Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 1s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

The Role of miRNA Let-7a-1 and Let-7f-1 in Regulating Inflammatory and Angiogenic Pathways in Endometriosis

Wahyuni Saddang[1, *2], Nusratuddin Abdullah[3], Firdaus Hamid[4], Rusdiana Bte Ladju[5], Irfan Idris[6], Sitti Wahyuni[7], Sriwijaya[3], Mila Maidarti[8]

[1]Doctoral Student, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[*2]Department of Obsetry and Gynecology, Faculty of Medicine, Universitas Muslim Indonesia, Makassar, Indonesia

[3]Department of Obsetry and Gynecology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[4]Department of Clinical Microbiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[5]Department of Pharmacology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[6]Department of Physiology, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[7]Department of Parasitogy, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia

[8]Department of Obsetry and Gynecology, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

[*]Corresponding Author:

Email ID: wahyunisaddang.fk@umi.ac.id

Cite this paper as: Wahyuni Saddang, Nusratuddin Abdullah, Firdaus Hamid, Rusdiana Bte Ladju, Irfan Idris, Sitti Wahyuni, Sriwijaya, Mila Maidarti, (2025) The Role of miRNA Let-7a-1 and Let-7f-1 in Regulating Inflammatory and Angiogenic Pathways in Endometriosis. *Journal of Neonatal Surgery*, 14 (1s), 675-684.

ABSTRACT

BACKGROUND

Endometriosis, a chronic gynecological disorder characterized by the ectopic growth of endometrial tissue, involves complex inflammatory and angiogenic mechanisms. MicroRNAs (miRNAs), particularly Let-7a-1 and Let-7f-1, have been identified as key regulators of these pathways, influencing the progression and symptoms of the disease.

OBJECTIVES

This review aims to explore the roles of miRNA Let-7a-1 and Let-7f-1 in the regulation of inflammatory and angiogenic pathways in endometriosis, highlighting their potential as biomarkers and therapeutic targets.

MATERIALS AND METHODS

A comprehensive literature search was conducted using databases such as PubMed, Scopus, and Web of Science. Relevant studies published between 2000 and 2024 were included, focusing on the expression, function, and regulatory mechanisms of Let-7a-1 and Let-7f-1 in endometriosis. Key findings were synthesized to provide an updated understanding of their biological and clinical relevance.

RESULTS

Evidence indicates that Let-7a-1 and Let-7f-1 play pivotal roles in modulating pro-inflammatory cytokines, angiogenic factors like VEGF, and cellular proliferation in endometriotic lesions. Dysregulated expression of these miRNAs is associated with enhanced inflammatory responses and aberrant angiogenesis, contributing to the persistence and progression of endometriosis. Furthermore, preclinical studies demonstrate that targeting Let-7 family miRNAs can mitigate these processes, suggesting their potential utility in therapeutic strategies.

CONCLUSION

Let-7a-1 and Let-7f-1 serve as critical modulators in the inflammatory and angiogenic pathways of endometriosis, offering insights into disease pathophysiology. Their roles as biomarkers and therapeutic targets warrant further investigation, paving the way for novel diagnostic and treatment approaches in endometriosis management.

Keywords: *endometriosis, miRNA let-7a-1, miRNA let-7f-1, biomarkers, molecular therapy*

1. INTRODUCTION

Endometriosis is a condition that includes chronic inflammation accompanied by the discovery of endometrial tissue outside the uterine cavity. Symptoms usually caused by this condition are dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility. Most endometriosis sufferers are women of reproductive age. This is certainly a big problem and has a negative impact on women's quality of life. The impact of endometriosis is not only in the field of women's physical health but also in the economic and mental health fields as it is known that as many as 86.5% of women with endometriosis experience depression while 87.5% experience anxiety disorders.[1]

Therefore, it is necessary to find effective diagnostic tests and treatments for endometriosis. It is recorded in global data that as many as 10-15% of women of reproductive age experience endometriosis. Endometriosis is a complex and chronic gynecological condition characterized by the presence of endometrial-like tissue outside the uterine cavity. Affecting up to 10% of women of reproductive age, the condition is associated with debilitating pelvic pain, infertility, and a significant reduction in quality of life. Despite extensive research, the precise pathophysiology of endometriosis remains incompletely understood, with inflammation and angiogenesis identified as two critical processes driving lesion establishment and progression.[2] MicroRNAs (miRNAs) are small, non-coding RNAs that play essential roles in post-transcriptional gene regulation. Recent studies have highlighted their involvement in various biological processes, including inflammation and angiogenesis, both of which are central to the pathogenesis of endometriosis. Among the miRNA families, the let-7 family has garnered attention for its regulatory effects on key inflammatory cytokines and angiogenic factors. MiRNA let-7a-1 and let-7f-1, members of the let-7 family, are known to modulate the expression of pivotal molecular mediators such as interleukin-6 (IL6), interleukin-8 (IL8), and vascular endothelial growth factor-A (VEGF-A). Dysregulation of these miRNAs has been implicated in the creation of a chronic inflammatory microenvironment and the promotion of neovascularization, both of which are vital for the survival and growth of endometriotic lesions.[3]

This review aims to synthesize current knowledge on the roles of miRNA let-7a-1 and let-7f-1 in regulating inflammatory and angiogenic pathways in endometriosis. By examining their interactions with IL6, IL8, and VEGF-A, we seek to elucidate their contributions to disease pathogenesis and explore their potential as diagnostic biomarkers and therapeutic targets. A deeper understanding of these molecular mechanisms could pave the way for innovative strategies to improve the clinical management of endometriosis, addressing an unmet need in gynecological healthcare. Although there is no data on the epidemiology of endometriosis in Indonesia, it is known that 15-25% of infertility in Indonesian women is caused by endometriosis.[4] This data can certainly reflect the magnitude of the problems caused by endometriosis on women's health. Therefore, specific and non-invasive early diagnostic tests are important to minimize the further impact of endometriosis. So far, endometriosis diagnosis is done by tissue biopsy with laparoscopy assistance. Although it can properly establish a diagnosis of endometriosis, this method is quite invasive. In terms of therapy, the management that has been given to endometriosis sufferers so far also includes symptom management and surgery.[5] Other examinations such as specific biological markers/biomarkers for endometriosis are not yet available. The pathogenesis of endometriosis is a complex process. In its course, endometriosis involves various factors that can ultimately cause pathological conditions. There are many theories that explain the pathogenesis of endometriosis, but they are not yet fully understood. The theory that has been most widely adopted is the theory proposed by Sampson, namely the implantation theory. According to Sampson, endometriosis begins with the presence of endometrial cells that reflux into the peritoneal cavity when a woman menstruates. These endometrial cells that are carried eventually implant and grow in organs outside the uterus. Unfortunately, this theory cannot explain the occurrence of endometriosis in women whose fallopian tubes are anatomically incompetent. Thus, several other theories have emerged such as the theory of immune dysfunction, metaplasia, and stem cell theory.[6]

There are various types and subtypes of miRNA that have been identified. The type that was first discovered in humans and has been investigated quite deeply is miRNA let-7. MicroRNA-let7 itself consists of various subtypes from miRNA-let7a to miRNA let-7i. Some of the interesting ones to study are miRNA let-7a-1 and miRNA let-7f-1. Functional analysis of miRNA has a significant influence on the expression of target genes involved in the physiological and pathological conditions involved. Aberrant miRNA expression is associated with several human diseases such as cancer, cardiovascular disorders, inflammatory diseases, and benign or malignant pathologies of the human female reproductive tract.

Existing research shows that miRNA let-7a has a strong bond with IL-6, a pro-inflammatory cytokine that is closely related to the pathogenesis of endometriosis.[7]

Still in the same type as miRNA-let7a, miRNA let-7f was also found to have an effect on factors that are known to be related to the pathogenesis of endometriosis. One of them is aromatase, an enzyme that functions to convert androgen into estrogen. Previous theory stated that estrogen activity is one of the factors that influence the occurrence of endometriosis. MicroRNA-let7f in the latest study was found to be able to inhibit the activity of aromatase P450, thereby reducing circulating estrogen levels, so miRNA let-7f is called an endogenous aromatase inhibitor. In addition, it is also known that miRNA let-7f has a role in the migration of ectopic endometriosis cells. One of the subtypes of miRNA-let7a is miRNA -let7a-1 and the subtype of miRNA-let7f is miRNA let-7f-1. Currently, there are not many studies that specifically investigate the relationship between miRNA let-7a-1 and miRNA let-7f-1 with endometriosis. Therefore, in this study, further research was conducted

on the two miRNA subtypes in the pathogenesis of endometriosis. The discovery of specific biomarkers for endometriosis is expected to open up opportunities for new non-invasive diagnostic tests and new therapeutic target candidates for endometriosis.[8] Until now, endometriosis management includes symptomatic management and surgical management. Symptomatic management is usually given in the form of anti-pain, anti-inflammatory, and estrogen level modulation. While surgical management is done by eliminating ectopic lesions that have been identified through imaging. Due to the limited treatment options and diagnostic methods for endometriosis, further studies are needed regarding the pathophysiology and pathogenesis of endometriosis, so that it is hoped that it can help researchers identify specific targets that can help the diagnostic process and management of endometriosis more effectively.[9]

2. MATERIALS AND METHODS

This review article was conducted using a structured and systematic approach to gather and analyze relevant literature on the role of miRNA let-7a-1 and let-7f-1 in regulating inflammatory and angiogenic pathways in endometriosis. The methodology consisted of the following steps: A comprehensive search was performed across multiple databases, including PubMed, Scopus, Web of Science, and Google Scholar, to identify peer-reviewed articles published in English. Keywords and search terms used included "miRNA let-7a-1," "miRNA let-7f-1," "inflammation," "angiogenesis," "VEGF-A," "IL6," "IL8," "endometriosis," and "molecular pathways." Boolean operators (AND, OR) were applied to refine the search. Articles were included if they discussed the expression or regulatory role of miRNA let-7a-1 or let-7f-1 in endometriosis.

Explored their association with inflammatory cytokines (IL6, IL8) or angiogenic factors (VEGF-A). Studies focusing on unrelated diseases, non-human subjects, or lacking detailed molecular analysis were excluded. Data were extracted from selected articles, including miRNA expression levels, target gene interactions, and their biological effects on inflammation and angiogenesis in endometriosis. A narrative synthesis was conducted to integrate findings from experimental, clinical, and bioinformatics studies. The quality of included studies was assessed based on methodology, sample size, and relevance to the topic. Bias and limitations in the existing literature were noted and discussed to provide a balanced and comprehensive review. As this study is a review of existing literature, no ethical approval was required. However, all sources were appropriately cited to ensure academic integrity.

3. RESULTS

This review synthesizes findings from a broad range of studies investigating the role of miRNA let-7a-1 and let-7f-1 in regulating inflammatory and angiogenic pathways in endometriosis. Expression Patterns of miRNA let-7a-1 and let-7f-1. Numerous studies report dysregulated expression of miRNA let-7a-1 and let-7f-1 in endometriotic tissues compared to eutopic endometrium and healthy controls. Reduced levels of these miRNAs are consistently observed in active lesions, suggesting a loss of regulatory control over inflammation and angiogenesis in endometriosis. miRNA let-7a-1 and let-7f-1 are shown to target and suppress pro-inflammatory cytokines, including IL6 and IL8, at the post-transcriptional level. Reduced miRNA expression leads to upregulation of IL6 and IL8, exacerbating the inflammatory microenvironment and promoting immune evasion by endometriotic lesions. VEGF-A, a key angiogenic factor, is identified as a direct target of miRNA let-7 family members.

Downregulation of let-7a-1 and let-7f-1 correlates with increased VEGF-A expression, driving neovascularization essential for lesion survival and growth. Studies highlight the dual role of these miRNAs in inhibiting endothelial cell proliferation and migration, suggesting their potential in modulating angiogenic activity. Aberrant expression of miRNA let-7a-1 and let-7f-1 is associated with disease severity and lesion progression in patients with endometriosis. These miRNAs demonstrate promise as biomarkers for early diagnosis and as molecular targets for therapeutic interventions aimed at disrupting inflammatory and angiogenic pathways. While significant progress has been made, further research is needed to elucidate the precise mechanisms by which miRNA let-7a-1 and let-7f-1 interact with their targets and contribute to the heterogeneity of endometriosis phenotypes.

4. DISCUSSION

4.1 Review of Immune Dysfunction Theory

Endometriosis is a pathological condition in which there is endometrium-like tissue outside the uterus accompanied by local chronic inflammation. This ectopic tissue can usually be found in the peritoneal cavity or pelvic cavity. This ectopic tissue has glands and stroma that can respond to hormonal stimuli, especially estrogen, both endogenous and exogenous. Endometriosis cases are common, especially in women of reproductive age and have been shown to have a major impact on a woman's life. Some problems that arise due to endometriosis include menstrual pain (dysmenorrhea), pain during sexual intercourse (dyspareunia), pain during defecation (dyschezia), pain during urination (dysuria), and infertility which can affect a woman's quality of life. In addition, it was also found that 1% of endometriosis cases can develop into malignancy.[10] This condition can also affect the patient's quality of life in terms of economy, emotion, and mental condition as explained that patients with endometriosis experience mental disorders such as depression, which is 86.5% and anxiety disorders, which is 87.5%. Although the patient's medical history, epidemiological data, and physical examination can help guide a doctor in

diagnosing endometriosis at an early stage, the diagnosis is often hampered by the unavailability of sufficiently accurate non-invasive diagnostic methods.[11]

Based on the studies that have been conducted, several theories have been proposed regarding the pathogenesis of endometriosis, including: implantation theory, metaplasia theory, immune dysfunction theory, and the theory of endometrial cells as stem cells. In a study was stated that autoimmune conditions are often found in women diagnosed with endometriosis. In the study, it was stated that women with endometriosis have macrophages with higher activity. Retrograde reflux of endometrial cells into the peritoneal cavity induces local inflammation which then triggers implantation and proliferation of endometriosis cells at that location. The occurrence of cell proliferation is mediated by cytokines and angiogenesis which are also part of the local inflammatory response. Immune cells and inflammatory processes that participate in endometrial pathogenesis are explained in **Figure 1.**[12]

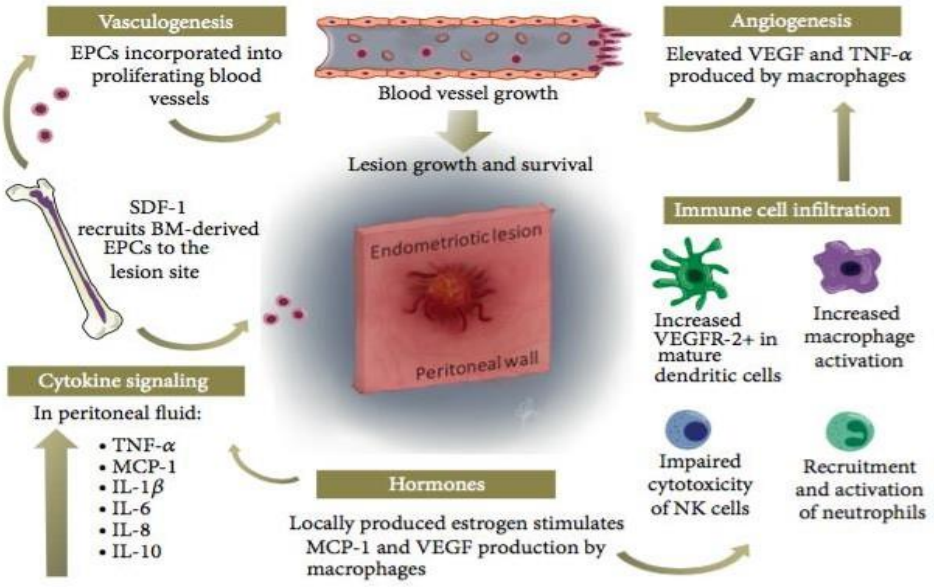

Figure 1. Overview of the theory of immune dysfunction.[12]

In **Figure 1.** It is shown that cytokines and angiogenesis factors play a role in the pathogenesis of endometriosis. Among the cytokines mentioned above, two of them are IL6 and IL-8. IL-6 is one of the cytokines that is predominantly produced by macrophages. Several studies have shown that IL-6 in the peritoneal fluid of women with endometriosis is increased compared to healthy women. Therefore, it is thought that IL-6 contributes to the development of endometriosis. IL-6 mediates the development of endometriosis through the cytokine network and through its interaction with cellular immune cells. Patients with endometriosis are known to produce haptoglobin molecules; a molecule that can help ectopic endometrial tissue to avoid the immune system by binding to macrophages. Increased IL-6 by macrophages can help increase the amount of haptoglobin, thereby further protecting ectopic endometrial cells from phagocytosis. IL-6 itself has various activities mediated by its receptors such as: Membrane binding receptor (mIL-6R) and soluble receptor (sIL-6R).[13]

In general, IL-6 receptors are commonly referred to as IL-6R. In the Li S study, it was also found that sIL-6R in peritoneal fluid increased in the group of women with endometriosis. In addition, inactive mIL-6R attached to the surface of macrophages decreased due to binding to IL-6 released into the peritoneal fluid environment. Similar to IL-6, IL-8 is also a pro-inflammatory cytokine. Previously, it was thought that IL-8 in peritoneal fluid could adhesion and proliferation of ectopic endometrial tissue. However, Arici A et al in their study found that in fact, adhesion of ectopic endometrial tissue to extracellular matrix components induces IL-8 expression. Thus, it is concluded that IL-8 and adhesion of ectopic endometrial tissue provide positive feedback to each other, thus creating an event that supports the progression of endometriosis. In addition, IL-8 was also found to help local invasion of ectopic endometrial cells on the peritoneal surface through increased metalloproteinases and proteases in these ectopic endometrial cells.[14]

4.2 Overview of the miRNA Formation Cascade

Initial diagnosis of endometriosis cases is usually based on the patient's history of complaints. Physical examination can also help, but not a few women show normal physical examinations. In addition, physical examination in women with endometriosis can overlap with other gynecological diseases. Pain on palpation of the posterior fornix is usually the most common physical examination finding. Pelvic pain is also a fairly common symptom of endometriosis.[15] However, pelvic

pain is also a symptom of several other diseases so it is important to do further examinations to exclude other possible etiologies.[16] Examinations such as pap smears, urinalysis, pregnancy tests, and vaginal or endocervical swabs are often used to exclude other possible diseases. Pelvic ultrasound is usually performed if the estimate tends to point to endometrioma, fibroids, and ovarian cysts. If the suspicion points to a pelvic mass, then transvaginal and transabdominal ultrasound are usually chosen. However, the gold standard for diagnosing endometriosis to date is inspection using laparoscopy followed by sampling through a biopsy for histological examination.[17]

However, laparoscopy is not an easy examination to be a first-line diagnostic tool because the procedure is quite invasive. Therefore, researchers are still looking for non-invasive early diagnosis methods.[18] Non-invasive diagnostic tests and early management are needed to prevent delays in treatment.[19] This is because the current condition is that there are still many cases of endometriosis that cannot be detected and treated early, which has a negative impact on women's quality of life. Therefore, various studies have been conducted to find potential biomarkers that can be used as early and non-invasive diagnostic tests as well as early management.[20] The hope is that diagnosis can be made earlier so that disease progression can be inhibited and appropriate management can be given more quickly and precisely. It was shown in a study by Moustafa et al. that microRNAs (miRNA) have the potential to be endometriosis biomarkers.[21] Several studies have observed various types of miRNA and their roles in the development of endometriosis and a number of other gynecological disorders. The discovery of specific biomarkers for endometriosis will certainly be a breakthrough in the world of health. Non-invasive diagnostic methods such as miRNA biomarkers will certainly minimize invasive procedures with greater risks such as laparoscopy and tissue biopsy.[22]

The discovery of biomarkers can also help in endometriosis therapy. MicroRNA (miRNA) is a small sequence that does not have a coding function.[23] However, this sequence can bind to its specific target mRNA. This sequence consisting of 19 to 22 nucleotides can regulate cellular processes through its binding to the 3'-UTR region of certain mRNA sequences and inhibit gene expression. Like other RNAs, miRNA biogenesis begins in the nucleus and begins with the formation of pri-miRNAs with the help of RNA polymerase II (RNA se II).[24] Furthermore, pri-miRNA is converted into pre-miRNA (which has 70-100 nucleotides) with the help of RNAse III. After being transported to the cytoplasm, pre-miRNA is cut by Dicer to form functional miRNA which is then integrated into the RNA-induced silencing complex (RISC) on an mRNA sequence (**Figure.2**).[25] Several miRNAs have been shown to be involved in neoplastic angiogenesis. In particular, VEGF expression in various cancer types has been recognized to be regulated by different miRNAs, such as miR-20 [45], miR-29b [46], miR-93 [47], miR-126 [48], miR-190 [49], miR-195 [50], miR-200 [51], miR-203 [52], miR-497 [53], miR-503 [54], and miR-638 [55]. Some of them, such as miR-29, inhibit angiogenesis by downregulating VEGF when overexpressed. Others, such as miRNA-195, promote angiogenesis and metastasis via VEGF and pro-metastatic factors.[26] In addition to directly targeting VEGF, a handful of miRNAs regulate VEGF-dependent tumor angiogenesis by targeting VEGF inducers, such as the HIF-1 pathway (miR-22 [56], miR-107 [57], miR-519c [58], miR-145 [59]). However, the direct relationship between the role of miRNAs in angiogenesis and cancer metastasis remains to be studied.[27]

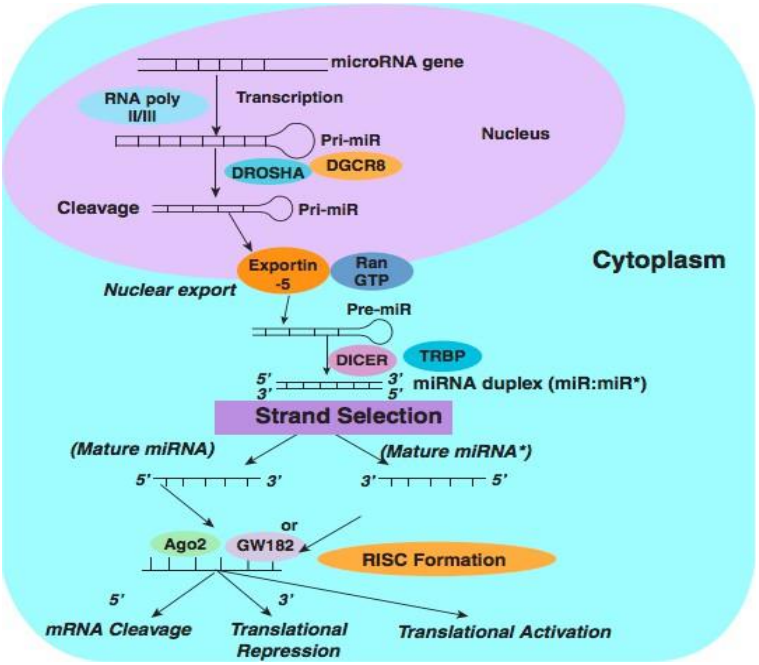

Figure 2. Cascade of miRNA formation.[27]

Figure 2. shows more than a thousand miRNAs encoded in the human genome. These microRNAs are known to play an important role in cell growth and differentiation, cell death, and cell metabolism. In recent years, it has been discovered that miRNAs also play a role in various types of pathological conditions such as cancer, autoimmune diseases, cardiovascular diseases, and so on.[28] The role of miRNAs in autoimmune conditions is reinforced by studies stating that miRNAs contribute to the activation of the innate immune system including macrophages, dendritic cells, granulocyte cells, and natural killer (NK) cells. Several studies have also found that miRNAs participate in the development and differentiation of B and T cells.[29] Based on these studies and reinforced by genetic studies, it is suspected that miRNA dysregulation can lead to immune-related diseases such as autoimmune diseases and cancer.[30] So far, it has been known that miRNAs are tissue-specific. Tumors with different types have different miRNA expressions. Identification of miRNAs that are not bound to certain cells or tissues. miRNA molecules are found in plasma, urine, saliva, seminal fluid, ascites, and cerebrospinal fluid. A study also said that the emergence of miRNA in body fluids is triggered by various factors, such as apoptosis necrosis, local inflammation, and active secretion by exosomes or microvesicles.[31]

4.3 Application of miRNA let-7 activation pathway

As mentioned in the paragraph above, there are more types of miRNA in the human body. One that is interesting to study further is the let-7 miRNA group. Let-7 microRNA is the first miRNA discovered in humans and has a primary function to help cell differentiation.[32] However, evidence suggests that dysregulation of the let-7 miRNA group can actually inhibit the pathogenesis of malignancy. Let-7 microRNA consists of various subtypes, namely let-7a miRNA to let-7g miRNA. Previous studies have tried to see the relationship between let-7 miRNA and endometriosis. In one study, it was found that let-7a miRNA, let-7b-5p miRNA, and let-7e-5p miRNA decreased in the serum of patients with endometriosis. A recent study by Heravi FM et al. showed that administering one of the let-7 miRNA subtypes, let-7b-5p miRNA, intraperitoneally to mice resulted in decreased lesion growth and decreased the number of genes active in the pathophysiology of endometriosis.[33] From the study, it was concluded that miRNA let7b-5p has activity to suppress tumor cells, where this finding is in accordance with the findings in other studies that have been done previously.23 It was said in the study by Seifer BJ that miRNA from the let-7 group has similar properties and roles to each other.[34] Therefore, further studies are needed to see the role of other let-7 miRNA subtypes in the pathogenesis of endometriosis. As shown in **Figure 3**. let-7a activation involves various factors. It is known that miRNA -let7 regulation occurs in a loop/cycle consisting of NFκB-Lin28-miRNAlet7-interleukin 6 (IL6). Lin28 and its subtypes are known to bind to the hairpin part of pre-miRNA -let7 and inhibit Dicer attachment, thereby inhibiting the process and biogenesis of pre-miRNA -let-7. NFκB was found to induce transcription of LIn28, thereby reducing miRNA-let7. Then, miRNA let-7 can inhibit IL-6 expression, which is basically able to activate NFκB.[35]

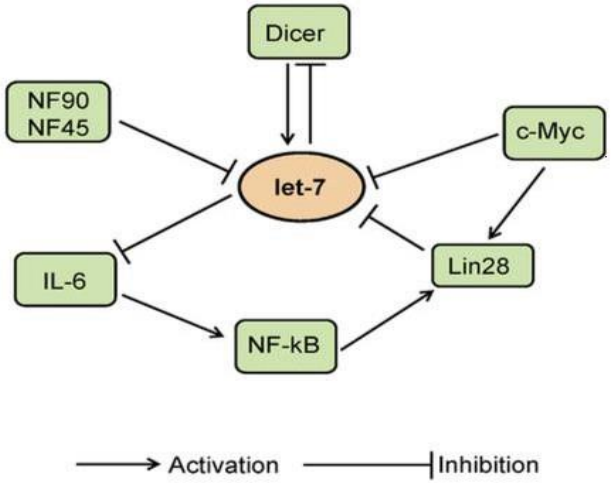

Figure 3. The let-7 miRNA activation pathway is influenced by several factors.[35]

Figure 3. show Another target of miRNA-let7 is c-Myc, a proto-oncogene. The expression of c-Myc is regulated by IMP1, whose activity can be inhibited by miRNA-let7. In addition, c-Myc has also been found to inhibit the expression of miRNA-let 7 through Lin28. This miRNA-let 7 regulatory loop shows that miRNA-let7 has many roles in cell signaling, including in cell growth and the pathogenesis of various pathological conditions.[36] Therefore, further studies on miRNA let-7 and its subtypes need to be conducted to be able to specifically examine the role of each miRNA let-7 subtype. Among the various miRNA let-7 subtypes, miRNA let-7a-1 and miRNA let-7f-1 still seem to provide room for researchers to explore. From previous studies, it was found that like miRNA let-7b-5p, miRNA let-7a also has a binding site with KRAS, a strong proto-oncogene.[37]

It was found that KRAS was upregulated in endometriosis. This finding is supported by the emergence of endometriosis in mice with mutations in KRAS. 26 Regulation of KRAS expression by miRNA let-7a is mediated by miRNA let-7a binding to its complementary site on the 3'-UTR of the KRAS gene. When this binding occurs, the total expression of KRAS protein decreases significantly. This significant decrease in KRAS is the same as a decrease in proto-oncogene activity, so that this cascade series ends in a decrease in activity that supports tumor cell development.[38] In addition to affecting KRAS, Zhao Y et al found that miRNA Regulation of KRAS expression by miRNA let-7a is mediated by miRNA let-7a binding to its complementary site on the 3'-UTR of the KRAS gene. When this binding occurs, the total expression of KRAS protein decreases significantly.[39] In the study, it was demonstrated that the effect of miRNA let-7a on estrogen receptors can affect the pathogenesis of breast cancer, especially ERα positive. ERα itself is a transcription factor that induces the expression of various genes such as cyclin D1, pS2, and c-Myc, all of which are proto-oncogenes.[40]

The study described that an increase in miRNA let-7a, miRNA let-7b, and miRNA let-7i was followed by a decrease in ERα. Although the study focused on breast cancer, it should be noted that endometriosis is also a disease related to estrogen, so estrogen receptors certainly have their own role in the pathogenesis of this condition. Another study found that miRNA let-7a actually has a specific binding site on the mRNA of IL-6, which is one of the molecules with a crucial role in the development of endometriosis.[41] In a study examining the relationship between miRNA let-7a and IL-6 in systemic lupus erythematosus (SLE), it was found that there was an increase in miRNA let-7a in mesangial cells increasing the expression of Tristetraprolin (TTP) which is an RNA binding protein that has a binding site on IL-6 in its 3'UTR region. Through this TTP, miRNA-let-7a can bind to IL-6 and suppress its activity. Another pathway that is also regulated by miRNA let-7a is JAK-STAT3 where miRNA let-7a can suppress the activity of this oncogenic pathway through suppression of IL-6. In the previous section, it was explained that JAK-STAT3 is one of the pathways that participates in the pathogenesis of several malignancies and recent studies have also found the possibility of STAT3 involvement in the pathogenesis of endometriosis.[42] Therefore, inhibition of JAK-STAT3 by miRNA let-7a is strongly suspected to be able to stop the development of endometriosis. From the above findings, miRNA subtypes let-7a such as let-7a-1 are suspected to also be involved in the pathogenesis of endometriosis.[43]

5. LIMITATION

This review article highlights the critical roles of miRNA Let-7a-1 and Let-7f-1 in regulating inflammatory and angiogenic pathways in endometriosis. However, several limitations must be acknowledged, the studies included in this review vary significantly in methodology, sample size, and patient populations, which may introduce biases and limit the generalizability of findings. Most of the evidence regarding the role of Let-7a-1 and Let-7f-1 is derived from in vitro and animal studies. Translational research and clinical trials are still limited, making it challenging to directly apply these findings to clinical practice. Although substantial progress has been made, the exact molecular mechanisms and downstream targets of Let-7a-1 and Let-7f-1 in endometriosis are not fully elucidated. This gap hampers the understanding of their precise roles in disease progression. The interplay of other miRNAs and signaling pathways in endometriosis adds complexity, making it difficult to attribute specific outcomes solely to Let-7a-1 and Let-7f-1.

6. CONCLUSION

Endometriosis remains a complex and multifaceted condition, marked by chronic inflammation and aberrant angiogenesis. This review underscores the significant role of miRNA let-7a-1 and let-7f-1 in the molecular landscape of endometriosis, particularly their correlation with the expression of inflammatory cytokines IL6 and IL8, as well as vascular growth factor VEGF-A. These molecular players are pivotal in sustaining the inflammatory microenvironment and promoting neovascularization, both critical in the pathogenesis and progression of endometriotic lesions. The regulatory influence of miRNA let-7 family members extends to key pathways that drive lesion establishment, immune evasion, and vascular remodeling. Dysregulation of these miRNAs disrupts the balance between pro-inflammatory and anti-inflammatory signals, exacerbating the chronic nature of the disease. Additionally, their involvement in modulating VEGF-A expression highlights their contribution to the angiogenic processes that support lesion survival and growth. This review highlights the diagnostic and therapeutic potential of miRNA let-7a-1 and let-7f-1 as biomarkers for early detection and as molecular targets for innovative treatments. The integration of miRNA profiling into clinical practice could enhance diagnostic precision and enable the development of personalized therapeutic strategies. The intricate interplay between miRNA let-7a-1, let-7f-1, IL6, IL8, and VEGF-A gene expression provides a deeper understanding of the molecular mechanisms underlying endometriosis. Future research should aim to further elucidate these relationships and translate these findings into clinical applications, offering hope for improved management and outcomes for patients affected by this debilitating condition.

7. CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We would like to express our heartfelt gratitude to all those who have contributed to the completion of this review. Special

thanks go to the Faculty of Medicine, Universitas Hasanuddin, Makassar, for providing an intellectually stimulating environment and resources that have greatly supported this work. I am also grateful to my research team and collaborators for their dedication and critical insights, which have significantly enriched the quality of this work. Lastly, I thank my family and friends for their unwavering support and encouragement, which have been a source of strength and motivation during this process.

REFERENCES

[1] Bendifallah S, Dabi Y, Suisse S, et al. A Bioinformatics Approach to MicroRNA-Sequencing Analysis Based on Human Saliva Samples of Patients with Endometriosis. *IJMS*. 2022;23(14):8045. doi:10.3390/ijms23148045

[2] Leonova A, Turpin VE, Agarwal SK, Leonardi M, Foster WG. A critical appraisal of the circulating levels of differentially expressed microRNA in endometriosis. *Biology of Reproduction*. 2021;105(5):1075-1085. doi:10.1093/biolre/ioab134

[3] Febriza A, Hatta M, Natzir R, Kasim VNA, Idrus HH. Activity of Antimicrobial Peptide; Cathelicidin, on Bacterial Infection. *TOBIOCJ*. 2019;13(1):45-53. doi:10.2174/1874091X01913010045

[4] Antonio LGL, Meola J, Rosa-e-Silva ACJDS, et al. Altered Differential Expression of Genes and microRNAs Related to Adhesion and Apoptosis Pathways in Patients with Different Phenotypes of Endometriosis. *IJMS*. 2023;24(5):4434. doi:10.3390/ijms24054434

[5] Brulport A, Bourdon M, Vaiman D, et al. An integrated multi-tissue approach for endometriosis candidate biomarkers: a systematic review. *Reprod Biol Endocrinol*. 2024;22(1):21. doi:10.1186/s12958-023-01181-8

[6] Zubrzycka A, Migdalska-Sęk M, Jędrzejczyk S, Brzeziańska-Lasota E. Assessment of BMP7, SMAD4, and CDH1 Expression Profile and Regulatory miRNA-542-3p in Eutopic and Ectopic Endometrium of Women with Endometriosis. *IJMS*. 2023;24(7):6637. doi:10.3390/ijms24076637

[7] Anastasiu CV, Moga MA, Elena Neculau A, et al. Biomarkers for the Noninvasive Diagnosis of Endometriosis: State of the Art and Future Perspectives. *IJMS*. 2020;21(5):1750. doi:10.3390/ijms21051750

[8] Nothnick WB, Al-Hendy A, Lue JR. Circulating Micro-RNAs as Diagnostic Biomarkers for Endometriosis: Privation and Promise. *Journal of Minimally Invasive Gynecology*. 2015;22(5):719-726. doi:10.1016/j.jmig.2015.02.021

[9] Zubrzycka A, Migdalska-Sęk M, Jędrzejczyk S, Brzeziańska-Lasota E. Circulating miRNAs Related to Epithelial–Mesenchymal Transitions (EMT) as the New Molecular Markers in Endometriosis. *CIMB*. 2021;43(2):900-916. doi:10.3390/cimb43020064

[10] Wu J, Fang X, Huang H, Huang W, Wang L, Xia X. Construction and topological analysis of an endometriosis-related exosomal circRNA-miRNA-mRNA regulatory network. *Aging*. 2021;13(9):12607-12630. doi:10.18632/aging.202937

[11] Febriza A, Natzir R, Hatta M, Alam G, Kasim VN, Idrus HH. Curcumin effects in inducing mRNA gene cathelidicin antimicrobial peptide in Balb/c mice infected with Salmonella typhi.

[12] Tian Z, Chang XH, Zhao Y, Zhu HL. Current biomarkers for the detection of endometriosis. *Chinese Medical Journal*. 2020;133(19):2346-2352. doi:10.1097/CM9.0000000000001063

[13] Chen G, Guo J, Li W, Zheng R, Shang H, Wang Y. Diagnostic value of the combination of circulating serum miRNAs and CA125 in endometriosis. *Medicine*. 2023;102(48):e36339. doi:10.1097/MD.0000000000036339

[14] Kasim V, Hatta M, Natzir R, Hadju V, Febriza A, Idrus H. Effects of lime (Citrus aurantifolia) peel to the expression of mRNA toll-like receptors 4 in balb/c mice-infected Salmonella typhi. *J Adv Pharm Technol Res*. 2020;11(4):169. doi:10.4103/japtr.JAPTR_48_20

[15] Cosar E, Mamillapalli R, Moridi I, Duleba A, Taylor HS. Serum MicroRNA Biomarkers Regulated by Simvastatin in a Primate Model of Endometriosis. *Reprod Sci*. 2019;26(10):1343-1350. doi:10.1177/1933719118765971

[16] Giudice LC, Oskotsky TT, Falako S, Opoku-Anane J, Sirota M. Endometriosis in the era of precision medicine and impact on sexual and reproductive health across the lifespan and in diverse populations. *The FASEB Journal*. 2023;37(9):e23130. doi:10.1096/fj.202300907

[17] Steinbuch SC, Lüß AM, Eltrop S, Götte M, Kiesel L. Endometriosis-Associated Ovarian Cancer: From Molecular Pathologies to Clinical Relevance. *IJMS*. 2024;25(8):4306. doi:10.3390/ijms25084306

[18] Wu Y, Yuan W, Ding H, Wu X. Serum exosomal miRNA from endometriosis patients correlates with disease severity. *Arch Gynecol Obstet*. 2022;305(1):117-127. doi:10.1007/s00404-021-06227-z

[19] Zubrzycka A, Migdalska-Sęk M, Jędrzejczyk S, Brzeziańska-Lasota E. The Expression of TGF-β1, SMAD3,

ILK and miRNA-21 in the Ectopic and Eutopic Endometrium of Women with Endometriosis. *IJMS*. 2023;24(3):2453. doi:10.3390/ijms24032453

[20] Sunarno S, Puspandari N, Fitriana F, Nikmah UA, Idrus HH, Panjaitan NSD. Extended spectrum beta lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* in Indonesia and South East Asian countries: GLASS Data 2018. *AIMSMICRO*. 2023;9(2):218-227. doi:10.3934/microbiol.2023013

[21] Ochoa Bernal MA, Fazleabas AT. The Known, the Unknown and the Future of the Pathophysiology of Endometriosis. *IJMS*. 2024;25(11):5815. doi:10.3390/ijms25115815

[22] Brinca AT, Peiró AM, Evangelio PM, et al. Follicular Fluid and Blood Monitorization of Infertility Biomarkers in Women with Endometriosis. *IJMS*. 2024;25(13):7177. doi:10.3390/ijms25137177

[23] Agrawal S, Tapmeier TT, Rahmioglu N, Kirtley S, Zondervan KT, Becker CM. The miRNA Mirage: How Close Are We to Finding a Non-Invasive Diagnostic Biomarker in Endometriosis? A Systematic Review. *IJMS*. 2018;19(2):599. doi:10.3390/ijms19020599

[24] Zhang L, Li H, Yuan M, Li D, Sun C, Wang G. Serum Exosomal MicroRNAs as Potential Circulating Biomarkers for Endometriosis. *Disease Markers*. 2020;2020:1-10. doi:10.1155/2020/2456340

[25] Perricos A, Proestling K, Husslein H, et al. Hsa-mir-135a Shows Potential as A Putative Diagnostic Biomarker in Saliva and Plasma for Endometriosis. *Biomolecules*. 2022;12(8):1144. doi:10.3390/biom12081144

[26] Nazri HM, Greaves E, Quenby S, Dragovic R, Tapmeier TT, Becker CM. The role of small extracellular vesicle-miRNAs in endometriosis. *Human Reproduction*. 2023;38(12):2296-2311. doi:10.1093/humrep/dead216

[27] Chico-Sordo L, Ruiz-Martínez T, Toribio M, et al. Identification of miR-30c-5p microRNA in Serum as a Candidate Biomarker to Diagnose Endometriosis. *IJMS*. 2024;25(3):1853. doi:10.3390/ijms25031853

[28] Kumari P, Sharma I, Saha SC, Srinivasan R, Bhardwaj P. Role of serum microRNAs as biomarkers for endometriosis, endometrioid carcinoma of ovary & endometrioid endometrial cancer. *Indian Journal of Medical Research*. 2022;156(3):516-523. doi:10.4103/ijmr.IJMR_288_20

[29] Collins KE, Wang X, Klymenko Y, et al. Transcriptomic analyses of ovarian clear-cell carcinoma with concurrent endometriosis. *Front Endocrinol*. 2023;14:1162786. doi:10.3389/fendo.2023.1162786

[30] Hosseini M, Hammami B, Kazemi M. Identification of potential diagnostic biomarkers and therapeutic targets for endometriosis based on bioinformatics and machine learning analysis. *J Assist Reprod Genet*. 2023;40(10):2439-2451. doi:10.1007/s10815-023-02903-y

[31] Marí-Alexandre J, Carcelén AP, Agababyan C, et al. Interplay Between MicroRNAs and Oxidative Stress in Ovarian Conditions with a Focus on Ovarian Cancer and Endometriosis. *IJMS*. 2019;20(21):5322. doi:10.3390/ijms20215322

[32] Wright KR, Mitchell B, Santanam N. Redox regulation of microRNAs in endometriosis-associated pain. *Redox Biology*. 2017;12:956-966. doi:10.1016/j.redox.2017.04.037

[33] Ronsini C, Fumiento P, Iavarone I, Greco PF, Cobellis L, De Franciscis P. Liquid Biopsy in Endometriosis: A Systematic Review. *IJMS*. 2023;24(7):6116. doi:10.3390/ijms24076116

[34] Vanhie A, O D, Peterse D, et al. Plasma miRNAs as biomarkers for endometriosis. *Human Reproduction*. 2019;34(9):1650-1660. doi:10.1093/humrep/dez116

[35] Li X, Zhang W, Fu J, et al. MicroRNA-451 is downregulated in the follicular fluid of women with endometriosis and influences mouse and human embryonic potential. *Reprod Biol Endocrinol*. 2019;17(1):96. doi:10.1186/s12958-019-0538-z

[36] Monnaka VU, Hernandes C, Heller D, Podgaec S. Overview of miRNAs for the non-invasive diagnosis of endometriosis: evidence, challenges and strategies. A systematic review. *Einstein (São Paulo)*. 2021;19:eRW5704. doi:10.31744/einstein_journal/2021RW5704

[37] Nothnick WB. MicroRNAs and Progesterone Receptor Signaling in Endometriosis Pathophysiology. *Cells*. 2022;11(7):1096. doi:10.3390/cells11071096

[38] Chico-Sordo L, García-Velasco JA. MicroRNAs as Biomarkers and Therapeutic Targets in Female Infertility. *IJMS*. 2024;25(23):12979. doi:10.3390/ijms252312979

[39] Marí-Alexandre J, Sánchez-Izquierdo D, Gilabert-Estellés J, Barceló-Molina M, Braza-Boïls A, Sandoval J. miRNAs Regulation and Its Role as Biomarkers in Endometriosis. *IJMS*. 2016;17(1):93. doi:10.3390/ijms17010093

[40] Bjorkman S, Taylor HS. MicroRNAs in endometriosis: biological function and emerging biomarker candidates†. Critchley HO, ed. *Biology of Reproduction*. 2019;101(6):1167-1178. doi:10.1093/biolre/ioz014

[41] Hon JX, Wahab NA, Karim AKA, Mokhtar NM, Mokhtar MH. MicroRNAs in Endometriosis: Insights into Inflammation and Progesterone Resistance. *IJMS*. 2023;24(19):15001. doi:10.3390/ijms241915001

[42] Bendifallah S, Dabi Y, Suisse S, et al. MicroRNome analysis generates a blood-based signature for endometriosis. *Sci Rep*. 2022;12(1):4051. doi:10.1038/s41598-022-07771-7

[43] Szubert M, Nowak-Glück A, Domańska-Senderowska D, et al. miRNA Expression Profiles in Ovarian Endometriosis and Two Types of Ovarian Cancer—Endometriosis-Associated Ovarian Cancer and High-Grade Ovarian Cancer. *IJMS*. 2023;24(24):17470. doi:10.3390/ijms242417470