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Review Article

Research progress on the interaction between intestinal flora and microRNA in pelvic inflammatory diseases

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ABSTRACT

Pelvic inflammatory disease (PID) is a common infectious disease of the female upper reproductive tract, and its pathological basis is immune inflammatory response. The imbalance of gut microflora (GM) may lead to the development of inflammatory process. A large number of studies have shown that fecal microbiota transplantation, probiotics, bacteria, prebiotics, and dietary intervention may play a potential role in remodeling GM and treating diseases. MicroRNAs (miRNAs) are involved in cell development, proliferation, apoptosis and other physiological processes. In addition, they play an important role in the inflammatory process, participating in the regulation of proinflammatory and anti-inflammatory pathways. Differences in miRNA profiles may be PID diagnostic tools and serve as prognostic markers of the disease. The relationship between miRNA and GM has not been fully elucidated. Recent studies have shown the role of miRNA in the regulation and induction of GM dysbiosis. In turn, microbiota can regulate the expression of miRNA and improve the immune status of the body. Therefore, this review aims to describe the interaction between GM and miRNA in PID, and to find potential precise targeted therapy for PID.

1. Introduction

Pelvic inflammatory disease (PID) is a common infectious disease of the female upper reproductive tract, traditionally classified into acute and chronic pelvic inflammatory disease; nowadays, it is divided into pelvic inflammatory disease and sequelae of pelvic inflammatory disease. Inflammation can be localized to one area or involve multiple areas, mainly including endometritis, salpingitis, tubo-ovarian inflammation, tubo-ovarian abscess or cyst, and pelvic peritonitis, among others [1]. Among these, salpingitis and tubo-ovarian inflammation are the most common in clinical diagnosis and treatment. If pelvic inflammation does not receive timely and effective treatment, the progression of the disease may lead to a series of sequelae, which can clinically manifest as pelvic adhesions, fallopian tube obstruction, and subsequently lead to infertility, ectopic pregnancy, and chronic pelvic pain (CPP) [2]. It is one of the common and frequently-occurring diseases in women, and in recent years, there has been a trend towards earlier onset, severely impacting women's reproductive health and quality of life, posing a threat to both physiological and psychological well-being [3].

It is now known that pathogen infections can cause disease, and their pathogenesis is related to immune factors such as relevant cytokines, free radicals, sex hormone levels, and apoptosis; the immune inflammatory response is the pathological basis [4]. The gut microflora (GM) is closely related to immune responses and plays an important role in maintaining health and influencing disease progression [5], affecting diseases both inside and outside the gastrointestinal tract through inflammation and metabolic changes [6,7]. Research reports indicate that intestinal microbial communities exist within the cervical canal of patients with pelvic inflammatory disease (PID), this microbiome exhibits natural resistance to multiple antibiotics and affects the normal gut microbiome in the vagina [8]. Treatments targeting GM structure and metabolites, such as dietary interventions, fecal microbiota transplantation, and polysaccharides from Chaga mushroom, are under investigation [9,10]. MicroRNA (miRNA) has emerged as a potential biomarker for disease progression in recent years. Studies have shown that miRNA is involved in the pathogenesis of PID and has been used as a diagnostic biomarker and therapeutic target. Besides its use as a biomarker for disease activity and treatment response, it may also serve as a prognostic marker for disease severity and complications. Some

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studies suggest that the expression profile of specific miRNAs associated with *Chlamydia* pathogenic variations in the early stages of the disease may indicate an increased risk of developing pelvic inflammatory disease [11]. Both GM and miRNA have been research hotspots in recent years, and understanding their roles and relationships in PID could lead to the development of more effective and accurate diagnostic tools and targeted therapies for PID. Therefore, this review aims to clarify the current research status regarding the interactions between GM and miRNA in PID.

2. Treatment options and potential drugs for pelvic inflammatory disease

The CDC 2015 Guideline for the Diagnosis and Treatment of Pelvic Inflammatory Disease [12] states that microbial infection is the main causative factor of PID, and antibiotics should follow the principles of empiric, broad-spectrum, timely, and individualized. Because *Chlamydia trachomatis* and *Neisseria gonorrhoeae* are important pathogens, the antibiotics selected for the treatment of pelvic inflammatory disease must be effective against both *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections. A broad-spectrum antibiotic must be chosen based on experience. In 2021, the Centers for Disease Control and Prevention (CDC) in the United States released the 2021 Sexually Transmitted Diseases Treatment Guidelines [13], which follow the 2015 diagnostic standards and treatment standards and still prioritize broad-spectrum, empiric antibiotics. The drug regimen has been slightly modified based on changes in the bacterial spectrum, as shown in Table 1.

A 2020 Cochrane systematic review of 39 randomized controlled trials [14], including 6894 women, assessing the best treatment options for PID therapy by evaluating the safety and effectiveness of antibiotic use, found that for mild to moderate or severe PID, the cure rate of various treatment options ranged from 62 % to 99 %. With adverse outcome rates ranging from 0 % to 8 %, it is not certain whether one treatment is safer or more effective than any other treatment, and macrolides (azithromycin clinical cure rate of 74 %–88 %) have a high cure rate for mild to moderate PID compared to tetracycline (doxycycline clinical cure rate of 69 %).

Studies have shown that miRNAs can positively or negatively regulate intestinal immunity and intestinal barrier function, and the intestinal microbiota maintains intestinal homeostasis through the interaction between miRNAs and the host [15]. This mechanism has been validated in a variety of inflammatory diseases such as chronic kidney disease [16], Hashimoto's thyroiditis [17], and adipose tissue inflammation [18]. Studies have shown that [19] miRNAs such as let-7b and miR-21 in feces are associated with colonic inflammation, however, in the absence of gut microbiota, let-7b-induced inflammation is eliminated, suggesting that the GM population plays a key role in miRNA-induced inflammation and is able to directly alter the composition and function of the gut microbiota. This means that by modulating the gut microbiota, miRNA expression can be affected, which in turn can improve inflammation symptoms. When the gut is stimulated by external stimuli to form inflammation, host cells secrete outer vesicles containing high levels of miR-181b-5p and miR-200b-3p to fight inflammation. miR-181b-5p can promote the polarization of M2 macrophages in the intestine and secrete anti-inflammatory factors, while miR-200b-3p can regulate the composition of microbiota, increase the abundance of probiotics and improve the structure of microbiota [20]. This protective response of host cells may also help improve inflammatory symptoms. Targeting the regulation of intestinal flora and miRNA has many advantages in improving inflammatory diseases, including regulating host-microbiome communication, anti-inflammatory effects, improving intestinal microecology, affecting estrogen metabolism and protective responses of host cells, providing new strategies and methods for the treatment of pelvic inflammatory disease.

Table 1
PID Guide Summary of antimicrobial agents.

Administration route	Recommend-ation level	CDC 2015	CDC 2021
iv	recommend	(1) Cefotetan 2 g, once/12 h, or cefoxitin 2 g, once/6 h; Isoformycin 100 mg orally or intravenously once/ 12 h; The treatment continued until the clinical condition improved for more than 24 h, followed by doxycycline 100 mg orally twice a day. Chlorlinomycin 900 mg once/8 h, plus gentamicin 2 mg/kg intravenous or intramuscular infusion, 1.5 mg/kg intravenous or intramuscular infusion 1 time/8 h, or a single dose of 3–5 mg/kg gentamicin daily; Treatment continued until clinical condition improved for more than 24 h followed by doxycycline 100 mg orally twice/day to 14 days, or chlorlinomycin 450 mg orally 4 times/day.	(1) Ceftriaxone 1 g, once/12 h, plus doxycycline 100 mg orally or intravenously once/ 12 h, plus metronidazole 500 mg orally or intravenously once/ 12 h; (2) Cefotetan 2 g, once/12 h, plus doxycycline 100 mg, orally or intravenously once/ 12 h. Cefoxitin 2 g, once/6 h, plus doxycycline 100 mg, orally or intravenously once/ 12 h.
	replace	Amoxicillin/ Sulbactam 3 g, once/6 h; Forminomycin 100 mg orally or intravenously twice a day. The treatment continued until the clinical condition improved for more than 24 h, and doxycycline 100 mg orally was used twice a day.	(1) Ampicillin/ sulbactam 3 g, once/ 6 h, plus doxycycline 100 mg, orally or intravenously once/ 12 h; Clindamycin 900 mg once/8h; Add gentamicin 2 mg/kg orally or intravenously once/ 8 h, then maintain a single daily dose of 1.5 mg/kg gentamicin; Or add a single daily dose of 3–5 mg/kg gentamicin.
im/po	recommend	(1) Ceftriaxone 250 mg intramuscular injection; Foraminomycin 100 mg was taken orally twice a day for 14 days; With or without metronidazole 500 mg orally twice a day. (2) Single intramuscular injection of cefoxitin 2 g; Plus methylsulfonamide 1 g orally; Foraminomycin 100 mg was taken orally twice a day for 14 days; With or without metronidazole 500 mg orally twice a day.	(1) Ceftriaxone 500 mg, single intramuscular injection; Doxycycline 100 mg orally twice a day; Or metronidazole 500 mg orally twice a day. (2) Single intramuscular injection of cefoxitin 2 g; A single intramuscular injection of plensulfanilamide 1 g; Doxycycline 100 mg orally 3 times/ day; Add metronidazole 500 mg orally 3 times/

(*continued on next page*)

Table 1 (*continued*)

Administration route	Recommendation level	CDC 2015	CDC 2021
			day; (3) Other oral third-generation cefgadoxycycline 100 mg orally 3 times/day, plus metronidazole 500 mg orally 3 times/ day.
	replace	(3) The other third generation of cephalosporin, such as cefotaxime or ceftizoxime combined with doxycycline; (2) Amoxicillin combined with metronidazole; Single dose ceftriaxone intramuscular injection combined with oral azithromycin. / In the absence of a clear solution, consider: (1) Amoxicillin/ clavulanic acid [illegible] 100 mg, were taken orally twice a day for a total of 14 days, with or without metronidazole 500 mg orally twice a day.	There is no clear treatment plan, it is recommended that cephalosporin allergy patients can consider: (1) Levofloxacin or moxifloxacin combined with metronidazole; Single dose injection amoxicillin combined with oral metronidazole.
note		Patients with tubal and ovarian abscess should be given chlorlinomycin or metronidazole.	Clindamycin or metronidazole were added for tubal and ovarian abscess.

Note: If there is no special label, the duration of administration is 14 days.

3. Gut microbiota and pelvic inflammatory disease

3.1. Overview of gut microbiota

The human gut contains 1014 colonies, including over 1000 species of bacteria, made up of bacteria, archaea, eukaryotes, viruses, and parasites. The main types of bacteria growing in it are Firmicutes, Bacteroidetes, Actinobacteria, Fusobacteria, Proteobacteria, Verrucomicrobia, and Cyanobacteria, with Bacteroidetes and Firmicutes accounting for 90 %, originating from human gut archaea [21]. Human GM develops in parallel with the host and has always played an important role, which is affected by genetic factors, related to diet, drugs, lifestyle and other factors, as well as different geographical locations and climatic environments [22–24]. Changes in GM can lead to metabolic disorders, exercise fatigue, reduced exercise capacity, hinder immunity tolerance reconstruction, and various immune metabolic and gastrointestinal diseases [25]. GM participates in the decomposition and fermentation of carbohydrates and dietary fibers to produce short-chain fatty acids and other products, which plays an important role in immune regulation [26].

3.2. Dysbiosis may trigger PID

The vaginal mucosa is an important line of defense for local immunity in the female reproductive tract, which resists the invasion of pathogens by rapidly shedding epithelial cells and secreting cytotoxic factors [8]. GM interacts with host cells such as dendritic cells, macrophages, and epithelial cells to promote, calibrate, and terminate the immune response that influences systemic inflammation [27]. GM dysregulation can disrupt the normal immune function of the human body, leading to an increase in pro-inflammatory cytokines, leading to decreased immune surveillance and changes in immune cell function [28], abnormal expression of cytokines is consistently accompanied by chronic inflammation.

SPID is characterized by widespread local fibrosis, a long disease course, and difficulty in healing, primarily due to the activation of inflammatory cells and immune damage [29]. Th1/Th2 (T helper cell, Th) can maintain normal cellular and humoral immune functions in the body, belonging to T cell subgroups, capable of secreting cytokines [30]. In the process of chronic inflammation, cytokines exhibit dual effects; when the body is stimulated by inflammation, it releases not only pro-inflammatory cytokines but also secretes anti-inflammatory cytokines [31]. On one hand, it leads to and promotes inflammation; on the other hand, it can inhibit the development of inflammation. Some studies [32] have shown that compared to healthy women, SPID patients have higher serum Th1/Th2 levels, and the level of Th1/Th2 correlates with the severity of SPID. Persistent cytokine activation can cause tissue damage, forming a vicious cycle; the abnormal expression of cytokines is closely related to the occurrence and development of chronic inflammation. Pattern recognition receptors such as Toll-like receptors can respond to gut microbial ligands and transmit signals to the entire body through cellular or hormonal circulation, producing regulatory cytokines such as IL-10 to regulate inflammation development and induce regulatory T cells like CD4 Foxp3 to control abnormal immune responses [33]. At the same time, abnormal GM activates the NF-κB signaling pathway through the Toll-like receptor signaling pathway, leading to the release of pro-inflammatory factors and exacerbating epithelial cell damage. Over time, this dysregulated immune microbiome can progress to a chronic inflammatory state, resulting in recurrent inflammation and prolonged non-healing.

There is experimental evidence that the relative abundances of thick-walled bacteria, Bacteroidetes, and Proteobacteria in SPID rats have changed, with increases in the relative abundances of *Lactobacillus*, *Clostridium*, *Ruminococcus*, and *Treponema*, along with a decrease in bacterial diversity, significantly disrupting the gut microbiota balance [34]. Genomic sequencing data analysis has shown that the intestinal microbiota in PID patients undergoes significant changes. Compared to normal individuals, CPP patients have a reduced abundance of families such as *Selenomonadaceae*, *Prevotella*, *Bifidobacterium*, and *Lactobacillus ruminis*. Additionally, immune markers in CPP patients have been altered, with increased expression of granulocyte colony-stimulating factor, endothelial growth factor, and others [35]. These substances can regulate the body's inflammatory response, assess the degree of inflammatory damage and tissue adhesion [36,37], and the mutual influence of gut microbiota and immune substances may be one of the conditions for the recurrent and persistent inflammation in PID (Fig. 1).

3.3. Regulating gut microbiota to alleviate PID currently

There are numerous studies focused on regulating gut microbiota homeostasis through dietary interventions, or the use of prebiotics, probiotics, and fecal microbiota transfer (FMT), which show significant research potential for guiding life, treatment, and prognosis in PID.

3.3.1. Dietary interventions

Some studies have found that appropriately increasing high-fiber foods in daily diets can improve the abundance of gut microbiota (GM) and the production capacity of short-chain fatty acids (SCFAs), maintaining intestinal homeostasis and alleviating inflammation [38]. A healthy dietary pattern rich in plant-based foods is beneficial for improving GM abundance, exhibiting higher fermentation levels of five types of carbohydrates, and increasing SCFA production. Compared to a diet high in red meat, saturated fatty acids, processed carbohydrates, added sugars, and low fiber, it has a role in suppressing the expression of pro-inflammatory cytokines and transcription factor genes, enhancing the body's immune level [39,40]. A low-fermentation oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet is characterized by osmotic effects that can lead to bloating, causing pain and bloating in those with visceral hypersensitivity (as seen in patients with chronic pelvic pain). Women with PID who avoid a FODMAP diet report less pain, but it remains unclear whether this pain relief is specifically

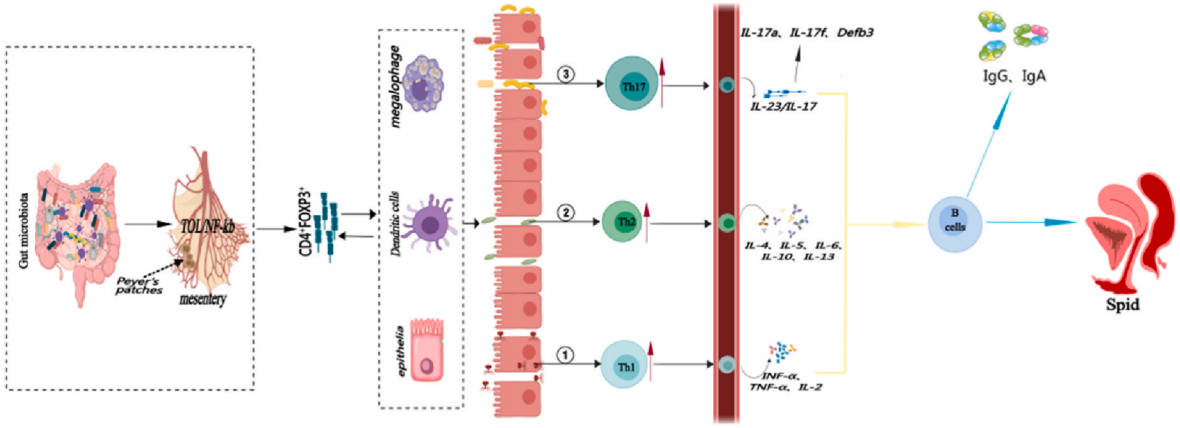

Fig. 1. The mechanism of intestinal flora involved in pelvic inflammatory diseases.
Note: This figure was created with MedPeer (medpeer.cn).

related to PID, and more research is needed [41,42].

3.3.2. Probiotics

Research indicates that probiotics can maintain vaginal homeostasis, protecting the host from pathogenic bacteria and triggering immune regulatory mechanisms that have anti-inflammatory effects [43]. *Lactobacillus*, a dominant microorganism in the vagina, when its abundance decreases, can lead to dysbiosis, causing single or mixed infections such as bacterial vaginosis, vulvovaginal candidiasis, aerobic vaginitis, human papillomavirus, human immunodeficiency virus, herpes simplex virus, gonorrhea, trichomoniasis, chlamydia, mycoplasma, and ureaplasma infections [44]. Studies show that 4.9 % of women with reproductive mycoplasma infections progress to PID, and 14.4 % with chlamydia infections [45]. Current PID treatments must consider the roles of mycoplasma, chlamydia, gonococcus, and related pathogens [46]. In recent years, *Lactobacillus* has been used as an alternative and adjunct to antibiotics, reducing the side effects such as antibiotic resistance associated with overuse of antibiotics [47,48]. Huang et al. found that acetate and lactate produced by *Lactobacillus* can improve the morphology of vaginal cells, ultimately leading to cell atrophy or rupture, inhibiting the formation of biofilms by vaginal bacteria, and restricting the growth and reproduction of vaginal bacteria [49,50]. Patients with bacterial vaginosis taking *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, etc., can significantly improve vaginal flora and increase the recovery rate from bacterial vaginosis while alleviating symptoms [51–53]. Probiotic *Lactobacillus rhamnosus* GR-1 can improve the ultrastructural damage of endometrial epithelial cells induced by *Escherichia coli*, subsequently reducing the percentage of apoptosis of endometrial epithelial cells and limiting inflammatory responses [54]. Tersigni et al. [55] found that oral administration of *Bifidobacterium longum* ES1 (GliadinES®) can inhibit intestinal permeability, lower serum LPS levels, and improve endometritis in women with recurrent miscarriage. Multiple studies have shown that lactic acid bacteria can significantly reduce chlamydia infections in animal models, and after reproductive chlamydia infection, administering a mixture of lactic acid bacteria in the vaginas of female BALB/c mice significantly reduces chlamydia discharge levels in the lower reproductive tract and intestines, decreases TNF-α, IFN-γ, and IL-1β in the vagina, weakens pathogenicity and inflammation in the upper reproductive tract, and after lactic acid bacteria administration, lower CD8/IFN-γ levels are secreted upon re-stimulation with chlamydial antigens, attenuating chlamydia-mediated Th1 immunity, thus providing valuable information for developing lactic acid bacteria as an adjunct therapy or vaccine for chlamydia infections [56].

3.3.3. Prebiotics

Prebiotics are indigestible carbohydrates that selectively stimulate bacterial growth. Oligofructose and galacto-oligosaccharides are commonly used to stimulate the growth of bifidobacteria and lactobacilli [57]. Weishi et al. [58] demonstrated through experiments that lactoferrin (a prebiotic formulation with good prebiotic activity) can bind and sequester lipopolysaccharides, thereby preventing the activation of pro-inflammatory mechanisms. Additionally, clinical trials have confirmed the effectiveness of prebiotics; a triple-blind randomized clinical trial conducted by Hakimi et al. [59] found that prebiotic vaginal gels as adjunctive therapy can improve the treatment outcomes of bacterial vaginosis.

3.3.4. FMT

FMT is believed to play an important role in treating female reproductive system diseases associated with microbial changes. Kutteh et al. [60] discovered that gut immunity can induce the secretion of specific antibodies in female reproductive tract secretions, which may occur through oral administration better inducing the immune response. Hu et al. [61] found through animal experiments that the gut microbiota exerts protective effects on *Staphylococcus aureus*-induced endometritis by regulating the levels of short-chain fatty acids and maintaining the phagocytic ability and reactivity of neutrophils (Fig. 2).

It remains unclear whether inflammation in PID causes GM dysbiosis or whether GM dysbiosis precedes disease occurrence; further research is needed to explore this better.

4. miRNA in pelvic inflammatory disease

miRNA is a type of single-stranded RNA composed of 22 RNA molecules, widely involved in biological functions, playing an important role in the cell lifecycle, and capable of regulating the immune system in multiple ways, closely related to the inflammatory response caused by pathogens [62–64]. miRNA has been shown to regulate molecules and signaling pathways during inflammation and disease progression in PID [65]. During the diagnosis and treatment of PID, miRNA plays an important role.

4.1. miRNA response to the activity of PID diseases

A study revealed that *Chlamydia* infection leads to increased expression of miR-142-3p, miR-520-3p, miR-147a, miR-147b, miR-449a, miR-449c, miR-519d, miR-6779, and miR-2467 in PID patients through miRNA expression profiling using small RNA sequencing and quantitative real-time PCR analysis [58]. With further research, more miRNAs have been discovered; salpingitis often causes ectopic

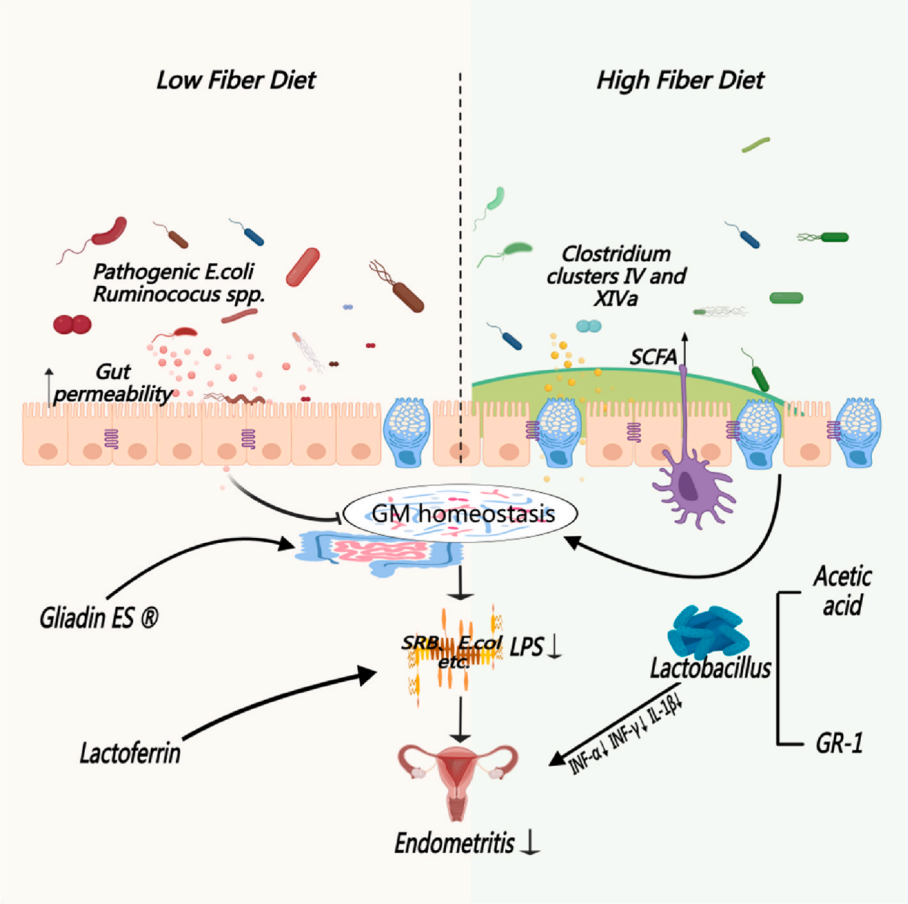

Fig. 2. Regulating Gut Microbiota to Alleviate PID Currently
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pregnancy. Zhang et al. [66] found that serum mir-1247 was significantly decreased in ectopic pregnancy patients, while mir-1269a was significantly increased, with a negative correlation between the expression levels of mir-1247 and mir-1269a, suggesting that their abnormal expression may be risk factors for salpingitis and ectopic pregnancy. Deng et al. [67] found that mir-196b showed higher disease activity correlation in ectopic pregnancy patients and was positively correlated with the expression of progesterone, estradiol, and HCG, showing promise as a potential indicator for clinical diagnosis of ectopic pregnancy. However, before using miRNAs as diagnostic tools, the specificity of miRNAs in PID diseases must be considered, as some miRNAs are known to be associated with other diseases; for instance, mir-196b is significantly elevated not only in ectopic pregnancy and salpingitis patients but also upregulated in ovarian cancer, oral cancer, and colon cancer [68–70].

4.2. *miRNA may become future therapeutic targets for PID*

Studies have found that some miRNAs act on the same inflammatory pathways as certain approved drugs for treating PID. miR-488 and miR-30a inhibit LPS and *Staphylococcus aureus*-induced endometritis by controlling the production of reactive oxygen species (ROS) and activating pathways such as AKT/NF-κB, MyD88/Nox2/ROS, closely related to immune responses and capable of suppressing pro-inflammatory factor production [71,72]. Research found that miR-233 was upregulated in endometritis and LPS-stimulated endometrial epithelial cells, but when nf-κb was activated, miR-233 synthesis markedly decreased. miR-233 is not only a regulator of nf-κb but also limits NLRP3 activation, thus avoiding the occurrence of inflammatory responses. This is similar to the mechanism of β-lactam antibiotics alone or in combination with doxycycline, which inhibit MAPK/NF-κB/NLRP3 protein expression in macrophages by blocking the binding of NorA to Atl, thereby reducing the expression of cytokines such as IL-1β and TNF-α [73,74], which have been included in PID treatment regimens by evidence-based medicine [75]. miR-643 can inhibit the formation of a complex between IL-17A receptor-associated kinase and MyD88, interfere with the docking of TRAF6 and MyD88, weaken the expression of downstream TAK1, significantly inhibit IL-17A-induced HBD-2 promoter activity, suppress NF-κB pathway activation, and limit the activation of TLR4 and NF-κB signaling pathways, potentially alleviating inflammatory damage and serving as a new method for treating inflammatory diseases [76–78]. Overexpression of Let-7c weakens the release of pro-inflammatory cytokines in endometritis by blocking the activation of the NF-κB signaling pathway, aiding in tissue healing through an anti-inflammatory role. Research has found that the role of miRNAs in the inflammatory cascade brings innovative perspectives to PID treatment, such as miRNA mimics and antagonists. Although there are drawbacks to both using miRNA antagonists and mimetics, future research needs to gain a deeper understanding of the miRNA profile in PID to clarify their roles in the triggering and sustaining process of PID inflammation. Major miRNAs in PID and their changes and target effects was shown in Table 2.

5. Interaction between miRNA and GM in pelvic inflammatory disease

In recent years, the interaction between miRNA and host as well as inflammation-related diseases has gained increasing attention and become a focus of current research. These studies indicate that miRNA

Table 2
Major miRNAs in PID and their changes and target effects.

miRNA	PID	Target
miR-142-3p	↑	/
miR-520-3p	↑	/
miR-147a	↑	/
miR-147b	↑	/
miR-449a	↑	/
miR-449c	↑	/
miR-519d	↑	/
miR-6779	↑	/
miR-2467	↑	/
mir-1247	Ectopic pregnancy due to salpingitis ↓	/
mir-1269a	Ectopic pregnancy due to salpingitis ↑	/
miR-196b	↓	/
miR-30a	Endometritis↑	Restrain MYD88
miR-233	Endometritis↑	Restrain NLRP3
miR-643	Endometritis↓	Restrain MyD88、nf-κb
Let-7c	Endometritis↓	Restrain nf-κb
miR-92b	Endometritis↓	PTEN
miR-148a	Endometritis↓	TLR4

participates in the regulation of PID and can induce ecological imbalance, while the microbiome can in turn regulate miRNA expression and inflammatory responses (Fig. 3).

5.1. The role of miRNA in regulating gut microbiota

miRNA is a key contributor to gut homeostasis, interacting with GM in a reciprocal manner and profoundly affecting host health. When imbalanced, it can lead to various diseases, including inflammatory diseases. Research has shown that bidirectional regulation occurs between host cells and GM through miRNA, which is involved in shaping the gut microbiome after being secreted from intestinal epithelial cells and accumulates in feces [79]. On the other hand, the expression of host miRNA can be influenced by microbiome-derived metabolites, potentially affecting host physiology [80]. Gut miRNA and microbiota co-evolve, and small RNAs present in bacteria have similar functions to miRNA [15]. Specific miRNAs can enter bacteria, co-localize with bacterial nucleic acids, regulate GM gene transcription, and subsequently affect the growth of microbiota. For example, miR-1226-5p promotes the growth of *Escherichia coli* [76], while the upregulation of miR-30c, miR-93, miR-106b, and miR-130a reduces the clearance of adhesive and invasive *E. coli* [81]. miR-155 can induce macrophage death and promote pro-inflammatory factor production by targeting SHIP-1, thereby facilitating Salmonella infection [82]. Additionally, miR-7267-3p can regulate the expression of indole-3-aldehyde in *Lactobacillus rhamnosus*, inducing the production of protective interleukin-22 (IL-22), with both factors mutually regulating to increase the abundance of this bacterium, making it a potential next-generation probiotic after *Lactobacillus* and *Bifidobacterium* [83]. Abnormally expressed miRNA found in PID patients can affect the proliferative activity of specific bacterial populations, such as *Lactobacillus reuteri*, Firmicutes, and *Clostridium* [84,85]. miR-142-3p has a predicted binding site on the 3′ UTR of IRAK1 mRNA; IRAK1 is a key component in the IL-1 receptor and TLR signaling pathways. Silencing or inhibiting miR-142-3p expression can limit the translation of IRAK1 protein, leading to its increased expression and thus the progression of inflammation [86], while its overexpression can significantly reduce the phagocytic capacity of the organism against *E. coli* and *Staphylococcus aureus* [87]. Therefore, miRNA regulation can affect the distribution of GM, thereby restoring the intestinal microecological environment.

In recent years, extracellular vesicles (EVs) have played an important role in the communication between mammals and gut microbiota. Starting in 2007, it was discovered that EVs can carry messenger RNA and small non-coding RNAs to transmit information between cells [88]. Alvarez et al. [89] demonstrated that EVs secreted by the probiotic *E. coli* Nissle 1917 (EcN) and the commensal bacterium ECOR63 can upregulate the expression of tight junction protein 1 (ZO-1) and claudin 14, as well as downregulate claudin-2 in human intestinal epithelial cells, enhancing the integrity of the intestinal epithelial barrier. Another study by the same authors showed that EVs isolated from EcN and ECOR63 protect cultured intestinal epithelial cells from infection by enteropathogenic *E. coli* (EPEC) [90]. Ashrafian et al. [91] found that mucin-derived EVs enhanced the expression of tight junction genes and downregulated toll-like receptor (TLR) gene expression, suggesting that mucin-derived EVs have potential roles in intestinal barrier permeability and strengthening while reducing inflammation. It can be inferred that exosomal miRNA can load bacteria and regulate bacterial gene expression to influence GM abundance by modulating intestinal barrier permeability [92]. Additionally, exogenous miRNA consumed through diet can enhance stability through processing methods, crossing biological barriers to regulate immune responses and mediate crosstalk between the host immune system and GM [93].

miRNA can also regulate GM through antimicrobial peptides (AMPs), such as intestinal α-defensins. Among them, α-defensin 5 (HD5) and α-defensin 6 (HD6) are the two main AMPs [94] secreted by intestinal Paneth cells [95], playing an important role in protecting the host from various commensal bacteria and pathogens. Algera et al. [96] found that Paneth cell function was enhanced in mir-802 knockout mice, with

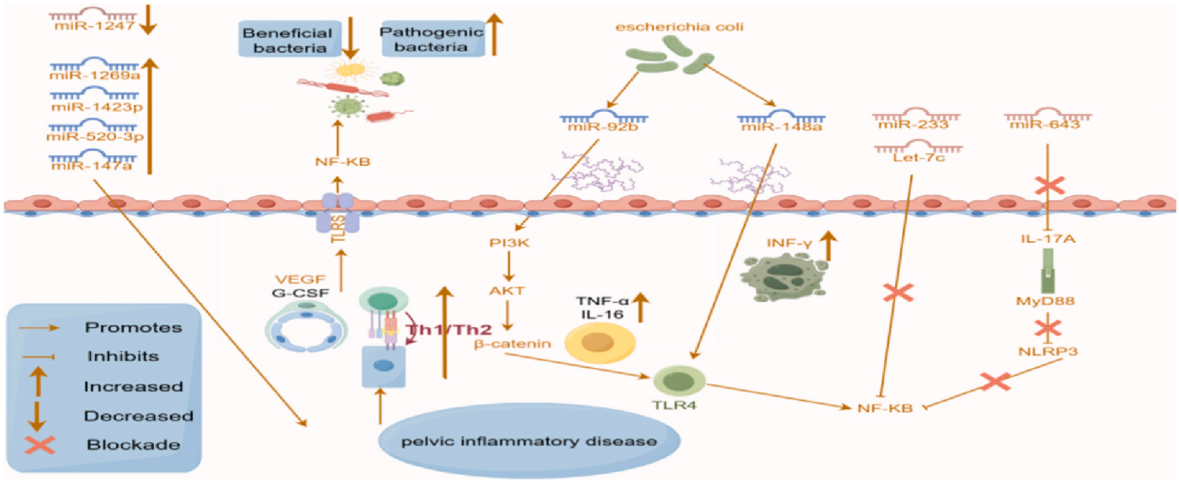

Fig. 3. Gut microbiota and differentially expressed miRN involved in the pathogenesis of pelvic inflammatory disease.
Note: This figure was created by Figdraw.

mir-802 negatively regulating HD5 expression. Miles et al. [97] discovered that miR-124 and miR-924 negatively regulate the expression of HD5 mRNA and protein. These data indicate that miRNA may indirectly affect GM abundance by participating in gut innate immune regulation and influencing gut homeostasis. Thus far, the regulatory mechanisms of miRNA on GM are not fully clarified, and their relationship still requires further study.

5.2. The role of gut microbiota in miRNA expression

The effects of pathogens such as Listeria, Salmonella, and Helicobacter pylori on host miRNA expression have been extensively studied [98]. Guillaume et al. [99] colonized germ-free mice with a non-pathogenic mouse microbiota and analyzed miRNA expression using miRNA arrays, showing different miRNA expression in colonized mice, proving that GM can regulate host miRNA expression, thereby adjusting gene expression. Fecal microbiota transplantation (FMT) can increase GM abundance, thereby restoring intestinal permeability, which can improve local inflammation and miRNA. Clinical trials have found that after autologous or allogenic FMT treatment, the expression of miR-23a, miR-26b, miR-130a, miR-150, miR-20a, and miR-28 changes, indicating that GM abundance changes induced by FMT modify the miRNA profile [100]. Studies have found that infection with adhesive invasive *E. coli* can activate nf-κb and upregulate the levels of miR-30c and miR-130a in T cells and intestinal cells of mice [101]. Gut microbiota may also regulate host miRNA and exert effects in areas outside the gut. Vikram et al. [102] found that GM can remotely regulate the expression of miR-204, which improves vascular endothelial injury by targeting Sirtuin1 lysine deacetylase (Sirt1). It has been discovered [103] that during the peak of diseases, fecal transfers from experimental autoimmune encephalomyelitis (EAE) models of multiple sclerosis (MS) improve the recipient's condition in a miRNA-dependent manner. miR-30d is enriched in the feces of mice at peak EAE and untreated MS patients, and oral synthetic miR-30d can improve EAE by amplifying regulatory T cells (Tregs). miR-30d regulates the expression of lactase in Akkermansia muciniphila, thereby increasing the abundance of Akkermansia in the gut; the expanded Akkermansia in turn increases Tregs to suppress EAE symptoms. Probiotics also influence GM and can improve miRNA expression; studies have found [104] that the probiotic *E. coli* Nissle 1917 can intervene in the expression levels of miRNAs involved in inflammatory responses, such as miR-143, miR-150, miR-155, miR-223, and miR-375, counteracting the ecological imbalance associated with the inflammatory process. Probiotic Lacticaseibacillus rhamnosus can regulate immune system responses by increasing miR-155 levels and decreasing miR-146a, while affecting gut integrity by suppressing miR-122a, thereby slowing the progression of alcoholic liver disease [105,106]. GM may affect the expression of host miRNA, thereby influencing the body's immune response, possibly through metabolites such as SCFAs [107].

5.3. Interaction of miRNA and GM in PID

In recent years, there has been increasing research on the role of miRNA in the host and GM, with extensive studies on the treatment of chronic inflammatory diseases. miR-92b is a key regulatory factor in various inflammatory diseases and is a potential therapeutic target for endometritis and other inflammatory diseases. It is activated by monocytes when stimulated by specific pathogen-associated molecular marker lipopolysaccharide (LPS) from *Escherichia coli*, inhibiting the TLR4 signaling pathway via the PI3K/AKT/β-catenin axis and suppressing the production of pro-inflammatory factors TNF-α and IL-6. This indicates that miRNA plays an anti-inflammatory role mediated by PI3K/AKT as a regulatory factor [108]. On one hand, pathogenic bacteria can lead to host dysfunction, amplified inflammatory response, and aggravated PID symptoms by regulating the expression of host miRNA. miR-148a is a specific miRNA altered in *E. coli* infections. Jiang et al. [109] discovered through *in vivo* and *in vitro* experiments using an LPS-induced endometritis model that miR-148a can inhibit the activation of TLR4/nf-κb p65 and suppress the levels of IL-1β and TNF-α, playing an important role in the pathogenesis of endometritis. miR-148a-3p can also promote the inflammatory response of LPS/IFN-γ-stimulated M1 macrophages by regulating the PTEN/AKT/NF-κB signaling pathway, participating in monocyte differentiation and macrophage activation [110]. Thus, it can be inferred that miRNA plays an important role in the communication between GM and the host, and miRNA can be used as a therapeutic tool targeting the host or GM, thereby benefiting PID patients. However, further research is still needed to better apply them in practice.

Multiple studies have emphasized the important role of GM dysbiosis in the development of PID. Strategies to maintain GM balance are also very useful for the treatment and prevention of this disease. Additionally, miRNA is also a focus of research, further promoting the understanding of the disease and bringing new perspectives for the diagnosis and treatment of PID patients. However, more research is needed in the future to better understand the complex interactions between GM and miRNA in the pathogenesis of PID, clarify their roles in diagnosis and treatment, and solidify their application in clinical practice.

CRediT authorship contribution statement

Shuhan Dong: Writing – original draft. **Yunpeng Du:** Conceptualization. **Haiyang Wang:** Data curation. **Wenhan Yuan:** Conceptualization. **Wenxia Ai:** Project administration. **Li Liu:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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