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REVIEW ARTICLE

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The role of intestinal and vaginal dysbiosis in endometrial cancer: an integrative review

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Abstract

The increase in the incidence of endometrial neoplasms in the female population is associated with increased life expectancy and the lifestyle adopted in our daily lives. The way we eat influences the profile of our bacterial flora and the production of substances that can work as suppressor tumors or oncogenic. Dysbiosis leads to changes in the intestinal and vaginal bacterial barrier and promotes chronic inflammation and metabolic and hormonal changes that influence the carcinogenesis of gynecological tumors. Chemotherapy treatments can also change the composition of the intestinal microbiota and influence the efficacy and toxic effects, as well as the quality of life of these patients. The use of prebiotics, probiotics, or fecal transplantation can be useful both in prevention and in obtaining better results with chemotherapy treatment and better quality of life. The objective of this review is to provide further elucidation about the interaction mechanisms between the intestinal microbiota and the gynecological tract and assess future perspectives through the modification of the feeding pattern, use of prebiotics, probiotics, and fecal transplant both in the prevention and during the treatment of carrier patients of endometrial neoplasm.

Keywords: Endometrial cancer. Dysbiosis. Gut microbiome. Vaginal microbiome.

Introduction

Microbiome and Dysbiosis

The intestinal epithelial barrier is maintained by a healthy and diverse intestine microbiome composed mainly of 4 phyla: Bacteriodetes, Firmicutes, Actinobacteria, and Proteobacteria. A balanced bacterial composition is key to maintaining intestinal immunity and homeostasis. An intestine with a healthy microbiome consists of more than 90% of its composition of species of the phylum Bacteroidetes and Firmicutes **[1]**.

However, it is not only the combined abundance of Bacteroidetes and Firmicutes that has been associated with the homeostasis of the intestinal microbiome. A lower Firmicutes/Bacteroidetes (F/B) ratio also correlates with health **[1]**. For example, humans and lean mice have a significantly lower F/B ratio compared to their obese counterparts **[1]**.

The dominant bacterial phyla that colonize the distal tract of the small intestine and colon in healthy individuals produce short-chain fatty acids (SCFAs) by fermentation of non-digestible carbohydrates, proteins, and peptides **[2]**. Acetate, propionate, and butyrate account for 90-95% of colon SCFAs and provide a key contribution to maintaining a low pH, which allows the growth of homeostasis-promoting bacteria such as Lactobacilli and Bifidobacteria, and prevents colonization by opportunistic pathogenic bacteria, including *Cridlostium* and *Escherichia coli* **[3]**.

SCFAs also contribute to the preservation of a functional intestinal barrier and the maintenance of host homeostasis, stimulating the regeneration of epithelial cells and the production of mucus and antimicrobial peptides **[3]**. These protective effects also have systemic implications, inhibiting the translocation of bacteria (metabolic bacteremia) and toxins (metabolic endotoxemia) into the bloodstream, conditions related to a chronic inflammatory state, obesity, metabolic syndrome, and ultimately carcinogenesis **[4]**.

SCFAs also modulate the control of food intake, increasing the production of hunger suppressor hormones such as glucagon-like peptide-1, yy peptide, and leptin, increasing satiety and reducing excessive

food intake [5]. Intestinal dysbiosis is defined as a persistent imbalance of the microbial community of the intestine [5]. Intestinal dysbiosis is characterized by a decrease in the diversity and stability of the microbial community, with potential overgrowth of opportunistic pathogenic bacteria, and it is now well known that this condition is related to various inflammatory and metabolic diseases, including inflammatory bowel diseases, diabetes mellitus, obesity, metabolic syndrome, and cancer [6].

The intestinal microbiome was shown to be influenced by estrogen, however, the intestinal microbiome also significantly impacts estrogen levels [6,7]. This impact occurs through the secretion of β-glucuronidase, an enzyme that disconjugates estrogen, allowing it to bind to estrogen receptors and leading to its subsequent physiological effects [7]. These deconjugated and unbound "active" estrogens enter the bloodstream and subsequently act on the alpha estrogen receptor (ERα) and the estrogen beta receptor (ERβ) [8]. The estrobolome is defined as the repertoire of genes from the intestinal microbiota that are capable of metabolizing estrogens [8].

The Cascade Of Inflammation Triggered By Dysbiosis

The microbiome may be involved in the initiation of inflammation including immunopathological changes that promote the development of cancer. The activation of immune receptors induces the cellular response by activating the signaling pathways of the mitogen-activated protein kinase (MAPK), NF-κB, or PI3K / AKT. Activation of these signaling pathways induces the expression of pro-inflammatory cytokines (e.g., TNF-α, IL-6, and IL-8) and/or antimicrobial peptides, which are involved in the development of inflammatory response [8].

Toll-like receptors are standard recognition receptors that act primarily as microbe sensors and are crucial for the development of inflammatory and immunological reactions. The expression profile of TLRs is broad, from immune cells, including B-beads, macrophages, dendritic cells (DCs), and neutrophils, to non-immune cells such as fibroblasts, keratinocytes, and epithelial cells. There are 10 TLRs in humans and 13 TLRs in mice. TLRs occupying the plasma membrane include TLR1, TLR2, TLR4-6, and TLR11. TLRs that are found in endosomes include TLR3 and TLR7–9 and detect nucleic acids [9].

After involvement with their cognate ligands, TLRs promote a response against pathogens through signaling cascades that are triggered when the intracellular TLR domain (IRT) interacts with adapting molecules, including MyD88, TRIF, TIRAP, or TRAM. Depending on the adapters, there are signs promoted by TLRs: dependent on MyD88 and its independent (or TRIF-dependent) pathways [9]. MyD88, the first member of the IRR family to be reported, is an adapter of all TLRs except TLR3, positive regulation of the production of inflammatory cytokines stimulating NF-κB and mitogen-activated protein kinases. Bacterial ligands that are detected by TLRs are common among entire classes of bacteria and are therefore also synthesized by suitable microorganisms.

Thus, the involvement of TLRs is also the main means by which the host and microbiota communicate to maintain tolerance against diners. TLRs can discriminate between benign colonization and the presence of pathogens and have developed ways to be responsive against microbes. This tolerance towards diners is maintained to keep the rate of inflammation low, since it can be harmful to the host, thus maintaining integrity and homeostasis [9]. In addition, the carcinogenic potential of intestinal bacteria leads to increased production of IL-6 and tumor necrosis factor (TNF), activation of signal transducer and transcription activator 3 (STAT3), and activation of il-17-IL-23 pathways. Collectively, these innate and adaptive host immune responses induced by the microbiota can contribute to tumor development and progression by triggering inflammation that promotes cancer and promotes resistance to cell death [9].

Endometrial Cancer

Endometrial cancer represents the eighth cause of cancer in women in Brazil and 6,540 new cases are expected for each year of the triennium 2020-2022 according to INCA data [10]. Endometrial cancer is classically divided into two types. Type I is the most common form of endometrial cancer (about 70%) and, along with breast tumors, represents the prototype of an estrogen-dependent tumor associated with obesity, type 2 diabetes mellitus, and metabolic syndrome. Histologically, these tumors are predominantly well differentiated and moderately differentiated endometrioid carcinomas. On the other hand, a type II tumor is not associated with obesity or metabolic or endocrine disorders, and histologically these entities are poorly differentiated tumors with aggressive clinical behavior and a worse prognosis than type I [11].

A strong relationship between intestinal microbiota, estrogen metabolism, and obesity suggests a potential role of intestinal and vaginal bacteria in the development of endometrial cancer type I [11].

Intestinal Microbiome and Treatment Efficacy

Endometrial cancer is treated primarily with surgery to determine the tumor stage as an initial step to identify patients who could benefit from chemotherapy or radiotherapy. Immunotherapy is increasingly being investigated and has shown favorable results in patients with microsatellite instability (MSI) **[12]**. However, these treatments, especially chemotherapy and radiotherapy, are very aggressive and can cause several side effects, especially at the intestinal level. Thus, up to 80% of patients have intestinal symptoms, such as abdominal pain and diarrhea, among others, during treatment.

Consequently, recent studies have investigated the possibility of exploring the microbiome to reduce toxicity induced by antitumor therapies and improve response to these therapies by incorporating, for example, probiotics as an adjunct treatment, or by projecting target molecules to microbial enzymes **[12]**. The microbiota may alter some mechanisms including translocation, immunomodulation, metabolism, and enzyme degradation depending on the type of therapy **[13]**. For example, the composition of the microbiota may affect the efficacy of chemotherapy such as irinotecan via changes in the metabolism of the drug including intestinal absorption and decreased activity of the irinotecan activating enzyme carboxylesterase **[14]**.

The microbiota has also been shown to affect the action of immunotherapy including PD-1/PD-L1 inhibitors by modulating the host immune system, particularly by mediating T-cell activation by promoting T-cell accumulation at the tumor site **[14]**. Doxorubicin is an anticancer chemotherapy drug belonging to the anthracycline family, used to treat various types of cancer, including endometrial cancer. It is characterized by its ability to inhibit the growth of cancer cells and bacteria through the generation of free radicals, DNA interleaving, alkylation and crosslinking of proteins, interference with DNA unwinding and Topoisomerase II, and direct damage to the membrane. However, the use of drugs belonging to the anthracycline family leads to the accumulation of toxic metabolites in healthy tissues **[15]**.

In addition to the heart, the intestine is also affected by toxicity associated with the use of doxorubicin. This drug causes damage to the intestinal epithelium by inducing apoptosis in the epithelial cells of the jejunum and damage to the mucosa, reducing the proliferation of crypts, so that fewer crypts are formed, and with minor villi **[15]**. Oral mucositis, another reaction associated with doxorubicin-induced toxicity, produces an increase in salivary flow, inflammation of the gums, and wound formation.

Oral mucositis produces dysbiosis by decreasing levels of the genus Streptococcus, Actinomyces, Gemella, Granulicatella, and Veillonella and increasing levels of other Gram-negative bacteria such as *Fusobacterium nucleatum* and *Prevotella oris*. *Fusobacterium nucleatum* has pro-inflammatory and pro-apoptotic activity, contributing to the damage produced in the mucosa **[15]**. On the other hand, bacteria from the intestinal microbiota have been implicated in the inactivation of some medications, including doxorubicin. Yan et al. identified *Raoultella planticola* as a powerful doxorubicin inactivator under anaerobic conditions and demonstrated that this bacterium deglycosylated doxorubicin in the metabolites 7-deoxydoxorubicinol and 7-deoxydoxorubicinoline by the reducing deglycosylation mechanism. Subsequently, doxorubicin was anaerobically degraded by *Klebsiella pneumoniae* and *Escherichia coli* **[15]**.

Modulating of Microbiome

The modulation of the microbiome can be done through the use of probiotics, prebiotics, fecal transplantation, and diet **[16]**. Prebiotics are compounds that act as nutrients and promote the growth and activity of beneficial microorganisms to improve health. Lactoferrin is a prebiotic agent used to modify the endometrial microbiome **[16]**.

Probiotics are defined as living microorganisms that when administered in adequate amounts can confer benefit to the recipient **[16]**. Fecal microbiota transplantation (FMT) has been studied for several indications, however, evidence demonstrating the efficiency only exists for Clostridium difficile infections. FMT of responding and non-responding patients to checkpoint inhibitors in immunotherapy treatments studied in animal models showed that the intestinal microbiome modulates the response to immunotherapy. In addition, FMT has been shown to reduce the toxic effects associated with radiotherapy and chemotherapy **[16]**.

These innovative studies have shown that FMT can be useful in cancer treatment. Recent evidence shows that the ketogenic diet and/or the Mediterranean diet have the potential to reduce the risk of cancer by influencing metabolic pathways, thereby increasing cancer immune vigilance **[17]**. The ketogenic diet is a high-fat and low-carbohydrate regimen with adequate protein intake. A classic ketogenic diet offers a 4:1 formulation of fat content for carbohydrates plus protein; however, a clear definition of this regimen is not available, and several protocols have been proposed

over the years [17].

The ketogenic diet increases the transition from glucose metabolism to ketone bodies, which has been associated with reduced tumor angiogenesis and inflammation, as well as increased apoptosis [17]. Regarding safety and viability, a recent randomized control study showed that among women with ovarian or endometrial cancer, a 12-week ketogenic diet produced a selective loss of total and visceral fat, maintaining lean body mass and decreasing cancer-related growth factors [18]. In addition, the ketogenic diet was not associated with worse quality of life and, on the other hand, improved physical function increased energy, and reduced specific binge eating [18].

The Mediterranean diet is characterized by high consumption of fruits and vegetables, vegetables, whole grains, nuts, seeds, and aromatic herbs. The main source of fat is represented by extra virgin olive oil and not by animal products. Dairy products (mainly yogurt and cheese), eggs, fish, and red wine are allowed in small amounts, while red meat intake is reduced, favoring lean meats. The Mediterranean diet determines changes in the composition of the intestinal microbiota leading to an increase in beneficial bacteria such as Lactobacillus, Bifidobacterium, and Prevotella, and a reduction in pathogenic bacteria such as Clostridium, leading to higher levels of fecal SCFA that increase the microbial diversity of the intestine [18].

Vaginal and Endometrial Dysbiosis

Vaginal dysbiosis is a condition characterized by a microbiota with a reduced number of lactobacilli, and the most common form of vaginal dysbiosis is represented by bacterial vaginosis [19]. A systematic review of 63 molecular studies on the vaginal microbiota described bacterial vaginosis as a polybacterial dysbiosis with Lactobacillus depletion and an increase in the diversity and bacterial load of other facultative anaerobic bacteria, particularly *Gardnerella vaginalis*, *Atopobium vaginae*, Prevotella, Eggerthella, Dialister, Megasphaera, Sneathia, Leptotrichia, Parvimonas, Veillonella, Bacteroides, Mobiluncus, Porphyromonas, Mycoplasma, Ureaplasma, Streptococcus, Staphylococcus, *Gemella* and *Escherichia* / *Shigella* [19].

Bacterial vaginosis represents the most prevalent lower genital tract infection, affecting approximately 23-29% of women of reproductive age, with a higher prevalence among black and Hispanic women, and is associated with several pathological conditions, including miscarriage, premature birth, increased risk of sexually transmitted infections, pelvic inflammatory disease, as well as gynecological cancer. Several host factors can affect the vaginal microbiota and induce bacterial vaginosis, e.g., smoking, vaginal showering, and some lubricants with high osmolarity [20].

When we approach the endometrial microbiome, Walther et al., identify *Porphyromones somerae* as the most abundant organism in patients with endometrial cancer. They also found that in addition to obesity and postmenopausal, a high vaginal pH is considered an additional risk factor for endometrium cancer [20]. In this study, they confirmed that *Porphyromonas somerae* is not associated with postmenopausal; it is, however, related to four other microorganisms *Anaerococcus tetra-dius*, *Anaerococcus lactolyticus*, *Peptoniphilus coxii*, and *Campylobacter ureolyticus* that are associated with postmenopausal conditions, suggesting that they could be first settlers to facilitate subsequent colonization by *Porphyromonas somerae* and others. *Porphyromones somerae* was found in 100% of the samples of patients with endometrial cancer Type II and 57% of patients with endometrial hyperplasia. Therefore, *Porphyromonas somerae* is considered a biomarker of the disease [20].

Conclusion

The interest in the interaction of the intestinal, vaginal, and endometrial microbiota with the environment and the association of dysbiosis as a trigger of the process of inflammation and carcinogenesis has increasingly aroused the interest of researchers. No direct evidence is yet available to associate endometrial cancer with the intestinal (dysbiosis), endometrial and vaginal microbiome. However, this review highlighted that the microbiome of these sites is intrinsically linked to estrogen metabolism, menopausal status, and also systemic inflammation in women. The use of prebiotics, probiotics, diet modification, and fecal transplantation has become an area of great interest in the treatment of tumors in general and maybe adjuvants in cancer treatment, and further studies are needed to better understand the new treatment approach.

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No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

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