276964 PMID: 21914793

[52] Kazazian, H.H., J.r. Mobile elements: Drivers of genome evolution. *Science,* **2004**, *303*(5664), 1626-1632. http://dx.doi.org/10.1126/science.1089670 PMID: 15016989

[53] Cordaux, R.; Batzer, M.A. The impact of retrotransposons on human genome evolution. *Nat. Rev. Genet.,* **2009**, *10*(10), 691-703. http://dx.doi.org/10.1038/nrg2640 PMID: 19763152

[54] Ng, K.W.; Anderson, C.; Marshall, E.A.; Minatel, B.C.; Enfield, K.S.S.; Saprunoff, H.L.; Lam, W.L.; Martinez, V.D. PIWI-interacting RNAs in cancer: Emerging functions and clinical utility. *Mol. Cancer,* **2016**, *15*(1), 5. http://dx.doi.org/10.1186/s12943-016-0491-9 PMID: 26768585

[55] Chénais, B. Transposable elements and human cancer: A causal relationship? *Biochim. Biophys. Acta (BBA)-. Rev. Can.,* **2013**, *1835*(1), 28-35.

[56] Mani, S.R.; Juliano, C.E. Untangling the web: The diverse functions of the PIWI/piRNA pathway. *Mol. Reprod. Dev.,* **2013**, *80*(8), 632-664. http://dx.doi.org/10.1002/mrd.22195 PMID: 23712694

[57] Huang, X.A.; Yin, H.; Sweeney, S.; Raha, D.; Snyder, M.; Lin, H. A major epigenetic programming mechanism guided by piRNAs. *Dev. Cell,* **2013**, *24*(5), 502-516. http://dx.doi.org/10.1016/j.devcel.2013.01.023 PMID: 23434410

[58] A novel epigenetic mechanism in Drosophila somatic cells mediated by PIWI and piRNAs. In: *Cold Spring Harbor symposia on quantitative biology*; Lin, H.; Yin, H., Eds.; Cold Spring Harbor Laboratory Press, **2008**.

[59] Chalbatani, G.M.; Dana, H.; Memari, F.; Gharagozlou, E.; Ashjaei, S.; Kheirandish, P.; Marmari, V.; Mahmoudzadeh, H.; Mozayani, F.; Maleki, A.R.; Sadeghian, E.; Nia, E.Z.; Miri, S.R.; Nia, N.; Rezaeian, O.; Eskandary, A.; Razavi, N.; Shirkhoda, M.; Rouzbahani, F.N. Biological function and molecular mechanism of piRNA in cancer. *Pract. Lab. Med.,* **2019**, *13*, e00113. http://dx.doi.org/10.1016/j.plabm.2018.e00113 PMID: 30705933

[60] Liu, Y.; Dou, M.; Song, X.; Dong, Y.; Liu, S.; Liu, H.; Tao, J.; Li, W.; Yin, X.; Xu, W. The emerging role of the piRNA/PIWI complex in cancer. *Mol. Cancer,* **2019**, *18*(1), 123. http://dx.doi.org/10.1186/s12943-019-1052-9 PMID: 31399034

[61] Tian, Y.; Simanshu, D.K.; Ma, J.B.; Patel, D.J. Structural basis for piRNA 2′-O-methylated 3′-end recognition by PIWI PAZ (PIWI/Argonaute/Zwille) domains. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(3), 903-910. http://dx.doi.org/10.1073/pnas.1017762108 PMID: 21193640

[62] Lim, S.L.; Ricciardelli, C.; Oehler, M.K.; De Arao Tan, I.M.D.; Russell, D.; Grützner, F. Overexpression of piRNA pathway genes in epithelial ovarian cancer. *PLoS One,* **2014**, *9*(6), e99687. http://dx.doi.org/10.1371/journal.pone.0099687 PMID: 24932571

[63] Lee, J.H.; Schütte, D.; Wulf, G.; Füzesi, L.; Radzun, H.J.; Schweyer, S.; Engel, W.; Nayernia, K. Stem-cell protein PIWIl2 is widely expressed in tumors and inhibits apoptosis through activation of Stat3/Bcl-XL pathway. *Hum. Mol. Genet.,* **2006**, *15*(2), 201-211. http://dx.doi.org/10.1093/hmg/ddi430 PMID: 16377660

[64] Ye, Y.; Yin, D.T.; Chen, L.; Zhou, Q.; Shen, R.; He, G.; Yan, Q.; Tong, Z.; Issekutz, A.C.; Shapiro, C.L.; Barsky, S.H.; Lin, H.; Li, J.J.; Gao, J.X. Identification of PIWIl2-

like (PL2L) proteins that promote tumorigenesis. *PLoS One,* **2010**, *5*(10), e13406. http://dx.doi.org/10.1371/journal.pone.0013406 PMID: 20975993

[65] Yao, Y.; Li, C.; Zhou, X.; Zhang, Y.; Lu, Y.; Chen, J.; Zheng, X.; Tao, D.; Liu, Y.; Ma, Y. PIWIL2 induces c-Myc expression by interacting with NME2 and regulates c-Myc-mediated tumor cell proliferation. *Oncotarget,* **2014**, *5*(18), 8466-8477. http://dx.doi.org/10.18632/oncotarget.2327 PMID: 25193865

[66] Klattenhoff, C.; Theurkauf, W. Biogenesis and germline functions of piRNAs. *Development,* **2008**, *135*(1), 3-9. http://dx.doi.org/10.1242/dev.006486 PMID: 18032451

[67] Wang, Q.E.; Han, C.; Milum, K.; Wani, A.A. Stem cell protein PIWIl2 modulates chromatin modifications upon cisplatin treatment. *Mutat. Res.,* **2011**, *708*(1-2), 59-68. http://dx.doi.org/10.1016/j.mrfmmm.2011.02.001 PMID: 21310163

[68] Liu, W.; Gao, Q.; Chen, K.; Xue, X.; Li, M.; Chen, Q.; Zhu, G.; Gao, Y. Hiwi facilitates chemoresistance as a cancer stem cell marker in cervical cancer. *Oncol. Rep.,* **2014**, *32*(5), 1853-1860. http://dx.doi.org/10.3892/or.2014.3401 PMID: 25119492

[69] Cox, D.N.; Chao, A.; Baker, J.; Chang, L.; Qiao, D.; Lin, H. A novel class of evolutionarily conserved genes defined by *PIWI* are essential for stem cell self-renewal. *Genes Dev.,* **1998**, *12*(23), 3715-3727. http://dx.doi.org/10.1101/gad.12.23.3715 PMID: 9851978

[70] Liu, W.K.; Jiang, X.Y.; Zhang, Z.X. Expression of PSCA, PIWIL1 and TBX2 and its correlation with HPV16 infection in formalin-fixed, paraffin-embedded cervical squamous cell carcinoma specimens. *Arch. Virol.,* **2010**, *155*(5), 657-663. http://dx.doi.org/10.1007/s00705-010-0635-y PMID: 20229117

[71] He, G.; Chen, L.; Ye, Y.; Xiao, Y.; Hua, K.; Jarjoura, D.; Nakano, T.; Barsky, S.H.; Shen, R.; Gao, J.X. PIWIl2 expressed in various stages of cervical neoplasia is a potential complementary marker for p16. *Am. J. Transl. Res.,* **2010**, *2*(2), 156-169. PMID: 20407605

[72] Dang, C.V. c-Myc target genes involved in cell growth, apoptosis, and metabolism. *Mol. Cell. Biol.,* **1999**, *19*(1), 1-11. http://dx.doi.org/10.1128/MCB.19.1.1 PMID: 9858526

[73] Dang, C.V. MYC on the path to cancer. *Cell,* **2012**, *149*(1), 22-35. http://dx.doi.org/10.1016/j.cell.2012.03.003 PMID: 22464321

[74] Su, C.; Ren, Z.J.; Wang, F.; Liu, M.; Li, X.; Tang, H. PIWIL4 regulates cervical cancer cell line growth and is involved in down-regulating the expression of p14ARF and p53. *FEBS Lett.,* **2012**, *586*(9), 1356-1362. http://dx.doi.org/10.1016/j.febslet.2012.03.053 PMID: 22483988

[75] Chen, C.; Liu, J.; Xu, G. Overexpression of PIWI proteins in human stage III epithelial ovarian cancer with lymph node metastasis. *Cancer Biomark.,* **2013**, *13*(5), 315-321. http://dx.doi.org/10.3233/CBM-130360 PMID: 24440970

[76] Tan, Y.; Liu, L.; Liao, M.; Zhang, C.; Hu, S.; Zou, M.; Gu, M.; Li, X. Emerging roles for PIWI proteins in cancer. *Acta Biochim. Biophys. Sin. (Shanghai),* **2015**, *47*(5), 315-324. http://dx.doi.org/10.1093/abbs/gmv018 PMID: 25854579

[77] Singh, G.; Roy, J.; Rout, P.; Mallick, B. Genome-wide profiling of the PIWI-interacting RNA-mRNA regulatory networks in epithelial ovarian cancers. *PLoS One,* **2018**, *13*(1), e0190485. http://dx.doi.org/10.1371/journal.pone.0190485 PMID: 29320577

[78] Bachmayr-Heyda, A.; Auer, K.; Sukhbaatar, N.; Aust, S.; Deycmar, S.; Reiner, A.T.; Polterauer, S.; Dekan, S.; Pils, D. Small RNAs and the competing endogenous RNA network in high grade serous ovarian cancer tumor spread. *Oncotarget,* **2016**, *7*(26), 39640-39653. http://dx.doi.org/10.18632/oncotarget.9243 PMID: 27172797

[79] Ravo, M.; Cordella, A.; Rinaldi, A.; Bruno, G.; Alexandrova, E.; Saggese, P.; Nassa, G.; Giurato, G.; Tarallo, R.; Marchese, G.; Rizzo, F.; Stellato, C.; Biancardi, R.; Troisi, J.; Di Spiezio Sardo, A.; Zullo, F.; Weisz, A.; Guida, M. Small non-coding RNA deregulation in endometrial carcinogenesis. *Oncotarget,* **2015**, *6*(7), 4677-4691. http://dx.doi.org/10.18632/oncotarget.2911 PMID: 25686835

[80] Chen, Z.; Che, Q.; He, X.; Wang, F.; Wang, H.; Zhu, M.; Sun, J.; Wan, X. Stem cell protein PIWIl1 endowed endometrial cancer cells with stem-like properties *via* inducing epithelial-mesenchymal transition. *BMC Cancer,* **2015**, *15*(1), 811. http://dx.doi.org/10.1186/s12885-015-1794-8 PMID: 26506848

[81] Chen, Z.; Che, Q.; Jiang, F.Z.; Wang, H.H.; Wang, F.Y.; Liao, Y.; Wan, X.P. PIWIl1 causes epigenetic alteration of PTEN gene *via* upregulation of DNA methyltransferase in type I endometrial cancer. *Biochem. Biophys. Res. Commun.,* **2015**, *463*(4), 876-880. http://dx.doi.org/10.1016/j.bbrc.2015.06.028 PMID: 26056945

[82] Liu, W.K.; Jiang, X.Y.; Zhang, Z.X. Expression of PSCA, PIWIL1, and TBX2 in endometrial adenocarcinoma. *Onkologie,* **2010**, *33*(5), 241-245. http://dx.doi.org/10.1159/000305098 PMID: 20502058