Original Research

MiRNAS' Role in Endometrial Cancer: Diagnosis and Prognosis

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Abstract:

Background:

Today the discussion of microRNAs (miRNAs) and their expression patterns in cancers, is a new and widely discussed topic in oncology. miRNAs are involved in biological processes and their irregular expression has been observed in many diseases and cancers, including colon cancer, ovarian cancer, and endometrial cancer. Here we review the miRNAs' role in endometrial cancer.

Methods:

This was a narrative review of the literature.

Results:

Our review highlighted the pathological roles of the MicroRNAs in endometrial cancer. miRNAs regulate a large number of cancer-inhibitory genes and oncogenes of endometrial cancer as well as the PTEN gene. This pathological knowledge is used in clinical era to determine the MicroRNAs linked with the diagnosis of the endometrial cancer; while as there are numerous numbers of miRNAs, many studies have proposed panels of miRNAs that indicate the diagnosis of cancer and single miRNAs are less introduced in literature. But more evidence supports the mir-18a and Let-7 family for diagnosis of endometrial cancer. Some other studies have investigated the miRNAs that can predict the prognosis of the endometrial cancer and we categorized the findings of these studies to good and poor prognostic miRNAs.

Conclusion:

To conclude, there seems to be potential diagnostic value in application of the miRNAs in endometrial cancer, while more critical review and pooled results are needed to draw a firm conclusion for wide clinical application.

Keywords: miRNAs, Endometrial Cancer, mir-18a, PTEN

Submitted: 18 October 2022, Revised: 27 October 2022 , Accepted: 19 November 2022

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Introduction

Endometrial cancer refers to the abnormal growth of cells lining the body of the uterus, the endometrium (1). Endometrial cancer is currently the most common cancer of the female reproductive system and fourth most common cancer in females in the US (2). Some infections, estrogen replacement therapies (without progesterone), premature menarche and late menopause, infertility and no-gravity, ovulation dysfunction, estrogen-producing tumors as well as demographic traits such as age, white race, high socioeconomic status, family history of endometrial cancer as well as comorbidities such as: diabetes, gallbladder disease, obesity, hypertension, history of pelvic radiotherapy are considered as risk factors for this cancer (3). Although the stage of the disease is the most important variable affecting the survival of the patient, but specific prognostic factors for disease recurrence or survival have been identified, which are: tumor stage, histology, pathology, patient age and surgical and pathological findings confirm the spread of the disease. Other factors such as tumor size, peritoneal cytology, hormone receptor status, flow cytometric analysis, and oncogenic perturbation are just as important in prognosis (4). Because endometrial cancer usually follows endometrial hyperplasia, which is manifested by an increase in endometrial thickness on vaginal ultrasound. Endometrial biopsy is performed in such circumstances (5); while it does not help diagnosing endometrial cancer at the initial stages. Therefore, new pathways to diagnose the early stages of endometrial cancer got emphasized in research era. At the molecular level, a number of genes and signaling pathways play important roles in the pathogenesis of endometrial cancer. Many of them may be used as molecular heads for treatment (6), however, no effective treatment has been proposed that can extend the overall survival of the patient till now. Among these, non-coding molecules such as microRNA have been reported to play a role in regulating gene expression and etiology of endometrial cancer, and these molecules have also been studied as molecular biomarkers in various cancers, including endometrial cancer (7,8).

MicroRNAs (miRNAs)

MicroRNAs are the progenitors of RNAs, with mean 22 nucleotides, and have been shown to play a key role in regulating gene expression by inhibiting target mRNAs. Many different MicroRNAs regulate signal transmission, apoptosis, and tumorigenesis (9). MicroRNAs are also important transcriptional regulators in hematopoiesis. However, the potential of these molecules in the treatment and diagnosis of cancer has fascinated many scientists (10). miRNAs can be expressed in abnormal tissues. More than 2,000 miRNAs have been identified to date, but the function of a large group of them remains unknown. miRNAs are monoclonal and non-coding forms that have a very short length of about 19-24 nucleotides (11) and play an important role in regulating gene expression at the post-transcriptional level, and also play a vital role in biological processes such as proliferation, differentiation, metabolism, and angiogenesis. miRNAs regulate the innate and acquired immune system and prevent autoimmunity (12). The 8-nucleotide sequence in complementary miRNA is a specific part of the target mRNA sequence called the seed region. If the binding is complete, the target mRNA will degrade, and if this binding does not occur in one or more nucleotides in this region, it will only prevent the translation of the target mRNA. Because miRNAs are small functional units (13); Mononucleotide changes and polymorphisms in their sequence increase or decrease expression and changes in biological function (14). Blood flow and other body fluids contain significant amounts of these miRNAs, and

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changes in plasma miRNA levels may be indicative of pathological changes (15). These miRNAs have many unique biomarker properties. For example, these molecules are resistant to exonucleases, very high temperatures, high pH, long shelf life, or frequent freezing. Thus, circulating miRNAs and their profiles in plasma have a high potential for conversion as non-invasive biomarkers (16).

miRNAs in Cancers

MicroRNAs can play a role in cancer by different mechanisms. One of these mechanisms is the hash in microRNA genes. At present, it is well established that expression of miRNAs can increase or decrease in malignant tissues. By increasing expression, miRNAs may act as oncogenes by inhibiting tumor-inhibitory genes (17). The results of computer analysis and laboratory research indicate that there are numerous microRNAs in humans, and more than 11% of these microRNAs are located at some point in the genome that have been genetically identified as a sensitive area. In many cancers, genetic abnormalities are seen in these sensitive areas. Many cancer-inhibitory genes and oncogenes are under the precise control of microRNAs. Using this feature, microRNAs can be used in the diagnosis, prevention (18).

Studies on microRNAs have examined the role of these epigenetic regulatory elements in the differentiation of hematopoietic cells and have shown that microRNAs play a significant role during this cellular process and is the linkage between blood cancers and microRNAs (19). By promoting cell division, suppression of apoptosis (programmed cell death) and induction of angiogenesis (angiogenesis), it is involved in accelerating tumor progression (20).

The immune system uses several mechanisms to fight cancer cells. One of these mechanisms is autophagy. Autophagy is a conserved catabolic process in which proteins and organelles are removed through lysosomes (21). During this process, parts of the cytoplasm are separated by special bi-membrane vesicles called autophagosomes, which combine rapidly with the endosome or lysosome to form an autolysome. Exposure of the inner part to lysosomal hydrolyzes destroys the cytoplasmic charge and ultimately destroys the products, which are then released into the cytosol for recycling. Multiple miRNAs are known to be involved in regulation of the autophagy (22).

miRNAs in endometrial cancer

Many proteins involved in key endometrial cancer signaling pathways, such as the PI3 kinase, Wnt-catenin, KRAS, P53, and TGF pathways are regulated by miRNAs (23,24), and the role of some miRNAs in endometrial cancer as oncogenes or tumor suppressors has been confirmed in recent studies, based on the meta-analysis study by Delangle et al. (25). Recent studies suggest mir-18a as an oncogenic miRNA in endometrial cancer (26). Elevated mir-18a has been reported in gastric, hepatocellular, pancreatic, colorectal and endometrial cancers (27). The Let-7 microRNA family is a group of microRNAs that act as both oncogenes and tumor inhibitors. Most cancers have a decrease in Let-7 microRNA expression, which plays a tumor-inhibiting role. Let-7 microRNA is located in cancer-related fragility in many genes (28). Simultaneously with the reduction of proliferating cells, while inhibition of these five microRNAs has increased the number of proliferating cells (29), on the other hand, Let-7 microRNA specifically targets caspase-3 and thus also plays a role in the regulation of apoptosis (). Let-7 microRNA plays a key role in regulating cell proliferation and cell apoptosis (30). Let7a was shown to inhibit

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endometrial cancer growth (31Liu). In endometrial cancer, to protect endometrial cancer cells from apoptosis, hsa-miR-181d was increased to control expression of the tumor suppressor PTEN gene (32).

The PTEN gene encodes a tumor suppressor phosphatase that antagonizes the signaling pathway through lipid phosphatase activity and regulates it through the activity of the phosphatidyl inositol phosphatase protein. The protein encoded by this phosphatase contains a second pseudotensin and a second catalyst similar to the dual specific tyrosine phosphatase protein (33). Unlike many tyrosine phosphatase proteins, this protein acts as a tumor suppressor by negatively regulating the intracellular levels of phosphatidyl inositol triphosphate in cells, in the signaling pathway. PTEN function is commonly impaired in endometrial cancer (34). Currently, the most common genetic change in endometrioid carcinoma is a mutation in the PTEN gene. In most cases of endometrioid carcinoma, these genetic changes are seen as a loss of PTEN gene activity. In endometrial hyperplasia, which is the precursor of endometrial carcinoma, the expression of PTEN gene has been identified in 30-63% of cases (35-37).

Elimination of PTEN expression in endometrial tumors has also been identified. In fact, PTEN mutations occur in the earliest stages of endometrial cancer, whereas these mutations are seen as the final events in tumorigenic progression in prostate and brain tissues (38).

Poor prognostic miRNA in endometrial cancer

Five particular predictive miRNA indicators were chosen to build a prognostic model, which was proven to be more successful than the FIGO staging method in identifying EC individuals at high risk of death (39).

In endometrial cancer, miRNAs, particularly miR-205, the miR-200 family, and miR-135b, -182, -183, and -223, have the potential to be useful diagnostic biomarkers (40), as well as the miR-200a, miR-200c, and miR-155 (41). Wu et al. proposed a different panel of miRNAs containing miRNAs of miR-4758, miR-876, miR-142, miR-190b (42), and Lu et al. identified an eleven-miRNA signature that was highly expressed in endometrial cancer cells (43). Montagnana et al. found 4 miRNAs of miR-222, miR-223, miR-186, and miR-204 to be linked with endometrial cancer (44).

Good miRNAs in endometrial cancer

Tumors with less than 50% of myometrial invasion and non-advanced tumors have greater levels of miRNA-205 expression (45). mir-199c was linked to a higher chance of surviving cancer (46). miR-142 cluster and miR-15a (47) and miR-497/EMX1, miR-23c/DMBX1, and miR-670/KCNS1 (48) were good prognostic factors for endometrial cancer. Other study indicated that MicroRNA34b expression improves endometrial cancer cells' chemosensitivity to paclitaxel (49).

Conclusion

The pathogenic functions of MicroRNAs in endometrial cancer were emphasized in our review. Endometrial cancer-inhibitory genes and oncogenes, as well as the PTEN gene, are all regulated by miRNAs. This pathological knowledge is used in the clinical era to identify MicroRNAs linked to the diagnosis of?endometrial cancer; however, because there are so many miRNAs, many studies have proposed?panels of miRNAs that indicate the diagnosis of cancer, and single miRNAs are less well-known in the literature. However, there is greater evidence that the mir-18a and Let-7 families may be used to diagnose endometrial cancer. Other research looked at miRNAs that can predict endometrial cancer

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prognosis, and the results were divided into favorable and poor prognostic miRNAs.

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