

Intestinal Microbiota and Immune System

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Abstract

The authors explain how the intestinal microbiota has revolutionized medical knowledge, by determining the different functions that this organ has. They assess the determinants that occur in the child, as well as the factors that influence their development, from the immune point of view and review how the intestinal microbiota modulates the immune system of adults, as well as briefly mention other functions, human development. They raise the question whether the intestinal microbiota will be able to correct health anomalies in the gastrointestinal system and regulate the behavior of other diseases.

Keywords: Intestinal Microbiota; Immune System; Lymphocytes

Immunology

The intestinal microbiota has several functions, including digestion, fermentation of carbohydrates, production of vitamins, and development and maturation of the immune system [1].

This development has innate and adapted mechanisms that protect the individual from environmental pathogens. The former function independently of exposures prior to infectious agents and the latter are composed of B, T, and molecular lymphocytes from the system adapted. Both mechanisms, which act in coordination, lead to immunological memory; which responds to re-exposure to the same antigen [2].

The first contacts with the maternal intestinal microbiota are carried by the fetus through the placenta and amniotic fluid [3]. Subsequently, the massive colonization of the fetal gut at birth is concretized by direct contact of the newborn with the maternal bacteria of the perianal region [4,5].

At birth, the newborn with immune system complete and immature, a reflection of the immaturity of the mediators and effectors of the immune response [6,7]. In this process of maturation, the commensal microorganisms play a key role and constitute one of the first stimuli immunogenic that the newborn faces [8-10], and their recognition is the responsibility of receptors present in the cells of the immune system nonspecific, essentially: dendritic cells (dc) and macrophages, which recognize molecular patterns associated to pathogens (PAMPs) expressed by bacteria, viruses, and fungi that make up the microbiota [11-13]. The magnitude and quality of this response depends on the type of microorganism, concentration and microenvironment [14-16].

In this process it involves, in addition, the action of cytokines, which act as mediators of the immune response. These are proteins secreted by cells of the immune system. The cytokines mainly involved in this process of regulation are: the transforming growth factor-beta

(TGF- β) and interleukin 10 (IL-10). Tolerance immune system is essential in the face of immunogens dietary and commensal microorganisms [17-19]. Guarantee the absence of immune response to the wide range of immunogens dietary and commensal microorganisms they are exposed to the individual. To deepen the molecular mechanisms involved in the recognition and induction of immune responses against the intestinal microbiota, it is a premise in search of therapeutic options, so that should increase the research efforts in this field.

The bacteria's in the intestine may express the same PAMPs pathogenic bacteria [20,21]. The recognition mediated by the T lymphocytes can induce tolerance or inflammation, in dependence of the microenvironment [22,23]. In the base side of the intestinal epithelial cells induce responses pro-inflammatory and limit the recognition of PAMPs for those microorganisms, usually pathogenic, that have been able to cross the epithelial barrier [24-26]. The activation of CD, and macrophages also has effect on the humoral response.

Studies conducted in Japan and the United States have shown that as a result of the cooperation of the cell between the lineages of B and T lymphocytes, specifically helper T lymphocytes, or T Helper 17 (TH 17) and B lymphocytes promotes the differentiation of B lymphocytes into plasma cells secreting immunoglobulin A (IgA) [27]. In this way, the intestinal microbiota establishes a link between the innate response and adaptive. The production of IgA decreases markedly in rodents without microbiota, the mechanisms regulating this process are not fully elucidated, and the evidence points towards the induction by commensal microorganisms of transcription factors for class switching to IgA [28]. Studies are required to assess the reversibility of this phenomenon, after the restitution of the intestinal microbiota.

Until a few years ago, it was considered that, immediately after birth, colonization of the gastrointestinal tract began, from the oral cavity and dependent on exposure to the extrauterine environment [29], but recent studies have shown that the development of the intestinal microbiota of the newborn is programmed from intrauterine life [30]. The theory that during the fetal stage the intestine is sterile and that exposures to maternal microorganisms occur after birth has been modified in the light of novel investigations which show that the first contacts with the maternal intestinal microbiota have the fetus through the placenta and amniotic fluid. Then, massive colonization of the fetal intestine continues during birth by contact with maternal bacteria in the perianal region [31].

The presence of bacteria from the intestinal and cutaneous microbiota of maternal origin in placental tissues demonstrates maternal-fetal microbiological transference. Initially these results were evaluated in placentas from preterm births, which was associated as a risk factor for prematurity; however, studies have shown a similar behavior, even for different delivery routes, either by cesarean or vaginal route, without association with a septic or inflammatory process [32]. These findings have relaxed the initial interpretation given to the presence of bacterial DNA of the maternal microbiota in amniotic fluid, placenta and meconium, as indicators of mucosal dysregulation and rupture of natural barriers.

It is now accepted by the international scientific community that intrauterine exposure to non-pathogenic maternal microorganisms occurs during gestation and is dependent on the nutritional, metabolic and immunological status of the mother [33,34]. The promotion of case-control investigations to characterize the maternal risk factors that influence the development of the intestinal microbiota of the newborn are of great interest in the field of current research.

The predisposition to atopic diseases, such as asthma and food allergy, is low in populations consuming fermented foods with an increase in lactobacillus concentrations. Studies in rodents indicate that the microbiota regulates the balance between the responses of different T helper strains: TH 1, TH 17 and TH 2. The reconstitution of the microorganism commensal murine free of microorganisms increases the concentrations of TH 1 lymphocytes and TH 17, and reduces TH 2 lymphocyte concentrations. This imbalance promotes inflammatory responses to commensal microorganisms [35-37].

The expansion of basophils and the increase in serum levels of immunoglobulin E (IgE) are findings after antimicrobial treatment. These results support the hygiene hypothesis, which emerged from the observation of a reduced incidence of allergic diseases in individu-

als exposed to bacteria during childhood [38,39]. The use of antimicrobials reduces concentrations of commensal colonies, and modifies the microenvironment where they develop [40,41]. The effect of antimicrobials on the microbiological population and the induction of TH 2 immune responses are predisposing factors for the development of allergic diseases in childhood [42,43].

Relating different antimicrobial families and their influence on commensal populations in a way should be explored in future drug-epidemiological investigations.

Despite the complexity of the intestinal microbiota, there is a delicate balance in bacterial populations such that any rupture leads to decreased resistance to pathogenic colonization. Obviously, genetic and environmental factors are important in the establishment of the intestinal microbiota; however, the relative contributions of these two groups of factors, and the mechanism by which they act, are areas of active research.

It has been shown that alterations in the microbiological colonization process predisposes and increases the risk of various diseases, such as: allergy, obesity or diabetes [44-46]. The relationship between diet, microbiota, inflammatory and atopic diseases is explicable from the role of the microbiota in the development of innate and adaptive immune responses [47]. Exploring the therapeutic benefits of using microbiota has allowed the design of interventions, such as fecal microbiota transplantation (FMT), which is very effective in the treatment of *Clostridium difficile* infection [48]. Enhancing the therapeutic use of the microbiota expands as a new pathway for the treatment of inflammatory and atopic diseases at present.

Intrauterine exposure to non-pathogenic maternal microorganisms occurs, and is dependent, on the nutritional, metabolic and immunological status of the mother [49,50]. The current research approach is directed towards the maternal risk factors that influence the development of the neonatal intestinal microbiota. It has been shown that breastfed babies have a larger and more active thymus than formula fed babies.

On the other hand, breastfeeding constitutes an important factor in the modification of the composition of the neonatal microbiota [51]. Human milk provides the infant with immunoglobulins, cytokines, probiotics, and prebiotics that modulate the colonization of microorganisms [52,53]. Also, through the nipple and ducts the infant is exposed to new microorganisms such as *staphylococci*, *corynebacterial*, *lactobacilli*, *micrococci* and *bifidobacterial* [54,55].

Comparative studies of intestinal microbiota among breastfed children and with artificial formulas establish that human milk is a potent inducer of immunological maturation [56].

TGF- β cytokine concentrations in breast milk are generally elevated, the increase of this biomolecule improves intestinal maturation of the newborn and has an immunoregulatory function that induces immune tolerance towards commensal microorganisms of maternal origin and, the inflammatory response to the developing intestinal microbiota [57,58].

The immaturity of mediators and effectors of immune response does not allow the neonate to have a mature immune system [59,60], in this process, commensal microorganisms play a very important role and represent one of the first immunogenic stimuli that the newborn faces [61], its recognition is the responsibility of the Toll Like Receptor (TLR), after which a series of biochemical signals are activated inside the dendritic cells and the macrophages that lead to the immune tolerance, that is, the absence of [62,63], the magnitude and quality of this response depends on the type of microorganism, concentration and microenvironment, which includes the action of cytokines (proteins secreted by the immune system), which act, also as mediators of the immune response. The cytokines involved in this regulatory process are: Transforming growth factor beta (TGF- β) and interleukin 10 (IL-10). Immune tolerance is essential against dietary immunogens and commensal microorganisms to which humans are exposed.

The gastrointestinal tract constitutes a sensitive interface for contact and communication between the individual and the external environment. For perfect homeostasis, the system has distinguished clearly between potential pathogens or pathogens, on the one hand, and commensal microbes in symbiosis with the host, on the other. In the first case, the body must equip itself with elements of adequate defense, while in the second case, the host has known how to tolerate to obtain the benefit of the symbiosis. The interactions between microorganisms, epithelium and intestinal lymphoid tissues are multiple, diverse in their characteristics and continuous, so that they constantly remodel the local and systemic mechanisms of immunity adapting them to the microbial environment [64]. The epithelial cell plays an important role in the logistics of the immune system. Its position in the first line and in contact with the intestinal lumen is crucial for the initial recognition of foreign molecules and for the generation of signals that are transmitted to the immunocompetent cells of the underlying tissue. Activation of defense mechanisms depends first on the rapid recognition of risk through innate receptors that detect structural components common to bacteria or viruses but absent in the eukaryotic cell. Activation of these sensors by bacterial invasion immediately generates signals that converge in the migration of transcription factors (NF-kappa B and others) to the cell nucleus, where they activate the expression of genes responsible for the synthesis of pro-inflammatory proteins [65]. Cytokines and inducible enzymes capable of generating inflammatory mediators. In this way, epithelial cells emit signals capable of attracting and activating leukocytes, increasing blood flow, increasing capillary permeability, etc. Enterocytes can act as antigen-presenting cells, suggesting that their role is not limited to defense, but they also participate in the initial step of acquired type responses (expansion of specific lymphocyte clones and generation of antibodies) [66]. The mucosal immune system has three anatomically differentiated compartments: organized structures (Peyer's plaques and lymphoid follicles), lamina propria and superficial epithelium [67]. Organized structures are sites of induction, while the lamina propria and the epithelial compartment contain mature and effector cells. The organized structures are covered by specialized epithelium (M cells, characteristic morphology), which transports microorganisms or antigenic structures from the light to the underlying lymphoid tissue.

The induction of acquired immune responses is a phenomenon that occurs mainly in the follicular structures of the intestinal mucosa. The processed antigens are presented to T lymphocytes in the "naive" state, and the expansion of the clones most closely related to the antigen is activated. T cell clonal expansion results in helper lymphocytes (Th cells) of different phenotype: Th1, Th2 or regulatory T (Th3, Tr1 or CD4CD25 cells). Regulatory T cells play a central role in immune tolerance because they secrete cytokines [68].

Anti-inflammatory (IL-10, TGF-beta) in response to antigens that are recognized as "commensal" and non-pathogenic. Under normal conditions, the intestinal mucosa contains few activated T cells of Th1 phenotype, and regulatory T cells predominate. This immunotolerance context allows continuous exposure to an overwhelming antigenic load (bacteria of the flora, food), without thereby triggering inflammatory reactions that would injure the intestinal tissue itself. The interaction with the microbial world in the intestinal lumen appears to be a primary mechanism in the conformation of the active immunoregulatory state mediated by regulatory T cells [69]. Some abnormalities in the development of the immune system could be due to defects in the interaction of the microbiota with the immunocompetent compartments of the mucosa. According to the hygiene hypothesis, in the westernized societies the increasing incidence of atopies (eczema, asthma, rhinitis, allergies), inflammatory bowel disease and autoimmune disorders (multiple sclerosis, type I diabetes) could be explained by a decrease in the microbial load in the first months of life. There is evidence to suggest that exposure to non-pathogenic microorganisms, including helminths, food-borne and gold-fecal, exerts a homeostatic impact [70].

Are there three forms of immunity.

These are, the anatomical barriers, the non-specific immune system and the specific immune system.

The skin is the first line of defense. The second is: inflammation, phagocytes, C-reactive protein and the third are vaccines, which generate learning.

These forms help the intestinal flora to determine the quality of our immune system in the mucous membranes in various ways.

They provide physical barriers to the colonization of harmful external microorganisms.

A weak gut flora allows yeasts and harmful bacteria to grow. A strong intestinal flora protects against invading microorganisms.

Lymphocytes read the histocompatibility of each cell and if it is not recognizable the attack. In the case of cancer, cancer cells are histocompatibility, which is why the immune system does not attack different types of cancer [71].

In the case of the intestine, it seems to have to do with lymph nodes and stromal cells, which communicate our immune system through histocompatibility antigens that should not attack good bacteria.

Another study showed that mice that had no intestinal flora - being raised in completely sterile isolation chambers - had all kinds of immune problems: lymphopenia, poorly developed or malformed lymphatic structures, compromised immune function, and high, poorly formed endothelial venules, which affect the immune response [72].

Wild animals do not care about these things, they live in ignorance of the hordes of bacteria that deal with their inner processes.

“Dysbiosis or dysbacteriosis” is defined as any change in the composition of the microbial flora of our organism [73,74].

It is known that changes in the structure of these communities may be responsible for erroneous responses of the immune system. There are several factors that influence these changes: diet, infections, antibiotic use or host genetics. There are several types of dysbiosis: one related to the loss of beneficial microorganisms, associated with the expansion of pathogenic microbes and the loss of microbial diversity [46,75-76].

Among the organs of our body, the gastrointestinal tract is the area most exposed to external antigens. For that reason, it is essential that the immune system acting in that place does so in a regulated and precise manner, being able to create tolerance to commensal antigens and/or antigens ingested in the diet while recognizing and triggering a response to harmful external agents. Flora plays an essential role in this process.

The microorganisms of the gastrointestinal tract avoid infections, competing against pathogenic organisms (adhesion to the tissue, competing for nutrients, secreting antimicrobial peptides, and maintaining intestinal pH) [77-79]. On the other hand, these bacteria have been shown to reduce inflammation by controlling cytokine levels [80]. Another observation suggests that intestinal epithelial cells express less Toll-like receptors and histocompatibility complex II molecules in the absence of microbiota [81].

In short, understanding the relationship between our immune system and our microbiota would help us to address new therapies that improve our digestive and intestinal health.

Will the microbiota solve all our health problems?

Diseases such as obesity, diabetes, cardiovascular disease or cancer, all responsible for much of the world's deaths, are linked to observable changes in the human intestinal microbiota. On the other hand, numerous chronic diseases - chronic inflammatory bowel diseases, asthma and allergies, rheumatoid arthritis or myalgia encephalomyelitis (chronic fatigue syndrome, MS/CFS) - have also been associated.

We could conclude that intestinal microbial colonization is essential for the maturation of the immune system and for the physiological regulation of the intestinal mucosa in the neonate. An intact and balanced immune system guarantees healthy development.

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