Review Article

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Human Colon Microbiota and Mucosal Immune System

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ABSTRACT

Number of microorganisms located in our microbiota is estimated to be about 10 times more than the host cells. Microbiota is located mostly in the gastrointestinal tract and it consists of a high number of mutualistic and commensal microorganisms. Microorganisms in this tract have a particular prominent localization in terminal ileum and colon. Colon microbiota is considered the most important component of the human mucosal immune system. Mucosal immune system also participates in immune defense of eyes, nasal mucosa, genitourinary and respiratory system. Composition, organization and concentration of colon microbiota are thought to be directly connected with pathogenesis of diseases such as Crohn's disease, Ulcerative Colitis, Irritable Bowel Syndrome, Coeliac disease, food allergies and colon cancer. In this article we will discuss about the general characteristics of human colon microbiota and its relationship with etiopathology diseases. The importance of its role in the pathogenesis of diseases and contributions to immune system has recently begun to be understood. Further researches will guide us to understand the etiopathology of these diseases much better and lead us to reveal more effective outcomes.

KEY WORDS: Colon Microbiota, Mucosal Immunity, MALT, Immun Tolerence

HUMAN COLON MICROBIOTA

The human being is not a simple organism but a *superorganism* which contains a big variety of cell types and organizations [1]. Number of microorganisms located in our microbiota is estimated to be about 10 times more than the host cells [2, 3]. The number of genes in microorganisms is about 100 times more than the number of genes of the human organism [2]. Microbiota is located mostly in the gastrointestinal tract and colonic microbiota forms a biomass about 1,5 kg [3]. Colonization of microorganisms depends on the environmental conditions. Acidic pH of *gaster*, alkaline environment of proximal *intestinum tenue* due to pacreatic secretions and bile, effects gastrointestinal tract microbiota. Towards the distal of the intestinum number of microorganisms increases [4]. Investigating the immun relationship between intestinal mucosal structure and microbiota will lead better understanding of gastrointestinal disorders such as Crohn's disease, Ulcerative Colitis, Irritable Bowel Syndrome, Coeliac disease, food allergies and colon cancer [5-7].

Majority of the microorganisms of our microbiota is located in the gastrointestinal tract. It is estimated that 500-1000 species are living commensally in our gastrointestinal tract which has approximately 250-400 m^2 surface area [3, 8]. Colony forming units per ml increases towards the distal of the GIS tract (Fig. 1) [2, 3]. All microbes inhabiting in a host or a part of a host (e.g. gastrointestinal tract) is called microbiota [9]. Microbiota is personal (microbiota fingerprint) and depends on genetic factors, diet, age, geographic origin, life style, birth form, antibiotic use, and ekzogenous-endogenous factors (Fig. 2) [10-12]. In microbiota, a strong numerical dominance of anaerobic cells is seen (there are 100-1000 anaerobic bacteria versus 1 aerobic bacteria) [13]. Through *Human Genome Project* (1990-2003), microbiota was found to be in close relationship with human body. As a result of this project, it has been found that 233 proteins are homologues with bacteria. The genes which produce these proteins, are thought to be taken from microbiota [14]. One of the main reasons making colon microbiota predominant is ileocecal valve (Others are: pH 6.8-7.3, small amount of oxygen facilitating the growth of anaerobic bacteria, lack of digestive enzymes, fibrous structures reaching up to colon which cannot be digested by humans, fecal content remains longer in the lumen of colon than the other intestinal segments). Decrease of intraluminal pressure in caecum opens the ileocecal valve for the passage of chyme from ileum to caecum; increase of pressure closes it to prevent regurgitation. Thus, it prevents invasion of the small intestine by the intense colonic microbiota. Function disorders of ileocecal valve causes "small intestinal bacterial overgrowth (SIBO)". Colonic microbiota invade small intestine due to reflux which is the consequences of valve dysfunction and causes nausea, bloating sensation, vomiting, diarrhea, malnutrition and weight loss [15, 16].

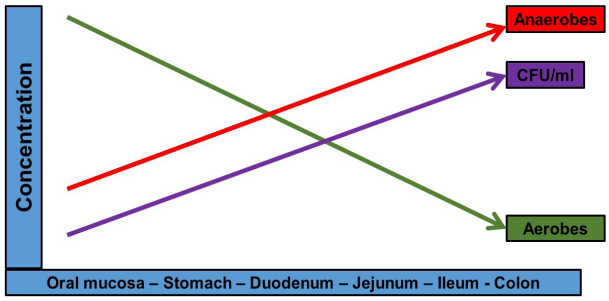

Figure 1. Towards the distal of the GIS, concentration of microbes

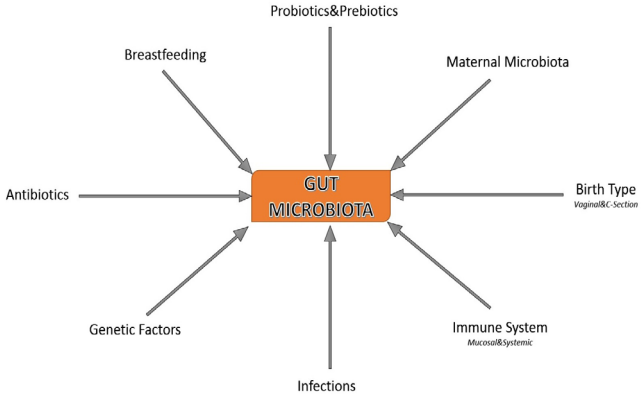

Figure 2. Factors affecting the formation of colon microbiota.

On the other hand, Haustra coli may be another reason for higher concentration of colonic microbiota. We think that each haustra makes a different chamber/microenvironment.

FORMATION AND DEVELOPMENT OF MICROBIOTA

While intrauterine life, fetus lives a sterile life and the first encounter with maternal microbiota during birth. This maternal derived microbiota develops with breastfeeding. In two years infant's microbiota becomes same as adult's microbiota. Several factors affects the first microbiota, such as Mother's diet, taking pro-prebiotics, type of birth (vaginal or surgical), gestational age, infant's diet (breast milk or formula). After understanding the impact of breast milk on the formation of microbiota, by adding probiotics and prebiotics, baby formula has been tried to be closer to breast milk. Babies born by cesarean section, encounter firstly with environmental microbiota. Microbiota development can not be normal even with feeding treatment. These individuals have increased susceptibility to many allergic diseases such as asthma [17].

DUTIES OF COLON MICROBIOTA

Even the effect of the microbiota on human cannot be understood completely, the known parts offer a wide range of research areas to the scientific world. The most important and prominent role of microbiota is to fight against pathogenic microorganisms. This fight continues by: holding the connection surfaces before the pathogens, competing against pathogens for food, secreting substances like bacteriocin which inhibiting the reproduction of pathogens and damaging pathogens with its metabolic wastes. Another task is to facilitate digestion. With secreted certain enzymes, colon microbiota simplifies digestion of proteins and fat also it prevents foreign antigens to access to the intestinal wall. Microbiota enables the production of K 2, B 1, B 2, B 3, B 6, B 12, folic acid, pantothenic acid and some amino acids [18]. It is a mystery that while giving strong respond to pathogens in the gastrointestinal tract, immune system remains silent against colon microbiata. At this point "*how colon microbiota is tolerated*?" comes to mind. Mucosal immune system (MIS) is the responsible mechanism.

MUCOSAL IMMUNE SYSTEM

Mucosal surfaces, an important point of defense, is protected and regulated by mucosal immune system, which is a specialized structure of the immune system. Basic structures of MIS are mucosa associated lymphoid tissue (MALT). Malt has different nomenclatures specifically for the organs. GALT (gut associated lymphoid tissue) consists peyer's patches, appendix and isolated lymphoid follicles. NALT (Nasopharynx-associated lymphoid tissue) is located in nasopharynx. Also BALT (bronchus-associated lymphoid tissue) is situated in bronchi. Also, other organs consist of mucosal structures called small-MALT-like lymphoid aggregates. These organs are conjunctiva, larynx, ocular and nasal ducts. Although respiratory system encounters many antigens, gastrointestinal system is understood better due to further researches [19].

If we investigate MIS from a section of a colon segment, primarily Microfold cells are observed as scattered between the enterocytes. Besides, antigen presenting cells with extending podosids between enterocytes cells to lumen are seen. Other than these cells, there are epithelial cells which surround the luminal surface (Fig. 3). The duty of these three cell types is to catch microorganisms or antigenic structures within the lumen. Captured structures are presented to the lymphocytes and other immune cells situated in the lamina propria. Information of antigenic structures which processed here (memory cells, plasma cells and Ig's), transferred to surrounding tissues by the lymphatic circulation path and then delivered to every element of immune system by Ductus Thoracis. The MALT is used for structures containing lymphoid follicles showing more organization [20, 21].

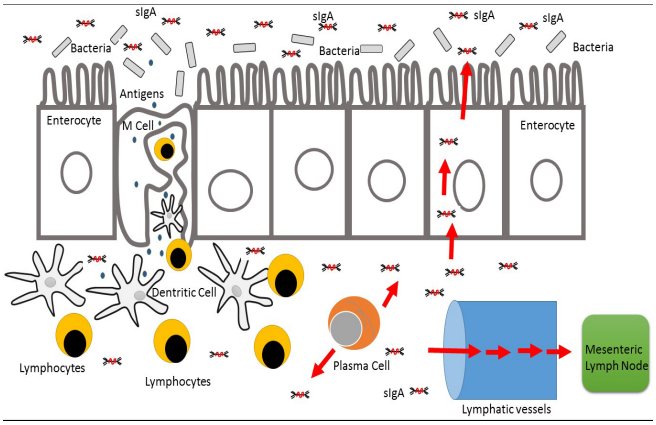

Figure 3. Mucosal Immune System Organization in the colon section. M cell: Microfold Cell, sIgA: Secretory Immunoglobulin A

Although the absence of afferent lymphatics and capsule, MALT is generally similar to the lymph nodes (B cell clusters, interfollicular T cells, antigen-presenting cells are located in MALT). MIS obtains exogenous structures (micro-organisms and other antigenic structures) by means of follicle associated epithelium (through the membrane or M cell). After processed by antigen-presenting cells, these structures would be introduced to the immune system through Thelper cells [22].

MUCOSAL IMMUNE SYSTEM AND MICROBIOTA RELATIONSHIP

Due to struggle with the microbiota of the gastrointestinal tract, 70% of immune system takes place in GIS, to regulate mucosal immune defense [23]. MIS presents nutritional antigens, microorganism derivated antigens or microorganisms themselves and immune cells in the mucosal still allowing the passage of the mucosal barrier.

MIS offers nutritional and microorganismal antigens to the mucosal immune cells within mucosa allowing the passage of mucosal barrier. With antigenic structures presented here, it is decided that which antigens/microorganisms will be answered with severe immune reaction or which antigen will be the new tolerogenic antigen [24].

As mentioned in the beginning; the human being lives with many microorganisms and this situation is also necessity for life. However there are some rules and principles of this mutualist and commensal relationship. Mucosal immune system manages this process. Through the secretion of secretory IgA, MIS decides that which microorganism belongs to microbiota or which does not belong and where they can live. Immune relationship between the host organism and microbiota is performed by sIgA under control of MIS [19, 21].

IMMUNE TOLERANCE

During the maturation of lymphocytes, T and B cell receptors are matured to be capable of recognizing numerous and various antigenic structures. Lymphocytes which recognize self-antigens are eliminated in bone marrow and thymus (Central Tolerance). Eliminated ones are not just limited with lymphocytes which indicate immune responses to self-antigens. Harmless antigenic structures of foods and commensal bacteria are accepted as the structures that must be tolerated. Except this mechanism, there are "Natural regulatory T cells" of organism which recognize self-antigens and express transcription factor Foxp3 [25]. The immune tolerance is achieved through these two mechanisms.

MICROBIOTA-MIS-DISEASE RELATIONSHIP

As noted above, microbiota has a lot of metabolic function and it is related with numerous immune mechanisms. Mucosal Immune System protects an area of 400 m^2 in the body and contains approximately 70% of immune cells. It shouldn't be thought that the structural and functional disorders of these two systems which have many tasks and a relationship won't cause any diseases.

The importance of having a healthy microbiota is understood better every day because microbiota is a training center for the immune system (especially for mucosal immune system). Every problem in microbiota will interfere with the immune system development and then the whole organism will be affected.

There is a precise predominance of Th2 over fetus's intrauterine life. After birth Th2 decrease and Th1 increase were observed for the formation of a healthy intestinal microbiota. Ultimately Th2 / Th1 ratio balance is established. With sliding of this balance towards Th2, allergic reactions increases and neutralizing of fungi and viruses gets difficult. In the opposite situation, the prevalence of autoimmune diseases increases [26-31]. In light of this information, to be exposed to various microorganisms in early life leads MIS maturation and it is provided for the formation of immune tolerance. Here not only pathogenic microorganisms should come to mind. Role of microbiota on the formation of immune tolerance cannot be undervalued [32-34]. The low frequency of infections in early life and the formation problems of normal mucosa lead to increase the dominance of Th2 cells over Th1 cells and this affects the mucosal immunity. Deformations on mucosal immunity causes deterioration of immune tolerance and many allergic diseases such as asthma are seen (Fig. 4) [35-37]. Regulatory T cells are necessary for the formation of immune tolerance. While Th2 / Th1 ratio is in balance, for the development of immune tolerance, the most important element is T regulatory cells which helps this development secreting anti-inflammatory substances (IL-10 and Transforming Growth Factor β) [38, 39].

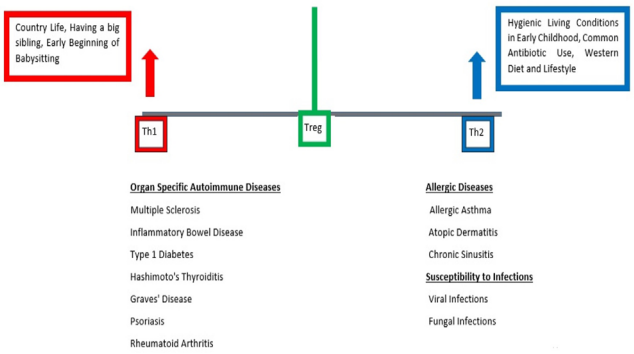

Figure 4. The diseases seen after the deterioration of balance between Th1 and Th2.

Failure of continuity of microbiota and deterioration of its internal dynamics may cause health problems. Especially, increased use of antibiotics and easy access to fast food (especially sugar derivatives) negatively affects microbiota [40]. Therefore, daily use of probiotics and prebiotics is almost becoming a necessity.

CONCLUSION

Microbiota is an indispensable organ for a healthy life. However in modern medicine, the importance of its role in the pathogenesis of diseases and contributions to immune system has recently begun to be understood. Composition, organization and concentration of colon microbiota are thought to be directly connected with pathogenesis of diseases. This situation guides us to understand the relationship between the colon structure and microbiota.

The authors declare that they have no conflict of interest.

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