The Potential Mechanisms and Therapeutic Approaches of Gut Microbiota and the Occurrence of Endometritis

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Abstract. Endometritis, a prevalent gynecological condition, remains incompletely understood in terms of its pathogenesis, with inflammatory responses being a key factor in its development. In recent years, a growing body of research has highlighted that gut microbiota imbalances may significantly impact the onset and progression of endometritis. Currently, antibiotics are the mainstay of clinical treatment for endometritis, but the emergence of drug resistance problems has brought many challenges to the treatment. Due to the incomplete clarification of the pathogenesis of endometritis, there is a lack of more targeted treatment strategies and methods. This study thoroughly examined the potential mechanisms linking gut microbiota to endometritis occurrence, and explored the corresponding treatment methods, initially screening out four possible action pathways and two potentially feasible treatment options, providing a theoretical basis and reference direction for subsequent related studies. However, these conclusions still need to be further verified through experimental studies. Future research should focus on conducting experimental work to deeply explore its mechanism and optimize the treatment strategy.

Keywords: Endometritis, Gut microbiota, Mechanisms and Treatment.

1. Introduction

Endometritis is a frequently encountered inflammatory condition in gynecology, which has a potential association with unexplained infertility and recurrent miscarriage [1]. Clinical data indicate that the prevalence of chronic endometritis in the broader population remains uncertain, with estimates varying widely from 0.8% to 27.1%. Among infertile patients, the incidence of chronic endometritis is reported to be between 2.8% and 30%. Notably, among individuals experiencing unexplained recurrent pregnancy loss or persistent implantation failure, this prevalence can soar to as high as 67.5%.

In recent years, an increasing number of studies have indicated that gut microbiota imbalance plays an important role in the occurrence and development of endometritis. The composition of gut microbiota in patients with endometritis is significantly different from that in healthy women, manifested as reduced flora diversity, decreased beneficial bacteria, and increased pathogenic bacteria. Gut microbiota imbalance can lead to impaired intestinal barrier and immune function, promoting the translocation of bacteria and their metabolites, and subsequently triggering the immune inflammatory response of the endometrium. Conversely, the occurrence of endometritis can also cause changes in the structure and metabolites of gut microbiota [2].

With the continuous development of biological technologies, the detection methods of this disease are also constantly improving. Technologies such as gene sequencing, metabolomics analysis, and big data analysis can be used to discover and understand the internal relationship between gut microbiota and endometritis from a more microscopic perspective. Currently, antibiotics are commonly used for clinical treatment, but their abuse can cause drug resistance and reduce treatment efficiency. Therefore, it is urgent to explore new treatment strategies. Animal experiments have shown that fecal microbiota transplantation (FMT) can alleviate endometritis, indicating that gut microbiota not only plays a role in the occurrence of endometritis but may also become a new therapeutic target [3]. In addition, some studies have also shown that the regulation of probiotics and prebiotics, as well as dietary intervention and metabolic regulation, can effectively alleviate the occurrence of endometritis. Although certain progress has been made in the research on the

relationship between gut microbiota and endometritis, many problems still await solutions. This article intends to deeply explore the potential mechanism between gut microbiota and their metabolites and endometritis, and based on the regulation of gut microbiota, provide a new idea for the treatment of endometritis.

2. Analysis of the Correlation between Gut Microbiota Imbalance and Endometritis

The gut microbiota is composed of a complex flora. The quantity of microorganisms residing in the human intestinal tract amounts to 1014 magnitude. Due to its great influence on human tissues and metabolism, it is also called the 'second human genome' [4]. The gut microbiota forms a symbiotic relationship with people's body, and its structure and function are shaped by various factors, including diet, environment, and genetic background. Dysbiosis of gut microbiota can impair the people's innate immune system and exacerbate inflammatory and infectious diseases [5]. Recent research has highlighted that individuals with endometritis often exhibit reduced gut microbiota diversity alongside an increase in pathogenic bacterial populations. This alteration in gut microbiota, characterized by decreased α diversity (reflecting overall species richness) and β diversity (indicating changes in microbial community composition), can disrupt hormonal balance or lead to abnormal hormone circulation, such as for insulin, estrogen, and steroids. Hormonal disturbances may be significantly implicated in the development of endometritis [6]. Additional research has indicated that the microbial composition in endometrial tissue cultures from individuals with endometritis does not align with that observed in cultures derived from vaginal or endocervical swabs. Under normal circumstances, the uterus should be relatively sterile. This indicates that the uterus of patients with endometritis may have been invaded by non-vaginal flora, possibly from other organs rich in flora in the body [7]. The aforementioned research has uncovered a certain correlation between the gut microbiota and endometritis. Nevertheless, the underlying mechanisms remain to be explored in greater depth.

3. The Potential Mechanism of Gut Microbiota Imbalance Inducing Endometriti

3.1. The Mechanism of Immune Regulation Imbalance

The gut microbiota indirectly affects the endometritis response by regulating the host immune system. Imbalances in the gut microbiota can trigger the release of pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), into the bloodstream. This event activates Toll-like receptor 4 (TLR4), which subsequently activates the nuclear factor-κB (NF-κB) signaling pathway. This cascade results in the overproduction of pro-inflammatory cytokines in the uterine environment, such as IL-6 and TNF-α, ultimately contributing to the development of endometritis [8]. In addition, the decrease in short-chain fatty acids (SCFAs), such as butyric acid, a metabolite of the gut microbiota, inhibits the differentiation of regulatory T cells (Treg), disrupts immune tolerance, and aggravates the inflammatory damage of the endometrium [9]. Animal experiments have shown that supplementing with butyric acid can significantly reduce the levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in the endometrium of mice and improve the inflammatory pathology of the endometrium [10]. This imbalance in immune regulation promotes the secretion of pro-inflammatory factors, forming an inflammatory environment in the endometrium and facilitating the occurrence and development of endometritis.

3.2. Indirect Effects Mediated by Metabolites

The metabolites of the gut microbiota may affect endometrial function through blood circulation. For instance, gut microbiota imbalance can result in the buildup of secondary bile acids (e.g.,

deoxycholic acid). These acids can activate the farnesoid X receptor (FXR) in endometrial cells, which may trigger mitochondrial dysfunction and the production of mitochondrial reactive oxygen species (ROS), thereby driving inflammatory responses [11]. The gut microbiota can produce indole metabolites, which are produced by tryptophan, including indole-3-propionic acid, and these metabolites can inhibit the NF-κB pathway by activating the aryl hydrocarbon receptor (AhR), reducing endometrial inflammation [12]. Clinical studies have found that the levels of indole metabolites in the serum of patients with endometritis are significantly lower than those in healthy people [13]. Another study found that supplementing specific probiotics (such as L. reuteri I5007) can alleviate the reduction in indole metabolite levels, thereby alleviating inflammation [14]. These results imply that indole metabolites might influence the development of endometritis via modulation of inflammatory reactions. Furthermore, SCFAs can impact the endometrial immune milieu through systemic circulation and contribute to the pathogenesis of endometritis. They possess anti-inflammatory and immunomodulatory properties, and a decline in their levels may contribute to a more severe inflammatory response in the endometrium. The above studies all indicate that the metabolites of the gut microbiota also play an important role in the occurrence of endometritis.

3.3. Intestinal Barrier Disruption and Microbiota Translocation

Disruptions in the composition of the gut microbiota can profoundly affect the integrity and functionality of the intestinal barrier, thereby triggering a series of health problems. Under normal circumstances, the intestinal barrier comprises intestinal mucosal epithelial cells, intercellular tight junctions, chemical defenses, and immune components. These components act in concert to prevent the translocation of intestinal bacteria and their metabolites into the systemic circulation. Imbalances in the gut microbiota can compromise the integrity of the intestinal barrier, allowing intestinal bacteria and their metabolites to translocate to other organs like the liver, lung, and brain via endogenous routes, thereby contributing to the development of associated diseases [15]. Several investigations have revealed that in individuals with endometriosis, imbalances in the gut microbiota can lead to compromised intestinal barrier function and heightened permeability. This disruption facilitates the movement of bacteria and their byproducts, such as lipopolysaccharide, across the intestinal wall [16]. This translocation can trigger chronic low-grade inflammation and activate the immune-inflammatory response of the endometrium, leading to the occurrence of endometritis. Therefore, gut microbiota dysbiosis not only affects intestinal health but may also indirectly affect the health of other organs by influencing intestinal barrier function.

3.4. Estrogen Metabolism Interference

Abnormal secretion of estrogen may lead to endometritis. Excessive estrogen may cause excessive proliferation of the endometrium, making it more fragile and vulnerable to pathogen invasion. Conversely, too low estrogen secretion can lead to thinning and atrophy of the endometrium, which is also prone to inflammation. In addition, abnormal estrogen can also affect the immune system, resulting in a decline in the body's immunity and thus inflammation. The gut microbiota is involved in the generation and circulation of estrogen, converting conjugated estrogen into the active form through β-glucuronidase (GUS) [17]. Dysbiosis can lead to abnormal estrogen metabolism, forming a high-estrogen microenvironment, promoting the expression of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in the endometrium, and intensifying the inflammatory response [18]. The interference in estrogen metabolism works in concert with other mechanisms to facilitate the occurrence and progression of endometritis. Therefore, ensuring a balanced gut microbiota and normal estrogen levels is essential for preventing endometritis.

4. Gut Microbiota Regulation in the Management of Endometritis

4.1. Application of Probiotics and Prebiotics

Probiotics, such as Lactobacillus and Bifidobacterium species, improve uterine inflammation through various mechanisms. Studies have shown that bacteriocins secreted by Lactobacillus exhibit anti-inflammatory and antibacterial potential in diseases such as inflammatory bowel disease (IBD), and they exert inhibitory effects on the pathogenic bacteria of endometritis through similar mechanisms [19, 20]. Additionally, Lactobacillus and Bifidobacterium upregulate tight junction proteins (TJ proteins), stimulate TLR2 receptor, increase the protein expression of occludin and zonula occludens-1 (ZO-1), and reposition these proteins to alleviate barrier disruption, thereby reducing endotoxin translocation [21]. Regarding immune modulation, Bifidobacterium has been shown to markedly enhance the secretion of IL-10 in peripheral blood mononuclear cells from patients with ulcerative colitis, while the production of the pro-inflammatory cytokine IL-8 is suppressed. This anti-inflammatory pathway could offer novel therapeutic insights for chronic endometritis [22]. Besides probiotics, prebiotics also reduce the occurrence of systemic inflammation by alleviating intestinal barrier permeability, strengthening the barrier cell layer and mucus layer, and conditioning immune signaling pathways, thereby reducing endometritis. These research results indicate that probiotics and prebiotics have potential clinical application value in improving uterine inflammation.

4.2. Dietary Intervention and Metabolic Regulation

At present, the main dietary intervention measures are high-fiber diet and Mediterranean diet. The high-fiber diet can effectively regulate the natural microbiota to improve the therapeutic effect. Dietary fiber is fermented by the microbiota to generate SCFAs, which inhibit histone deacetylase (HDAC) and promote endometrial repair. The Mediterranean diet is rich in polyphenols and Omega-3 fatty acids, which can inhibit the proliferation of pathogenic bacteria and reduce oxidative stress damage to the endometrium [23]. In addition, some drug extracts can also have therapeutic effects, such as IOP and Liriodendrin, etc. Among them, mouse experiments have proved that IOP can directly act on uterine tissue, reduce the damage of inflammation to uterine tissue, reduce the release of pro-inflammatory factors, promote the repair of uterine tissue and restore the normal physiological state, and boost the abundance of advantageous bacteria within the gut microbiota [24]. For Liriodendrin, experiments have shown that it can alleviate the inflammatory response of uterine tissue by reducing the pathological changes of the uterus in CE rats, inhibiting the secretion of pro-inflammatory cytokines, promoting the secretion of anti-inflammatory cytokines, regulating the structure and abundance of the gut microbiota, changing serum metabolites and inhibiting the L-arginine/NO metabolic pathway [25]. The above intervention measures can effectively improve the symptoms of endometritis by regulating the composition of the gut microbiota, restoring the intestinal barrier function, and inhibiting the inflammatory response.

5. Conclusion

To sum up, there exists a complex and potential mechanism connection between the gut microbiota and the occurrence of endometritis. Gut microbiota dysbiosis can indirectly affect the microenvironment of the endometrium through pathways such as immune imbalance mechanisms, the indirect effects of metabolites, disruption of the intestinal barrier, and interference with estrogen metabolism, thereby increasing the risk of endometritis. In terms of treatment, regulating the gut microbiota provides a new idea for the treatment of endometritis. For example, the application of probiotics and prebiotics has shown a protective effect against endometrial infection in experiments, and dietary intervention and metabolic regulation can also reduce the occurrence and development of endometritis by changing the composition of the gut microbiota.

Although the gut microbiota holds broad prospects for the treatment strategy of endometritis, it still faces challenges. Firstly, although existing studies have shown an association between the gut microbiota and endometritis, the causal relationship has not been fully clarified. Current research is mostly observational, prone to the interference of confounding factors or reverse causality, and at present, most of it is indirectly proved by the fact that the gut microbiota causes systemic inflammation and thereby causes endometritis. It is hoped that more direct evidence can be found in the future. Secondly, the treatment effect may be affected due to different host genetic backgrounds and different pathogenesis. In addition, due to the importance of endometritis for livestock production, current studies are mostly based on animal models such as mice or cattle. For the increasingly serious issue of female reproductive health, more in-depth and targeted experiments are still needed for research and large-scale randomized controlled trials for clinical verification.

Future research can conduct more in-depth studies based on traditional treatment strategies. The condition of symptom relief in patients with endometritis through the treatment method of fecal microbiota transplantation (FMT) can be explored. Through multi-omics technologies, such as metagenomics, metabolomics, and single-cell transcriptomics, the microbiota-host interaction network can be revealed, targeted gut microbiota can be sought, the possible indicative or therapeutic impact of the gut microbiota on the pathogenesis of endometritis can be investigated, and the possibility of formulating individualized treatment strategies can be explored to find new strategies for the treatment of endometritis.

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