The gut microbiota: a puppet master in the pathogenesis of endometriosis?

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Endometriosis is a frequent estrogen-dependent disease among women of reproductive age, which is defined by the presence of endometriotic lesions (ie, endometrial glands and stroma) outside the uterus.[1] Affected patients experience a broad spectrum of pain symptoms in the pelvis and lower abdomen.[2-4] Moreover, endometriosis is often associated with subfertility and infertility.[5] Specific biomarkers for the noninvasive diagnosis of the disease are still missing.[6,7] Current pharmacologic and surgical approaches for the treatment of endometriotic lesions bear the risk of substantial side-effects and high recurrence rates.[8,9] Hence, there is an urgent need to unravel the complex pathophysiologic condition of endometriosis, which may set the basis for the development of novel diagnostic and therapeutic strategies.

According to the widely postulated implantation theory, endometriotic lesions originate from shed endometrial tissue, which enters the peritoneal cavity through the Fallopian tubes during retrograde menstruation and implants onto the peritoneal surface and pelvic organs.[10] This theory is supported by the fact that women with cervical stenosis or other congenital outflow obstructions have an increased risk of the development of endometriosis.[11,12] Moreover, experimental transplantation of endometrial tissue in animals results in the formation of endometriosis-like lesions, which exhibit the histomorphologic characteristics of lesions of endometriosis patients.[13-15] However, up to 90% of healthy women undergo retrograde menstruation, whereas only 10% of women experience endometriosis.[16] This indicates that the pathogenesis of the disease is much more complex. In fact, endometriosis is considered a typical multifactorial condition, which may be determined crucially by genetic, immunologic, and environmental factors.[17-19]

In recent years, an increasing number of studies have demonstrated that the gut microbiota (ie, all the living microorganisms colonizing the gastrointestinal tract) is of major importance for human health and disease.[20] It contains a dynamic and vast array of approximately 10^{14} microbes, including bacteria, bacteriophages, eukaryotic viruses, fungi, and protozoa. Hence, the number of these microbes is 10 times higher than the number of all cells in the human body. Based on sophisticated analyses of the gut microbiome (ie, the collective genomes of all microbes), they can be classified systematically into characteristic population profiles.[21] For this purpose, next-generation high-throughput DNA sequencing technologies are available.[22] 16S ribosomal-RNA gene sequencing is the standard method specifically to identify bacteria by the 16S ribosomal-RNA gene of their genome. In contrast, whole genome shotgun sequencing also can be used for the identification of other types of microorganisms and additionally yields information about their gene content.

Gut bacteria fulfill many central functions in food metabolism and intestinal physiologic condition. They supply essential nutrients, synthetize vitamins, and promote angiogenesis and epithelial repair.[23,24] On the other hand, experimental and clinical studies have shown that changes of the gut microbiota contribute to the development and progression of various diseases, such as inflammatory bowel diseases, arthritis, psoriasis, and even cancer.[20,25] This can be ascribed particularly to the potent immunoregulatory capacity of gut bacteria, which markedly affects systemic inflammatory cell responses.[25] Abnormal levels of inflammatory cytokines and immune cell activation in the peritoneal cavity are, in turn, major hallmarks in the pathogenesis of endometriosis.[26] Hence, we outline a hypothetical rationale for the involvement of the gut microbiota in the pathogenesis of endometriosis.

The gut microbiota and endometriosis

The initial establishment of endometriotic lesions is associated with the activation of the innate immune system.[27] Menstrual blood and endometrial tissue fragments that reach the peritoneal cavity by retrograde menstruation release damage-associated molecular pattern molecules, such as heat shock protein-70[28] or members of the S100 family of calcium-modulated proteins.[29,30] Iron and high amounts of reactive oxygen species that arise from menstrual debris further contribute to the activation of macrophages, neutrophils, and mast cells.[31,32] Consequently, these cells secrete into the peritoneal fluid proinflammatory cytokines and angiogenic growth factors that promote the formation of vascularized endometriotic lesions and their progressive spread within the peritoneal cavity.[33,34]

Because only 10% of the women with retrograde menstruation also experience endometriosis, it may be speculated that the quality and extent of this initial immune reaction determines the onset of the disease. The gut microbiota, in turn, has been shown to be a major regulator of such inflammatory processes outside the gastrointestinal tract. In fact, Karmarkar and Rock[35] recently reported that

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prestimulation of neutrophils by the intestinal flora through a myeloid differentiation primary response gene-dependent pathway is a major precondition for their recruitment to sites of zymosan- or crystal-induced inflammation within the peritoneal cavity. Lakritz et al[36] further demonstrated that host neutrophil-associated immune responses to intestinal tract microbes significantly impact mammary tumorigenesis. Therefore, they suggested gut bacteria as novel targets for extraintestinal cancer therapy.

Besides neutrophils, peritoneal macrophages may be influenced markedly by inflammatory changes in the gut and enhanced gut permeability. Emani et al[37] found that leakage of bacterial products from the gut results in increased numbers of macrophages in the peritoneal cavity. However, these macrophages exhibit a poor tumor necrosis factor-α cytokine response to lipopolysaccharide stimulation and high expression of interleukin (IL)-1 receptor-associated kinase-M, which indicates their adaptation to bacterial toll-like receptor-4 ligand. Hence, it is tempting to assume that such a priming of peritoneal macrophages by gut-derived microbial signals may also affect their capacity to phagocytose endometrial debris and to attack newly developing endometriotic lesions.

In addition, there is strong evidence from murine studies that the interaction between the gut microbiota and the host determines the overall level of activation of $CD4^+$ T-lymphocytes, which produce IL-17.[25,38] Of interest, Zhang et al[39] found that the concentration of IL-17 was significantly higher in the peritoneal fluid of patients with minimal-to-mild endometriosis when compared with those with moderate-to-severe endometriosis and those without the disease. IL-17 stimulates the production of proangiogenic cytokines, such as IL-8 or -1β. Therefore, they proposed which IL-17 may play a crucial role in the initiation of endometriosis by hypervascularization of the peritoneal surface which facilitates the survival, implantation, and proliferation of ectopic endometrial tissue.

Another hint for a possible link between the gut microbiota and endometriosis-associated inflammation is the antiinflammatory effect of omega-3 polyunsaturated fatty acids (PUFAs) diet in murine endometriosis models[40,41] and the observation that women with a high omega-3 PUFA intake exhibit a lower risk for endometriosis.[42,43] It may be speculated that these findings at least are caused partly by diet-induced changes of the gut microbiota. In fact, preliminary research indicates that modification of the gut flora by PUFAs and pre- and probiotic-supplemented diets is a promising approach for the prevention and therapy of various diseases, such as osteoporosis, diabetes mellitus, and obesity.[44,45]

Finally, the gut microbiota may influence not only inflammatory processes but also other essential mechanisms in the pathogenesis of endometriosis. It should be considered that the microbiota is involved in the regulation of estrogen cycling. Gut dysbiosis increases the levels of circulating estrogen,[46,47] which markedly may stimulate the growth and cyclic bleeding of endometriotic lesions. Moreover, an increasing number of studies indicates the involvement of bone marrow-derived stem and progenitor cells in the development of endometriosis.[48,49] These cells are mobilized and recruited via the blood stream into endometriotic lesions, where they are incorporated into the ectopic endometrial tissue and its newly developing microvasculature.[50,51] Of interest, first reports demonstrate now that the composition of the gut microbiota correlates with the number and proportions of stem and progenitor cells in the bone marrow, which suggests a modulating role of the microbiota in stem-cell homeostasis.[52]

Taken together, the present findings indicate that there may be a direct link between pathologic changes of the gut microbiota and the onset and progression of endometriosis. This hypothetical view is supported by a study of Bailey and Coe[53] that demonstrated that endometriosis in rhesus monkeys is associated with an altered profile of intestinal bacteria. They also found a higher prevalence of intestinal inflammation in monkeys with endometriosis when compared with healthy controls. Moreover, in a nationwide Danish cohort study, Jess et al[54] recently reported a 50% increase in the risk of inflammatory bowel disease in women with endometriosis. Hence, there is growing experimental and clinical evidence for a strong interaction between immunologic processes in the gut and endometriotic lesions. The underlying pathophysiologic mechanisms may be clarified in the future by means of sophisticated in vivo models that allow the analysis of endometriotic lesion development in animals with a defined composition of the gut microbiota. Next-generation sequencing of stool samples from patients with endometriosis in different stages of the disease may identify potential microbiota-based diagnostic and prognostic biomarker profiles. If this succeeds, it may be even possible to develop novel preventive and therapeutic strategies for endometriosis by the modulation of the intestinal flora with new antibiotics, probiotics, or microbiota transplants. ■

REFERENCES

1. Giudice LC. Clinical practice: endometriosis. N Engl J Med 2010;362:2389-98.
2. Falcone T, Lebovic DI. Clinical management of endometriosis. Obstet Gynecol 2011;118:691-705.
3. Bourdel N, Alves J, Pickering G, Ramilo I, Roman H, Canis M. Systematic review of endometriosis pain assessment: how to choose a scale? Hum Reprod Update 2015;21:136-52.
4. McKinnon BD, Bertschi D, Bersinger NA, Mueller MD. Inflammation and nerve fiber interaction in endometriotic pain. Trends Endocrinol Metab 2015;26:1-10.
5. Macer ML, Taylor HS. Endometriosis and infertility: a review of the pathogenesis and treatment of endometriosis-associated infertility. Obstet Gynecol Clin North Am 2012;39:535-49.
6. May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM. Peripheral biomarkers of endometriosis: a systematic review. Hum Reprod Update 2010;16:651-74.
7. Fassbender A, Burney RO, O DF, D'Hooghe T, Giudice L. Update on biomarkers for the detection of endometriosis. Biomed Res Int 2015;2015:130854.
8. Vercellini P, Somigliana E, Viganò P, Abbiati A, Daguati R, Crosignani PG. Endometriosis: current and future medical therapies. Best Pract Res Clin Obstet Gynaecol 2008;22:275-306.