Original Research

MiRNAS' Role in Endometrial Cancer: Diagnosis and Prognosis

Soroush Ghodratizadeh[1*]

1. Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran.

***Corresponding Author: Soroush Ghodratizadeh,** Department of Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran. Emal:soroush_gh10@yahoo.com. Orcid: 0000-0002-5840-8784

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

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

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

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

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

References

1. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, Tatebe K, Veneris JL. Current recommendations and recent progress in endometrial cancer. CA: a cancer journal for clinicians. 2019 Jul;69(4):258-79.
2. Passarello K, Kurian S, Villanueva V. Endometrial cancer: an overview of pathophysiology, management, and care. InSeminars in oncology nursing 2019 Apr 1 (Vol. 35, No. 2, pp. 157-165). WB Saunders.
3. Van Nyen T, Moiola CP, Colas E, Annibali D, Amant F. Modeling endometrial cancer: past, present, and future. International journal of molecular sciences. 2018 Aug;19(8):2348.
4. Arend RC, Jones BA, Martinez A, Goodfellow P. Endometrial cancer: Molecular markers and management of advanced stage disease. Gynecologic oncology. 2018 Sep 1;150(3):569-80.
5. Gentry-Maharaj A, Karpinskyj C. Current and future approaches to screening for endometrial cancer. Best practice & research Clinical obstetrics & gynaecology. 2020 May 1;65:79-97.
6. Di Tucci C, Capone C, Galati G, Iacobelli V, Schiavi MC, Di Donato V, Muzii L, Panici PB. Immunotherapy in endometrial cancer: new scenarios on the horizon. Journal of gynecologic oncology. 2019 May 1;30(3).
7. Donkers H, Bekkers R, Galaal K. Diagnostic value of microRNA panel in endometrial cancer: A systematic review. Oncotarget. 2020 May 26;11(21):2010.
8. Fan X, Zou X, Liu C, Cheng W, Zhang S, Geng X, Zhu W. MicroRNA expression profile in serum reveals novel diagnostic biomarkers for endometrial cancer. Bioscience reports. 2021 May 28;41(6).
9. Hanna J, Hossain GS, Kocerha J. The potential for microRNA therapeutics and clinical research. Frontiers in genetics. 2019 May 16;10:478.
10. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Frontiers in endocrinology. 2018 Aug 3;9:402.
11. Ali Syeda Z, Langden SS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. International journal of molecular sciences. 2020 Jan;21(5):1723.
12. Yu H, Guan Z, Cuk K, Brenner H, Zhang Y. Circulating microRNA biomarkers for lung cancer detection in Western populations. Cancer medicine. 2018 Oct;7(10):4849-62.
13. Króliczewski J, Sobolewska A, Lejnowski D, Collawn JF, Bartoszewski R. microRNA single polynucleotide polymorphism influences on microRNA biogenesis and mRNA target specificity. Gene. 2018 Jan 15;640:66-72.
14. Cui M, Wang H, Yao X, Zhang D, Xie Y, Cui R, Zhang X. Circulating microRNAs in cancer: potential and challenge. Frontiers in Genetics. 2019 Jul 18;10:626.
15. Yi M, Xu L, Jiao Y, Luo S, Li A, Wu K. The role of cancer-derived microRNAs in cancer immune escape. Journal of hematology & oncology. 2020 Dec;13(1):1-4.
16. Filipów S, Łaczmański Ł. Blood circulating miRNAs as cancer biomarkers for diagnosis and surgical treatment response. Frontiers in genetics. 2019 Mar 11;10:169.
17. Ingenito F, Roscigno G, Affinito A, Nuzzo S, Scognamiglio I, Quintavalle C, Condorelli G. The role of exo-miRNAs in cancer: a focus on therapeutic and diagnostic applications. International Journal of Molecular Sciences. 2019 Jan;20(19):4687.
18. Khan AQ, Ahmed EI, Elareer NR, Junejo K, Steinhoff M, Uddin S. Role of

miRNA-regulated cancer stem cells in the pathogenesis of human malignancies. Cells. 2019 Aug;8(8):840.

19. Segal M, Slack FJ. Challenges identifying efficacious miRNA therapeutics for cancer. Expert opinion on drug discovery. 2020 Sep 1;15(9):987-91.

20. Arif KM, Elliott EK, Haupt LM, Griffiths LR. Regulatory mechanisms of epigenetic miRNA relationships in human cancer and potential as therapeutic targets. Cancers. 2020 Oct;12(10):2922.

21. Ali Syeda Z, Langden SS, Munkhzul C, Lee M, Song SJ. Regulatory mechanism of microRNA expression in cancer. International journal of molecular sciences. 2020 Jan;21(5):1723.

22. Akkoc Y, Gozuacik D. MicroRNAs as major regulators of the autophagy pathway. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2020 May 1;1867(5):118662.

23. Lee LJ, Ratner E, Uduman M, Winter K, Boeke M, Greven KM, King S, Burke TW, Underhill K, Kim H, Boulware RJ. The KRAS-variant and miRNA expression in RTOG endometrial cancer clinical trials 9708 and 9905. PloS one. 2014 Apr 14;9(4):e94167.

24. Chen HY, Chiang YF, Huang JS, Huang TC, Shih YH, Wang KL, Ali M, Hong YH, Shieh TM, Hsia SM. Isoliquiritigenin reverses epithelial-mesenchymal transition through modulation of the tgf-β/smad signaling pathway in endometrial cancer. Cancers. 2021 Jan;13(6):1236.

25. Delangle R, De Foucher T, Larsen AK, Sabbah M, Azaïs H, Bendifallah S, Daraï E, Ballester M, Mehats C, Uzan C, Canlorbe G. The use of microRNAs in the management of endometrial cancer: a meta-analysis. Cancers. 2019 Jun;11(6):832.

26. Dong H, Li Y, Zhou J, Song J. MiR-18a-5p Promotes Proliferation, Migration, and Invasion of Endometrial Cancer Cells by Targeting THBD. Critical Reviews™ in Eukaryotic Gene Expression. 2021;31(2).

27. Kolenda T, Guglas K, Kopczyńska M, Sobocińska J, Teresiak A, Bliźniak R, Lamperska K. Good or not good: Role of miR-18a in cancer biology. Reports of Practical Oncology and Radiotherapy. 2020;25(5):808-19.

28. Liu P, Qi M, Ma C, Lao G, Liu Y, Liu Y, Liu Y. Let7a inhibits the growth of endometrial carcinoma cells by targeting Aurora-B. FEBS letters. 2013 Aug 19;587(16):2523-9.

29. Djati MS, Rifa'i M. Role of MicroRNAs in carcinogenesis that potential for biomarker of endometrial cancer. Annals of medicine and surgery. 2016 May 1;7:9-13.

30. Buonfiglioli A, Efe IE, Guneykaya D, Ivanov A, Huang Y, Orlowski E, Krüger C, Deisz RA, Markovic D, Flüh C, Newman AG. let-7 MicroRNAs regulate microglial function and suppress glioma growth through toll-like receptor 7. Cell Reports. 2019 Dec 10;29(11):3460-71.

31. Salazar C, Yañez O, Elorza AA, Cortes N, García-Beltrán O, Tiznado W, Ruiz LM. Biosystem analysis of the hypoxia inducible domain family member 2A: Implications in cancer biology. Genes. 2020 Feb;11(2):206.

32. Yang HP, Meeker A, Guido R, Gunter MJ, Huang GS, Luhn P, d'Ambrosio L, Wentzensen N, Sherman ME. PTEN expression in benign human endometrial tissue and cancer in relation to endometrial cancer risk factors. Cancer Causes & Control. 2015 Dec;26(12):1729-36.

33. Risinger JI, Hayes K, Maxwell GL, Carney ME, Dodge RK, Barrett JC, Berchuck A. PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics. Clinical Cancer Research. 1998 Dec 1;4(12):3005-10.

34. Forster MD, Dedes KJ, Sandhu S, Frentzas S, Kristeleit R, Ashworth A, Poole CJ,

Weigelt B, Kaye SB, Molife L. Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. Nature reviews Clinical oncology. 2011 May;8(5):302-6.

35. Terakawa N, Kanamori Y, Yoshida S. Loss of PTEN expression followed by Akt phosphorylation is a poor prognostic factor for patients with endometrial cancer. Endocrine-related cancer. 2003 Jun 1;10(2):203-8.

36. Bilbao C, Rodríguez G, Ramírez R, Falcón O, León L, Chirino R, Rivero JF, Falcón Jr O, Díaz-Chico BN, Díaz-Chico JC, Perucho M. The relationship between microsatellite instability and PTEN gene mutations in endometrial cancer. International journal of cancer. 2006 Aug 1;119(3):563-70.

37. Travaglino A, Raffone A, Saccone G, Insabato L, Mollo A, De Placido G, Zullo F. PTEN as a predictive marker of response to conservative treatment in endometrial hyperplasia and early endometrial cancer. A systematic review and meta-analysis. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Dec 1;231:104-10.

38. Risinger JI, Hayes AK, Berchuck A, Barrett JC. PTEN/MMAC1 mutations in endometrial cancers. Cancer research. 1997 Nov 1;57(21):4736-8.

39. Wang Q, Xu K, Tong Y, Dai X, Xu T, He D, Ying J. Novel miRNA markers for the diagnosis and prognosis of endometrial cancer. Journal of Cellular and Molecular Medicine. 2020 Apr;24(8):4533-46.

40. Donkers H, Bekkers R, Galaal K. Diagnostic value of microRNA panel in endometrial cancer: A systematic review. Oncotarget. 2020 May 26;11(21):2010.

41. Hermyt E, Zmarzły N, Grabarek B, Kruszniewska-Rajs C, Gola J, Jęda-Golonka A, Szczepanek K, Mazurek U, Witek A. Interplay between miRNAs and genes associated with cell proliferation in endometrial cancer. International journal of molecular sciences. 2019 Jan;20(23):6011.

42. Wu YS, Lin H, Chen D, Yi Z, Zeng B, Jiang Y, Ren G. A four-miRNA signature as a novel biomarker for predicting survival in endometrial cancer. Gene. 2019 May 20;697:86-93.

43. Lu J, Liang J, Xu M, Wu Z, Cheng W, Wu J. Identification of an eleven-miRNA signature to predict the prognosis of endometrial cancer. Bioengineered. 2021 Jan 1;12(1):4201-16.

44. Montagnana M, Benati M, Danese E, Giudici S, Perfranceschi M, Ruzzenenete O, Salvagno GL, Bassi A, Gelati M, Paviati E, Guidi GC. Aberrant MicroRNA expression in patients with endometrial cancer. International Journal of Gynecologic Cancer. 2017 Mar 1;27(3).

45. Wilczynski M, Danielska J, Dzieniecka M, Szymanska B, Wojciechowski M, Malinowski A. Prognostic and clinical significance of miRNA-205 in endometrioid endometrial cancer. PLoS One. 2016 Oct 13;11(10):e0164687.

46. Cohn DE, Fabbri M, Valeri N, Alder H, Ivanov I, Liu CG, Croce CM, Resnick KE. Comprehensive miRNA profiling of surgically staged endometrial cancer. American journal of obstetrics and gynecology. 2010 Jun 1;202(6):656-e1.

47. Jayaraman M, Radhakrishnan R, Mathews CA, Yan M, Husain S, Moxley KM, Song YS, Dhanasekaran DN. Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer. Genes & cancer. 2017 May;8(5-6):566.

48. Xu X, Liu T, Wang Y, Fu J, Yang Q, Wu J, Zhou H. MiRNA–mRNA associated with survival in endometrial cancer. Frontiers in genetics. 2019:743.

49. Yanokura M, Banno K, Aoki D. MicroRNA 34b expression enhances chemosensitivity of endometrial cancer cells to

paclitaxel. International journal of oncology. 2020 Nov 1;57(5):1145-56.