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Correlation between changes in the normal gut microbiota and autoimmune Crohn's disease

[1]Liza Mariamidze, [1]Keti Kebadze, [1]Mariam Gigiadze, [2]Elene Vardosanidze, [1]Tatia Chikhladze, [2]Ana Abuladze, [1]Natia Chikhladze, [1]Mariam Dvaladze, [1]Giorgi Mariamidze, [1]Tura Mamedova, [1]Mariam Beriashvili, [3]Tea Bezhanishvili, [3]Bezhan Bezhanishvili.
[1]Tbilisi State Medical University, Faculty of Medicine, Tbilisi, Georgia;
[2]Tbilisi State Medical University, Faculty of Public Health, Tbilisi, Georgia;
[3]Petre Shotadze Tbilisi Medical Academy, Faculty of Medicine, Tbilisi, Georgia

Supervisor: Nino Didbaridze, Assistant Professor of Immunology, Tbilisi State Medical University, Tbilisi, Georgia

Abstract: Crohn's disease (CD) is a chronic inflammatory bowel disease that causes life-threatening complications. Although the etiology of CD is unknown, changes in the intestinal microbiota (dysbiosis) are considered a new factor involved in its pathogenesis. The intestinal microbiota acts as a metabolic organ and contributes to the performance of various physiological functions in human's health. Changes in the intestinal microbiota, both at the genetic and morphological levels, cause various diseases, including impact on the immune system, in view of the fact, that changes in the microbiota disrupt the strictly maintained homeostatic relationship between the microbiota and the immune system. As a result, the immune system loses tolerance to its own bacterial flora and tissues. The following review proposes to demonstrate the correlation between changes in the intestinal microbiota and the development of autoimmune Crohn's disease. Gut microbiota-based therapeutic studies have proved evidence that Crohn's disease develops in the setting of a dysregulated microbiota, suggesting that the gut flora may be a promising new therapeutic target for the treatment of CD.[5][13]
Keywords: Chron's disease (CD); Immune system; Intestine microbiota; Dysbiosys.

Introduction

Crohn's disease is a type of inflammatory bowel disease (IBD) which causes autoimmune inflammation of tissues in the digestive tract and is morphologically detected by granulomas. In patients the localization of inflammation is different, although mainly the inflammation of the small intestine develops, reaching the deep layers of the tissue. The disease is characterized by relapse, as well as periodic exacerbation and remission phases. Remission can last from several weeks to years and is not predicted.[2][4]

Depending on location, Crohn's disease can be manifested by following types:

Ileocolitis - Inflammation occurs in the small intestine and partly in large intestine. Ileocolitis is the commonest type of Crohn's disease. Ileitis - Swelling and inflammation develops in the small intestine (ileum). Gastroduodenal-Inflammation and irritation affects the stomach and the upper part of the small intestine (duodenal). The small intestine-Inflammatory areas develop in the upper half of the small intestine. Inflammation of the intestine eventually leads to its necrosis and radical intervention (e.g. excision) becomes necessary.

Crohn's disease is characterized by various morphological and physiological changes throughout the digestive tract (from the oral cavity, including the anus). During the disease following are observed: abdominal pain, chronic diarrhea, feeling of fullness, fever, loss of appetite, weight loss, abnormal skin signs (usually in the buttock area), anal fissures and fistulas, rectal bleeding.

In cases of Crohn's disease, the primary symptoms are: persistent diarrhea, pain in the groin or unexplained weight loss. Diagnosis is made by: The blood test - for large numbers of white blood

cells, which may indicate inflammation or infection. The test also gives information about low red blood cell counts or anemia. About one in three people with Crohn's disease have anemia. A stool sample is examined for checking bacteria or parasites. The main goal of this analysis is also to exclude infections that cause chronic diarrhea. Colonoscopy, Biopsy, Computed Tomography (CT), Gastrointestinal (GI) endoscopy, X-ray. [5][2]

According to EFCCA, 10 million people worldwide have Crohn's disease. The disease is observed in any ethnic origin, as well as in any age range, although it is mainly manifested by the age of 20-30.[5] The etiology of Crohn's disease, like other autoimmune pathologies, has not been studied, although there are four main theories about its development mechanism: genetic theory, antigen formation theory, infectious theory and autoimmune theory.[3]

The following article discusses the correlation between the degeneration of the normal gut microbiota and the development of Crohn's disease.

Intestine microbiome and its genome

All mammals, including humans, appear in the world from a sterile environment, after which microorganisms gradually colonize the surface of the skin, mouth and nose, genitals, respiratory tract and digestive tract, which are covered by epithelium. The human intestine is colonized by various microorganisms, the totality of which is called the intestinal microbiota, which has a reciprocal relationship with the host. The gut microbiota is a major source of microbes that can exert both beneficial and pathogenic effects on host health. In addition, the gut microbiota hosted by the gastrointestinal tract is the largest microflora exposed to the external environment and comprises approximately two-thirds of the human microbial commensal community. The establishment and development of beneficial microbiota composition occurs in early infancy, affecting health and immune homeostasis in adulthood, and disruption of this early-life microbiota establishment can have negative consequences.[13] The progression of the gut microbiome in early life goes through the following three phases: Developmental (3-14 months), traditional (15-30 months) and stable (31-46 months). Breastfeeding is the most important factor associated with the development of the microbiome. In addition to a major role in maintaining gastrointestinal homeostasis, the microbiota is also fundamental for maintaining the act of feeding, metabolic functions in nutrient digestion, detoxification, vitamin synthesis, and immunological homeostasis in the host. Although the gut microbiota includes viruses, fungi, protozoa, archaea and bacteria, the bacterial component is the most studied and maintains a symbiotic relationship with the host.[5]

The bacterial microbiota is divided into aerobic, facultative anaerobic and obligate anaerobic bacteria. The human microbiota consists of more than 1014 microorganisms that inhabit various parts of the body, among which the largest community is in the intestine. The main groups of the intestinal microbiota include Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria. In the past decade, it has been gradually revealed that the intestinal microbiome encodes 3.3 million genes, which is 100 times more than the number of human genes. Therefore, the intestinal microbiome is also called the "second human genome". The components of the intestinal microbiota are divided into three groups according to their functions, which are called commensal beneficial microorganisms, potentially susceptible pathogens and pathogenic bacteria. Components of the gut microbiota, classified as commensal "beneficial" microorganisms, maintain a healthy host environment and provide benefits, as well as interacting with host tissues in a cooperative and non-pathogenic manner. During disease, an imbalance occurs in the "sensitive" one. The greatest diversity and number of species is observed in the large intestine, and various factors such as genetics, geographical area, lifestyle, and environmental conditions influence the composition of the human gut microbiota, with changes in the microbiota during individual ontogeny mainly influencing the etiology and pathogenesis of various diseases.

Intestine microbiome and its relations with immune system

Modern research indicates that the formation of acquired immunity begins in a newborn's body with the disruption of a sterile environment. Specifically, from the moment the fetus passes through the

birth canal, commensal microorganisms, previously absent in the intestines, begin to colonize and multiply. This process is directly linked to the formation of the first acquired immune responses.
These studies are conducted on germ-free (GF) models, where animals are raised in a sterile environment and have never been exposed to microorganisms. Both the innate and adaptive immune systems of such animals differ significantly from those of normal organisms. It is also noteworthy that the normal gut microbiota shapes not only the immune system of the gut itself but also the generalized immune system of the entire body.[13]
The gut microbiota facilitates the production of IL-10 by dendritic cells in Peyer's patches and promotes the non-inflammatory proliferation of macrophages, leading to the development of so-called "inflammatory anergy." The gut microbiota establishes a homeostatic relationship and balance between microbial stimulation and the immune cell response. Research conducted on GF animals demonstrated that the reduction of gut dendritic cells was compensated by the monoclonalization of the animals with Escherichia coli. Recent studies have revealed that the recognition of peptidoglycan from the gut microbiota by the cytosolic receptor nucleotide oligomerization domain 1 (NOD1) enhances the activity of neutrophils in the bone marrow. These findings illustrate how the gut microbiota can achieve systemic immunomodulation.[5]
CD4 T-cells, CD8 T-cells, B cells, CD14 monocytes, and natural killer cells are crucial for autoimmune responses. Their production is stimulated by changes in the microbiome. Patients with Crohn's disease (CD) exhibit T cell hyperactivity and high levels of cytokines, especially IL-12 and IFN-γ.[7][4]
Natural killer cells are part of the innate immune system; they can identify transformed and infected cells and attack them using IFN-γ or perforin. Recent research has identified two types of NK cells that express the natural cytotoxic receptor NKp46 in the intestinal mucosa. One type of NKp46-positive cell in the intestine is similar to NK cells in function. However, there are other NKp46-positive cells that differ from natural killer cells due to their lack of perforin production; furthermore, they have a limited ability to produce IFN-γ. One of the main characteristics of these cells is the expression of ORPHAN receptors (IL-22, T and γ). GF (germ-free) mice do not have IL-22-producing NKp46+ cells, which may provide evidence of the microbiome's crucial role in the differentiation of IL-22+ NKp46+ cells.[12]
Decreased IL-22 levels in mice with AhR deficiency activate SFB (immune system activator), which particularly leads to Th17 cell proliferation. The microbiome also plays a significant role in the migration of mast cells from the intestinal epithelium. This occurs through the induction of CXCR2 ligands from IEC (intestinal epithelial cells) and TLR signaling. TLR signals activate specific molecules that, in turn, activate NF-κB and IRF transcription factors. This cascade triggers the innate immune response. Mast cells regulate blood flow, coagulation, smooth muscle contraction, and electrolyte exchange in the intestinal epithelium.
If mast cells and other immune cells cannot function normally, it is suspected that a person will develop an autoimmune disease such as Crohn's disease. There is evidence that patients with Crohn's disease have an abnormal microbiome, with a decreased number of Firmicutes and Bacteroides, and a controversially increased number of Proteobacteria.[13]

Correlation between intestinal dysbiosis and Crohn's disease

The change in the gut microbiota is also reflected in alterations to its microbiome, specifically, genetic changes in microorganisms provide a plausible assumption regarding the pathogenesis of Crohn's disease. T-bet is a member of the T-box transcription factor family, which plays a crucial role in the regulation of immune cells. T-bet−/−Rag−/− ulcerative colitis (TRUC) mice exhibit colonic inflammation resembling Crohn's disease in humans. Gene transfer from TRUC mice to wild-type recipients leads to the transmission of colitis. Later studies showed that the presence of Klebsiella pneumoniae and Proteus mirabilis in TRUC mice can induce colitis in SPF (specific pathogen-free) mice, but not in GF (germ-free) wild-type mice. This suggests that the development of the disease is likely influenced by the microbiota.[9][3]

Changes in the normal gut microbiota, due to the disruption of the combined functions of innate and acquired immunity, contribute to the development of Crohn's disease. Crohn's disease is a multifactorial pathology, with immune system alterations and inflammation playing a central role. The innate immune system is involved in defects in the mucosal barrier (Mut2 and FUT2 genes), which ultimately leads to intestinal necrosis, the most complicated stage of Crohn's disease. Meanwhile, the adaptive immune system relies on a TH1 lymphocytic response and TREG cells, which mediate cytokines such as TNF-α, IL-12, IL-34, and IL-23. Increased migration to inflammation sites is also associated with alterations in the extracellular matrix.[7][9]

Correlation between intestinal dysbiosis and autoimmune system

The most convincing are recent studies that demonstrate a close correlation between the disruption of homeostatic balance caused by the degeneration of the normal intestinal microbiota and the immune system, which subsequently leads to a loss of tolerance to self-tissues and an immune attack on the intestinal tissue, resulting in its inflammatory changes and the formation of granulomas, which ultimately lead to necrosis of the intestinal wall and life-threatening complications.[2] It is reasonable to assume that the increasing incidence of autoimmune diseases, including Crohn's disease, is due to significant changes in the intestinal microbiota after multifactorial causes, including dietary changes and the widespread use of antibiotics. Post-translational modification of autoantigens and cross-reactivity with autoantigens are mechanisms by which the intestinal microbiota mediates autoimmunity at the molecular level. The intestinal microbiota interferes with immune sensitivity, in particular, in the discrimination of self and non-self, which leads to the development of autoimmune diseases. This also explains why patients with any autoimmune diseases usually show signs of intestinal barrier dysfunction, which can lead to immune effects on intestinal commensal bacteria. In addition, impaired mucosal immune tolerance leads to inappropriate and pathological immune responses to the intestinal microbiota, which contributes to the severity of the disease.[2]

Conclusion

There are many reasons that lead to the degeneration of the normal intestinal flora. Wrong lifestyle, unhealthy diet, consumption of certain genetically modified foods, improperly planned diets, starvation, antibiotics, medications, viral infections and diseases, as well as various internal factors.
Crohn's disease is one of the autoimmune diseases that is still etiologically unknown. Of the existing hypotheses about its development.

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