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Mini Review

Microbioma and Cancer

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Abstract

The authors, based on the experience that has been given them by the transplantation of Intestinal microbiota carry out exhaustive review of the gastro-intestinal Cancer, related to the microbiota. They analyze the different aspects that occur in the inflammatory processes, as well as the immune and those potentially carcinogenic.

Analyze the probable causes that can occur in the gastric, vesicular, colorectal and hepatocellular carcinoma.

They suggest a number of procedures that may shorten the use of microbiota in gastrointestinal cancer, and point out what they believe will happen in the future.

Keywords: *Microbiota; Cancer; Intestine*

Review

Under normal conditions, the intestinal microbiota (IM) and its host thrive in perfect symbiosis status. The healthy fetal gut is considered sterile. Fetal gut have intense colonization process, that begins during childbirth or in the uterus to give rise to an ecological succession, which ends with the establishment of a pattern of colonization characterized by the presence of mostly benign bacteria known as commensal IM observed In adults [1,2]. These microorganisms coexist in direct contact with man, and maintain a symbiotic relationship with bi-directional benefits [3,4].

The intestinal microbiota plays active role in digestion and fermentation of carbohydrates, in the production of vitamins, in the development and maturation of the immune system of the gastrointestinal mucosa, and in the defense against intestinal pathogens. The development of the intestinal microbiota of the newly born is scheduled from insemination life [3,5]. The fetus has the first contacts with the native intestinal microbiota through the placenta and amniotic fluid [6]. Subsequently, the massive colonization of the fetal intestine during birth is concretized by direct contact of the newborn with maternal bacteria in the perianal region [7,8]. Intra-utero to non-pathogenic microorganisms, maternal exposure occurs, and is dependent on the nutritional, metabolic, and immune status of the mother [9-11]. The current focus of research is directed towards maternal risk factors that influence the development of the intestinal microbiota of the newborn [12,13]. On the other hand, breastfeeding is an important factor in the subsequent modification of the composition of the microbiota neonatal [14]. The human milk provides infant immunoglobulins, cytokines, probiotics and Prebiotics that modulate the colonization of microorganisms [15,16], also through the nipple and the milk ducts the newborn is exposed to new microorganisms such as *Staphylococci, Micrococci* and *Corynebacteria, Lactobacilli, Bifidobacteria* [17,18]. Comparative studies of intestinal microbiota between children fed with breast milk and artificial formulas, establish that human milk is a potent inducer of immune maturation. The cytokine TGF-β concentrations contained in breast milk are usually high. The increase of this biomolecule improves intestinal maturation of the newborn and has immuno-regulatory function that induces the immune tolerance of maternal origin commensal organisms and reduces the inflammatory response of the intestinal microbiota on development [19,20]. The immaturity of mediators and effectors of the im-

mune response do not allow that the newborn has a mature immune system [21], in this process, the commensal organisms play a very important role and represent one of the first stimulus immunogenic than the newborn faces [22], its recognition is borne by the Toll Like Receptor, after which activate a series of biochemical signals inside dendritic cells and macrophages that lead to the immune tolerance, that is, the absence of immune response against commensal organisms. The magnitude and quality of this response depends on the type of organism, concentration and microenvironment, which includes the action of cytokines (secreted by immune system proteins), who also act as mediators of immune response. Cytokines involved in this process of adjustment are: beta transforming growth factor and interleukin [9]. Immune tolerance is essential dietary immunogens and commensal organisms to which man is exposed. We could conclude that the intestinal microbial colonization is essential for the maturation of the immune system and for the physiological regulation of the intestinal mucosa in the neonate. A full and balanced immune system guarantees a healthy child development.

A considerable group of diseases have been associated with changes in IM due to alterations that lead to dysbiosis, also called dysbacteriosis, which describes the presence of microbial irregularities within the organism. Dysbiosis is most commonly reported as a disruption of the gastrointestinal tract especially during bacterial growth of the small intestine or excessive growth of fungi [23,24].

There is increasing evidence from clinical, epidemiological and experimental studies in which the association between IM dysbiosis and increased risk of inflammatory, autoimmune, metabolic and chronic gastroenterological disorders has been demonstrated. Include ulcerative colitis, Crohn's disease, celiac disease and colorectal and gastric cancers. The role of the human microbiota in the health-disease process has been redefined during recent years and its physiological role has been enriched [9,25].

IM that colonizes newborns plays a critical role in the education of the immune system. Alterations in the early interactions between these commensal microorganisms and their host have been associated with long-term effects in the development of the process of "Immunity and host Metabolism"

The commensal microbiota can also modify the virulence of pathogenic microorganisms. Through competition with oxygen and cytokine synthesis, such as interleukins (IL) IL-23 and IL-22, inducers of activation and differentiation of cell pattern of TH lymphocytes 17. Recent studies demonstrated that cytokines secreted by TH 17 lymphocytes may have a dual action: pro and anti-inflammatory [26-28] in an inflammatory micro-environment induced by the presence of pathogenic microorganisms. TH 17 potentiate the inflammatory activity of macrophages and polymorphonuclears, whereas, in the presence of a predominance of commensal microorganisms, immune tolerance is generated [29]. This antagonistic action expressed by cytokines secreted by TH 17 lymphocytes demonstrates the complexity of the process, and the guiding role of the micro-environment in the development of the mucosal immune response.

These conditions have been traditionally described as diseases characterized by an overreaching or aberrant T helper effector (Th 1, Th 2, Th 17) and/or reduced regulatory T lymphocyte (Tregs) responses and have known roots in the early epochs of life [30]. Components of colonic IM, particularly Clostridium sporulated Gram-positive and anaerobic bacilli of Clusters IV, XIV a and XVIII (group or genetic cluster in a dendrogram), as well as secondary metabolites such as Short-chain fatty acids (dysbiosis) has been "Tregs" responses in the colonic mucosa in experimental animals (murine model).

Selected Clostridium species, isolated from human deposition and inoculated in mice, have been shown to induce "Tregs" responses in the colonic mucosa of these animals, bypassing experimental colitis. Moreover, Clostridium species regulate the function of innate lymphoid cells and intestinal epithelial permeability by inducing Interleukins (IL-22 and 23), which is associated with an increase in mucus production and secretion of proteins anti-bacterial in the gut. Since Tregs, play a fundamental role in the maintenance of mucosal homeostasis, suppressing inflammation and, in the components of IM that alter the balance between effector and regulatory cells, are of vital importance in what can be considered as the healthy state of the intestine and represent, likely point of intervention for diseases, related to microbiota and/or immunity. There is promising evidence regarding the role of IM in the development of tolerogenic immune responses and its action as a modulator in the late expression of allergic manifestations.

The microbiota and its host make up a complex organism in which the symbiotic relationship as we have already mentioned confer benefits in both senses. Defects in host regulatory circuits that control bacterial detection and homeostasis or alterations of the microbiome through environmental changes such as infection, diet or lifestyle can alter this symbiotic relationship and promote disease. There is increasing evidence to indicate the relationship of bacterial microbiota to carcinogenesis. Research on microbial interactions with humans has focused on unique pathogens, however, many pathogens, particularly viruses, are known to promote cancer through well-described genetic mechanisms [31-33], other pathogens, such as *H. pylori* and hepatitis C virus, promote the development of cancer through epithelial lesions and inflammation. However, recent evidence suggests that disease in humans is attributable not only to individual pathogens, but also to global changes in our microbiome [34,35], this one contains a metagenome that exceeds our own genome 100 times. The relationship between the bacterial and the metagenome and its relevant role in metabolism and inflammation has now been defined with certainty [36,37], factors that contribute to carcinogenesis [38,39].

Gastric cancer is the leading example of bacterial-borne carcinogenesis that is caused by infection with a specific bacterial pathogen [40,41].

H. pylori infection, classified as carcinogenic by the International Agency for Research on Cancer, may lead to sequential development of gastritis, gastric ulcer, atrophy, intestinal metaplasia, dysplasia and finally gastric cancer [42], presence of *H. pylori* and hypochlorhydria, favors bacterial overgrowth, subsequently increases the bacterial conversion of dietary nitrates into carcinogens. In contrast, *H. pylori* infection reduces the risk of esophageal adenocarcinoma in humans, which emphasizes the organ-specific effects of the bacterial microbiota on carcinogenesis.

Other examples of carcinogenesis promoted by specific bacterial pathogens are gallbladder cancer that is associated with chronic infection of *Salmonella* enteric subsp [43,44]. and lymphoid lymphomas type MALT characterized by the clonal expansion of B cells and helper-reactive helper T cells derived from *H. pylori*-derived antigens [45,46].

Recent studies suggest that a high-fat diet alters the gut microbiome and raises levels of secondary bile acid DCA, which is a metabolite produced only by bacterial 7α-dehydroxylation. The high-fat diet model, supplementation of DCA increases the development of HCC, while the reduction of DCA-producing bacteria by antibiotics decreases. DCA is also known to promote colon and esophageal cancer, suggesting that the microbiome can also affect these cancers through the production of DCA [47].

However, the functional relevance of human microbiomes for the development of cancer has not been established. The transfer of human cancer microbiomes to preclinical models would help to evaluate the tumorigenic potential of the microbiota associated with cancer. Experiments using transplantation between species need to take the host's specific microbiota effects on the immune system, which are an important component of the carcinogenic process [48].

Multifaceted and large-scale approaches integrating metagenomic, meta-transactional and metabolomic analysis of large patient cohorts and healthy controls will be essential to establish the role of microbiomes in cancer development, particularly to determine if changes in composition or Microbial richness at the metagenomic level affect the development of cancer. Validation of the cancer-inducing potential of bacterial clinical isolates would require the use of several animal models, combined with different pathogen-free and germ-free living conditions, as well as gnotobiotic to clearly establish cause-effect.

In the coming years we will witness an explosion in the literature of clinical studies and development of the intestinal microbiome in children, likewise in impact on health and disease, experimentally oriented not only to describe the effects of IM references on physiological responses of the hosts, but also interventional studies to produce modifications or recover imbalances as a powerful and cost-effective therapeutic tool. Do not Is far from where we will have available microbiota profiles that account for metabolic or therapeutic aspects.

Conclusions

- The intestinal microbiota and its host maintain a symbiotic relationship with bi-directional benefits. The intestinal microbiota through its metabolic functions becomes a protective barrier of pathogens, it also favors the development and homeostasis of the immune system, that is, there is a perfect balance between the microbiome and its host that translates into health.

- Defects in host regulatory circuits from T-regulatory lymphocytes that generate persistent anti-inflammatory immune system suppression or alterations of the microbiome through environmental changes such as infection, diet or lifestyle can alter this relationship symbiotic and promote disease.

- Dysbiosis of the intestinal microbiota is more commonly reported as an alteration of the gastrointestinal tract especially when there is bacterial overgrowth or, excessive growth of fungi in the small intestine.

- Loss of microbial diversity, overgrowth of oxygen-resistant bacteria, decreased production of short-chain fatty acids (Dysbiosis) has been shown to increase the risk of inflammatory, autoimmune, metabolic and chronic gastroenterological disorders, among those that exclude colorectal cancer, gastric cancer and hepato- cellular carcinoma, the relationship between the bacterial microbiome and the metagenome and its relevant role in metabolism and inflammation have also been defined with certainty, contributing factors to carcinogenesis.

- The connection between the bacterial flora and the immune system can predict or improve outcomes in the treatment of cancer with chemotherapy. The new research works, even preliminary ones, have been very interesting from the oncologic point of view. The next step is to begin clinical trials to see if a transplant of feces or specific bacteria can increase the success rates of immunotherapy.

- Understanding the diverse contributions of bacterial microbiota to carcinogenesis will open new possibilities for diagnostic, preventive and therapeutic approaches. Today it clearly represents the next frontier of medical research.

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