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The Function and Mechanism of PIWI/Pirna in Colorectal Cancer

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Abstract

Piwi proteins are RNA binding proteins belonging to one of the subfamilies of the Paz / piwi domain family Piwi proteins often function in a functional complex in combination with small non coding RNAs (piRNAs) called ' piwi interacting small non coding RNAs ' (piRNAs) The piwi piRNA pathway is best known for its essential role in repressing transposons and germ line development In addition to its superior role in the germline, piwi proteins have also gained much attention in recent years because they are normally expressed only in germ cells and barely in normal somatic tissues, but piwi proteins are aberrantly expressed in cancerous tumor tissues, making them promising excellent targets for precision targeted therapy In this review, we first review how piwi proteins interact with piRNAs to regulate the expression of many different types of RNAs, then briefly introduce the expression and function of piwi proteins and piRNAs in different types of cancer, and explore recent years about the important functions and significance of piwi and piRNAs in different family members in colon cancer research.

Keywords

PIWI; PiRNA; Colorectal cancer.

1. Colorectal Cancer

Colorectal cancer (CRC) refers to cancerous lesions that occur in the colon or rectum. It can occur in any part of the colorectum, especially the rectum and sigmoid colon. Colorectal cancer is one of the five most common cancers. The survey showed that the incidence of colorectal cancer in my country showed a clear upward trend, and the incidence rate of males in urban areas increased the fastest. 75-95% of colorectal cancers are not related to genetic factors or have no obvious relationship, and are only caused by increasing age and lifestyle factors[1][2], 5-25% of colorectal cancers are due to underlying genetic diseases. caused. At present, the etiology of colorectal cancer has been relatively clear, including: dietary factors, genetic factors, polyposis disease factors and chronic inflammatory factors. Risk factors include poor diet, poor lifestyle habits, bacterial infections, and inflammatory bowel disease (Crohn's disease and ulcerative colitis). Some genetic disorders that can lead to colorectal cancer include familial adenomatous multiple cancers and hereditary nonmultiple colon cancers, which usually start as benign tumors and often appear as polyps that can develop over time into become cancerous. The study found that people with two or more first-degree relatives (such as parents or siblings) with a family history of colorectal cancer had a 2-3 times higher risk of developing the disease than those without genetic factors. 20% of cases. Many genetic syndromes are also associated with a higher incidence of colorectal cancer. The most common of these is hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which accounts for approximately 3% of colorectal cancer patients [3]. The most common polyposis syndrome affecting the colon is serrated polyposis syndrome [4], which is associated with a 25-40% risk of CRC [5]. Currently, clinical treatments for colorectal cancer include surgery, radiation therapy, chemotherapy, and targeted therapy. Cancers confined to the colon wall can be cured by surgery, while those that spread or metastasize are usually incurable. Therefore, it is

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particularly important to timely control the deterioration of colorectal cancer and determine the degree of tumor differentiation through molecular indicators.

2. PiRNA

2.1. Basic Overview

Currently recognized non-coding RNA (ncRNA) mainly include siRNA (small interfering RNA), miRNA (microRNA) and piRNA (piwi-interacting RNA), and some scholars classify the newly discovered rasiRNA as piRNA. piRNA is a kind of non-coding small RNA first discovered in the germ cells of Drosophila, and is mainly involved in the development of germ cells, the silencing of transposons, the formation of heterochromatin, and the maintenance of DNA integrity in germ cells. The stable regulation of genetic material and its expression is of great significance[6][7][8].

2.2. PiRNA Biosynthesis Mechanism

The biosynthesis of piRNA is extremely complex, involving multiple structural proteins and enzymes based on the PIWI protein system, with precise subcellular localization and regulatory processes [14]. There are two known models of mature piRNA biosynthesis: the primary synthetic pathway and the secondary synthetic pathway (this process is often referred to as the 'ping-pong cycle').

The synthesis process and function of piRNA involves many genes. The whole process can be divided into two parts. One is the synthesis process of Pre-piRNA (as shown in Fig.1). First, the primary transcription of piRNA is generated under the action of RNA polymerase II and MYBL1. Then, piRNA precursors are transferred from the nucleus to the cytoplasm with the help of Uap56, Nxt1, Nxf2, Nup154, and Nup43, and the first cleavage occurs under the action of PLD6; the second is the amplification and entry of piRNA into the nucleus (such as Fig.2), piRNA first binds to PIWIL2, undergoes 3'-end modification and methylation successively with the assistance of molecules such as PNLDC1 and HENMT1, and expands through the 'ping-pong cycle', and finally binds to PIWIL4 and enters the nucleus to play a role effect. The roles of genes involved in the whole process and their expression products in piRNA synthesis have been described in detail previously [14].

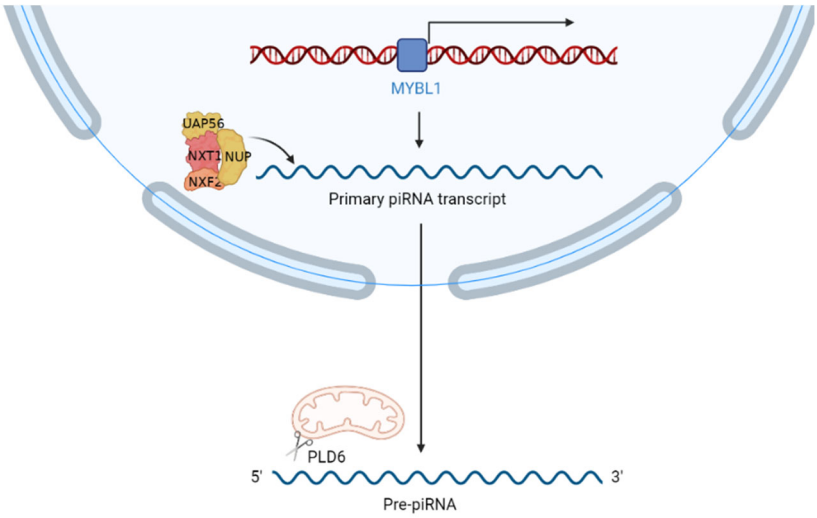

Figure 1. Synthesis of Pre-piRNA

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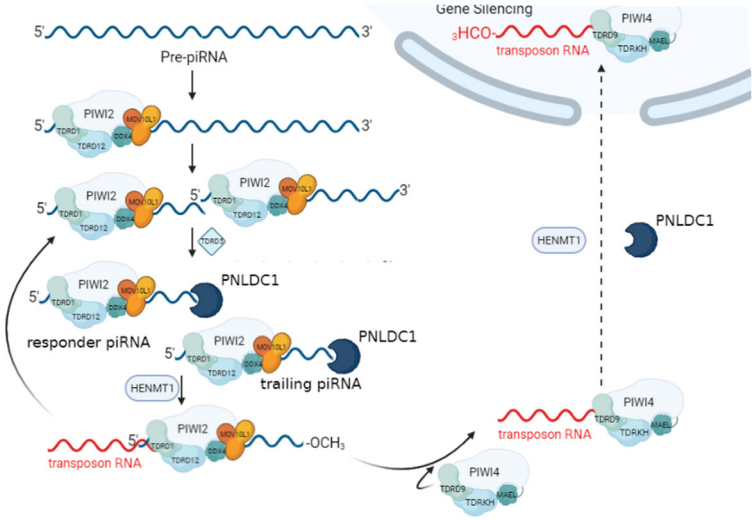

Figure 2. Amplification and nuclear entry of piRNA

2.3. Biological Roles of piRNAs

The realization of piRNA function depends on the Argonuat (Ago) protein family. piRNAs specifically bind to Piwi subfamily proteins in the Ago protein family and can direct PIWI proteins and their associated epigenetic mechanisms to program the genome or transcriptome by recognizing a large number of piRNA complements, leading to transcriptional silencing of specific target genes At the same time, it helps to maintain DNA integrity, participate in the differentiation of tumor stem cells, realize epigenetic regulation and embryonic development, and affect the occurrence and development of diseases [7-13].

3. PiRNA Pathway and Colorectal Cancer

The piRNA pathway consists of piRNAs and a series of related pathway genes involved in piRNA biogenesis. PiRNAs are highly expressed in cells with high proliferation activity and multi-directional differentiation potential, so early research on piRNAs mainly focused on germ cells and stem cells. This distribution feature also suggests that piRNAs have epigenetics in cell differentiation, genetic expression regulation and other biological effects [9]. Based on this, whether cancer stem cells with infinite proliferation potential also have the feature of high expression of certain piRNAs has attracted people's attention, and many research results have also shown that the occurrence and development of certain tumors are closely related to the content and function of piRNAs. inseparable connection.

3.1. PiRNA and Colorectal Cancer

PiRNA itself can promote the occurrence of colorectal cancer through various pathways. For example, piR-1245 is mainly found to be overexpressed in cancer stem cell (CRC) tissues, and can regulate the normal physiological processes of cells such as apoptosis, DNA replication and repair. and the expression of genes related to intercellular communication [19]. The study found that up-regulated piR-54265 promoted CRC cell proliferation and invasion ability through the STAT3 pathway, and piR-823 activated the expression of heat shock transcription factor 1 (HSF1) by promoting its phosphorylation at Ser326, and affected the development of colorectal cancer [20].

3.2. PiRNA Complexes and Colorectal Cancer

The piRNA complex also plays an important role in colorectal carcinogenesis, it is enriched in colorectal cancer stem cells (CRCSCs) and is involved in the regulation of CRCSCs[21][22], possibly through the Wnt/β-catenin, Notch and Hedgehog pathways It promotes the cellular atypia and metastatic ability of CRCSCs to exert oncogenic effects [23]. piRNA complexes can

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also cause abnormalities in DNA methylation and genome silencing, promoting cancer development [24].

3.3. PiRNA-related Pathway Genes and Colorectal Cancer

Nowadays, piRNA-related pathway genes (PIWIL2, PIWIL4, TDRD1, and MAEL, etc.) have received increasing attention, and in recent years, they have been found to be abnormally expressed in a variety of cancers. The core biosynthetic pathway genes are mainly PIWI genes (PIWI1-4) [25]. The PIWI gene is highly conserved in structure and function and was originally thought to be expressed only in germ cells [26]. Subsequent studies have shown that it is abnormally expressed in a variety of human cancer cells, and in vitro/in vivo studies have shown that PIWIL protein is not only a marker of malignancy, but also involved in cell cycle regulation, tumorigenesis, drug resistance, and acquisition of self-renewal ability [27]. Abnormal expression of PIWIL1 is associated with tumor differentiation status, invasion, lymph node invasion and metastasis [28]; patients with PIWIL1 overexpression also showed lower overall survival and disease-free survival [29]. In addition, the expression of PIWIL1 in CRC was positively correlated with the mRNA level of the cancer stem cell marker OCT4, suggesting that this gene may be closely related to cancer stem cells [30]. The expression rate of PIWI2 in colon cancer tissues was significantly lower than that in non-cancerous tissues [31], and it was positively correlated with the tumor stem cell marker SOX2 [30], and may control the proliferation and metastasis of colon cancer cells by regulating MMP9 [32]. Knockdown of PIWIL2 in CRCSCs significantly reduced cancer cell proliferation, migration and aggregation, resulting in increased apoptosis in vitro and decreased cell proliferation in vivo [33]. There are few studies on PIWI3 in cancer, only experiments show that it is significantly higher in colon cancer tissues than in adjacent non-tumor tissues [31], but the specific mechanism is not clear. PIWIL4 is an important molecule that exerts transposon inhibition in the nucleus, involves chromatin modification in human somatic cells, and is involved in p16 (CDKN2A) site-mediated H3 methylation [34]. Cervical cancer [36] and gastric cancer [37] are more highly expressed in tumor tissues of primary and metastatic lesions than their adjacent tissues. Guo Limin et al [38] used semi-quantitative RT-PCR to detect that PIWIL4 was involved in the occurrence and development of ovarian cancer. The overexpression of PIWIL4 protein in human cancers is closely related to tumorigenesis, highly expressed lymph node metastasis, clinical TNM staging and shorter patient survival time [39][40]. Existing studies have shown that on the one hand, PIWI can bind piRNA to suppress transposons independently of each other, and on the other hand, through a secondary generation pathway, PIWI2-piRNA complexes can be converted into PIWI4-piRNA complexes, and the simultaneous generation of silenced transposons can occur. A large number of piRNAs and PIWI mutations lead to increased expression of transposons, which increases the chance of carcinogenesis [41][42].

In addition to PIWIL genes, genes involved in piRNA synthesis are also important regulatory sites, including DDX4, HENMT1, MAEL, PLD6, TDRD1, and TDRD9. Studies have shown that mutations in such regulatory genes can lead to abnormal expression and function of piRNAs [43]-[47]. In recent years, more and more experiments have shown that these piRNA pathway genes are closely related to tumors. In the study of Lee et al. [48], the expression of MAEL and HENMT1 was increased, while the expression of TDRD1 was decreased when comparing benign and malignant uterine tumors. In addition, this experiment shows that HENMT1 is involved in the differentiation of high-grade OC, and TDRD1 may also be a biomarker of low-grade OC. Experiments by von Eyss B et al. [49] showed that PLD6 localized to the mitochondrial outer membrane may load mitochondrial energy metabolism to suppress YAP/TAZ function in breast cancer. The TDRD family has been confirmed to be mutated in various cancer cells such as breast cancer [50] and liver cancer [51]. However, the relationship

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between colorectal cancer and these pathway genes has rarely been discussed, and only some studies have shown a possible association with TRRD1, 4, 9 [52].

4. Conclusion

After a comprehensive analysis of the above, we noticed that the PIWI family is involved in the regulation of nuclear genes by piRNA, and PIWIL4 is closely related to colorectal cancer metastasis and staging, and may be a therapeutic target.

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