Microbiome and Coloproctology: Foundations for Understanding

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Introduction

The characterization of the intestinal microbiome (IMB) is a line of research that is growing exponentially given its potential impact on the prevention and treatment of highly prevalent diseases. This rise is a direct consequence of technological advances that allow significantly more accurate analysis than traditional crop-based studies. In the specific context of colorectal cancer management, MBI emerges as a promising biomarker in the primary, secondary and tertiary prevention phases. The purpose of this editorial is to introduce coloproctologists to the subject and motivate them to deepen these concepts with the growing evidence available in the indexed literature.

What is the Microbiome?

The human microbiota encompasses a wide diversity of microorganisms, including bacteria, viruses, fungi, protozoa, and archaea distributed in various regions of the body. It is estimated that the gastrointestinal tract has approximately 100 trillion microorganisms. Current sequencing methods have led to its characterization in genetic terms, which introduced the concept of “microbiome”. The total genetic material in the microbiome is 100 to 150 times greater than that of the human genome. This community is acquired at birth through the commensal flora of the mother's skin, vagina and feces and remains relatively stable from the age of two, playing a critical role in both health status and disease.

Physiologically, IMB is not only a natural defensive barrier against infection, but is also involved in numerous protective (e.g. immunomodulation), structural (e.g. protein synthesis) and metabolic (e.g. production of short-chain fatty acids) of the intestinal epithelium that impact health and disease states. In addition, two regulatory axes related to the central nervous system are recognized: the hypothalamic-pituitary adrenal neuroendocrine axis and the intestinal brain axis, which explain its relationship between numerous extraintestinal diseases such as arthritis, diabetes, and Alzheimer's, among others. Unlike the difficulty involved in genetic manipulation, MBI can be modified through relatively simple and low-cost interventions, such as dietary change, prebiotics (non-digestible dietary ingredients such as inulin), probiotics (*Lactobacillus*), postbiotics (products of bacterial fermentation such as short-chain fatty acids), antibiotics and fecal transplantation. This makes it possible to outline easy-to-implement alternatives that can improve primary, secondary, and tertiary prevention of various diseases.

Where and how to study the microbiome?

In the field of CRC and other pathologies, the microbiome is mainly studied on the feces. However, it is crucial to note that there are notable disparities not only between the microbiomes of different regions of the body, but also between the various sections of the gastrointestinal tract and, specifically, in the colonic location. In addition, a microbiome associated with epithelium (known as "biofilm") has been identified, which could have a relevance comparable to or even greater than the luminal microbiome. The presence of microbiome has also been observed in some tumors, even those considered "uncontaminated", such as breast cancer.

It is important to note that most current research is limited by the circumstance that characterization is done on samples that represent only a fraction of the human microbiome.

From a technological perspective, the importance of not only next-generation sequencers, but also high-throughput analysis equipment such as mass spectrometers is highlighted. These instruments play a crucial role in molecular characterization through disciplines such as metagenomics (genomic approach), transcriptomics (mRNA analysis), proteomics, and metabolomics (study of proteins and metabolites respectively). Among these methodologies, metagenomics is distinguished by its accessible implementation and wide applicability, constituting the basis of most publications. This technique enables taxonomic characterization by sequencing whole genomes or various genomic regions, including 16S ribosomal RNA (16S rRNA), thus providing detailed information on the composition and diversity of the MBI. Species diversity is a closely examined aspect of colorectal cancer and reveals a clear association with lifestyle. Particularly, Western habits are linked to reduced microbial diversity or changes in microbial diversity suggestive of triggering processes that contribute to carcinogenesis.

Microbiome and Colorectal Cancer: Cause or Consequence?

Colorectal cancer is related to the consumption of diets that are low in fiber and high in fat calories. In turn, the type of diet determines the diversity of the microbiome (reversible changes are observed within a few days of changing diet). Although the association between CRC and an altered or dysbiotic microbiome has been well established for decades, it was only in recent years that evidence began to be generated for how certain bacterial species can promote colorectal carcinogenesis, mainly through chronic inflammatory processes, genotoxins and alterations in metabolism. Among the genotoxins are *Fusobacterium nucleatum FadA (activates the Wnt/β-catenin signaling pathway),* Escherichia coli adhesins (*adheres to and invades the intestinal epithelium)* and Bacteroides fragilis BFT ł *(activates the Wnt/β-catenin signaling pathway and the NF-B* factor). Microbiome-derived metabolism can affect colorectal carcinogenesis through the generation of secondary bile acids, activation of procarcinogens, and modification of inflammation pathways.

Microbiome and anastomotic dehiscence: a new risk factor?

Research on blood samples, peritoneal fluid, and drains has revealed a marked association with *Enterococcus faecalis* and *Pseudomonas aeruginosa*. These two pathogens exhibit remarkable collagenolytic activity. Experiments in rats have corroborated that both pathogens induce anastomotic dehiscence through the production of type I and IV collagenases, which play a critical role in the healing process of anastomosis. The integral impact of the bacterial community as a causative element of anastomotic dehiscence is currently being addressed through research in animal models. It has been observed that in the first week after surgery, there is an increase in the relative abundance of up to 500 times of *Escherichia coli* and *Enterococcus.* A significant finding of the study was the detection of pathogenicity-associated factors in tissue samples from anastomosis, suggesting that the microbiome linked to anastomosis plays a more crucial role in the healing process than the microbiome present in the gut lumen. The large number of factors potentially associated with dehiscence and the microbiome (antibiotic prophylaxis, mechanical preparation, nutrition, obesity, smoking, surgical technique, etc.) constitute the major limitation to designing studies that demonstrate a causative association.

What role does the microbiome play in screening and as prognostic-predictive factor?

Although video colonoscopy is the screening method of choice, its cost and availability make fecal occult blood a current strategy even in developed countries. Studies conducted in England have shown that the characterization of MBI increases the sensitivity and specificity of occult blood, although the cost-benefit has not been evaluated. In relation to prognosis, a recent

systematic review of 27 studies reported that the presence of *Fusobacterium nucleatum* and *Bacteroides fragilis* was associated with a decrease in global survival (HR 1,5, IC95%: 1,1–1,9). An association with more advanced tumor stages was also observed in 10 of these studies. There is also evidence that MBI modifies not only its antitumor activity but also the toxicity of chemotherapy drugs, probably affecting its pharmacokinetics. The association with response to chemotherapy has been explored primarily in melanoma, lung, and kidney. However, evidence is growing on drugs used in CRC such as irinotecan, oxaliplatin, and 5-fluorouracil. It is worth noting the recent evidence on colorectal cancer in the effectiveness of checkpoint inhibitors (e.g., anti-PD-1) used in new immunotherapy schemes for tumors with repair deficiency (unstable tumors).

Final Thoughts

The close relationship between the gut microbiome and colorectal cancer poses a challenge in determining whether such a relationship is causal. Although understanding this link is intricate, more recent evidence has provided clarity on various causative mechanisms. In any case, given the potential impact that this association exerts in the fields of primary, secondary and tertiary prevention, and considering the inherent ability to modify MBI, its research emerges as one of the most attractive fields in translational research. This approach promises not only to advance the understanding of the microbiome-cancer relationship, but also to open doors to innovative preventive and therapeutic strategies.

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