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Analysis of the Importance of Microbiota in the Human Body in the Formation of Immunity or Immune Reactions

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Annotation: Microbiota are important for the formation, training and functioning of the host's immune system, including the human body. In turn, the immune system has largely evolved to support the symbiotic interaction of the host with these extremely diverse and evolving microbes. When the immune system and microbiota work together perfectly, they can trigger protective responses to pathogens and support regulatory mechanisms that help maintain tolerance to harmful antigens. But in high-income countries, the microbiota has become less diverse and resilient due to the overuse of antibiotics, dietary changes and the disappearance of such permanent partners as nematodes. All this is necessary for the formation of balanced immune responses. It is assumed that this phenomenon is partly due to the sharp increase in the number of autoimmune and inflammatory diseases in those areas of the world where our symbiotic relationship with the microbiota has been most affected. We will talk about what we know today about the causal interactions of the host immune system and the microbiome, the problems and limitations we face, and how they affect immune-mediated diseases. We also discuss how this data can be

used to develop future therapeutic interventions targeting the microbiome.

Keywords: Microbiota, immune system, defense reaction, human symbionts, CD4+ T cells, T helper cells.

Introduction. Multicellular organisms are meta-organisms consisting of both a macroscopic host and a commensal microbiota living inside it. Human symbionts, consisting of approximately 100 trillion cells, are at least ten times more numerous than host cells and express at least ten times more unique genes than the host gene. These complex communities of microbes, which include bacteria, fungi, viruses and other microbial and eukaryotic species, have extremely high enzymatic activity and are crucial for regulating most aspects of host physiology. In the field of immunology, over the past few years there has been a revolution in understanding the main role of the microbiota in the formation and functioning of the mammalian immune system [1,2,3,4].

The immune system consists of a complex system of innate and adaptive components that are uniquely able to adapt and respond to various hazards. In general, this cellular network supports the homeostasis of the body, allowing tissues to maintain and restore their functions in conditions of interaction with microorganisms and the environment. The mammalian immune system consists of a complex network of innate and adaptive components in all tissues and performs a vital function of protecting the body from various potentially harmful external factors and homeostasis disorders within the body. Mammals and their symbiotic microorganisms have jointly evolved towards mutualism and hemostasis from an ecological point of view [5,6,7]. The host's immunity must work properly in such close relationships so as not to use the host's resources by the commensals, while maintaining tolerance to harmful stimuli. The emergence of a complex microbiota coincided with the development of individual parts of the immune system, especially those associated with adaptive immunity, which supports the idea that most of this mechanism has evolved to maintain symbiotic relationships with these extremely diverse microbial communities. In turn, the microbiota controls and promotes the development of all components of the immune system [8,9].

In this article, we discuss and provide examples of current research and key ideas related to the development and functioning of the immune system. We identify some existing mechanistic elements of the multifaceted interaction between the microbiome and the immune system in both normal and pathological conditions. In addition, we discuss the problems and prospects of microbiome-oriented methods, such as studying the pathogenesis of diseases and developing new treatments. Since a large amount of data on the interaction of the host immune system and the microbiome cannot be summarized in one review, we will try to present the main ideas and examples of these interactions, as well as their potential impact on human health and disease risk. We also refer to numerous other reviews that have recently focused on specific aspects of these new interactions [10, 11, 12,13].

The main purpose of the presented manuscript is to conduct a brief analysis of the microbes existing in the human body in terms of their importance for immune reactions or the formation of immunity, their relevance, prospects and role in the development of diseases.

Early development of bacteria in the intestine. Microbes have an initial effect in the womb and increase significantly after birth. The gut microbiome of newborns and infants is formed and affects many things, but this is mainly due to the exchange of microbiota between mother and child. The first event of mass colonization is birth. The newborn is exposed to the microflora of the maternal vagina, feces and skin. Thus, the initial microbiome significantly affects the method of delivery, whether it is vaginal delivery or cesarean section. Babies born by caesarean section are colonized by cutaneous bacteria such as *Staphyloccocus, Corynebacterium* and

Propionibacterium, as well as *Bacteroides* and *Bifidobacterium*, as well as *Clostridioides difficile (C. difficile)* instead of vaginal microorganisms such as *Lactobacillus, Prevotella* and *Sneathia* [14, 15, 16, 17]. Interestingly, the composition of the intestinal microbiome changed within seven years after birth, depending on the method of delivery. It is still unclear how the method of delivery and subsequent changes in the gut microbiome affect the development of the immune system in the long term. In one study, the gut microbiota and immune responses of T helper cells (Th) in newborns born naturally were compared with those of newborns born by caesarean section. Infants born by caesarean section had less diversity of microorganisms, including fewer representatives of the *Bacteroidetes* type and fewer chemokines associated with type 1 T helper cells (Th1). This led to a decrease in Th1 cell response during the first two years of life [1, 11, 12, 14]. It should be noted that the function of the gut microbiome is not limited to the gut. In mice with a genetic mutation, there are no lymphoid zones in the spleen and mesenteric lymph nodes. This indicates a long-term and systemic effect of the intestinal microbiome on the host body and gives an idea of the possible pathological development of many diseases in the future. In addition, the next introduction of a normal microbiome does not seem to be able to fix some of the immune system problems caused by the defect of early interaction. The ability of mice with a genetic predisposition to gluten disease is limited to a short period at the beginning of life, after which the intestinal immune system cannot fully develop into adulthood. This shows that there is a "window of opportunity" for influencing the gut microbiome and the immune responses associated with it [17,18,19,20].

Gut microbiota and immune homeostasis. Signals from the gut microbiota have been shown to be crucial for the development of the immune system. This includes microbial-free environment (GF) models in which animals are raised in completely sterile conditions where they never come into contact with microorganisms. This effective method demonstrates the role of the microbiota in the formation of adaptive and innate immunity. In addition, the manipulation of the microbiota with antibiotics or microbiota restoration is an important proof of the role of the microbiota in immune homeostasis [1,8,11,17]. In the next section, we will look at the role of the microbiota in autoimmune diseases. It is important to note that the gut microbiota affects not only the local intestinal immune system, but also systemic immune responses. In this section, we will look at how the gut microbiota creates innate and adaptive immunity to achieve immune homeostasis [16,18,19].

The microbiome and its role in the development of the immune system. Colonization of mammalian mucous membranes at an early age is crucial for the development of the host's immune system. The main changes in host immunity can occur in the first years of life, when the composition of the microbiota changes more intra- and interindividually, before reaching a more stable form characteristic of an adult at about three years of age. However, creating such a "window of opportunity" may also make infants more susceptible to environmental effects on the microbiota, which may have negative effects on immunity in the long term [20,21,22]. Newborns and infants have a higher susceptibility to various infectious pathogens, which makes infectious diseases the main cause of infant mortality. However, premature babies are also prone to excessive inflammation. Necrotizing enterocolitis, for example, is a potentially fatal disease. To date, most studies have not revealed reproducible microbial colonization in utero, and most colonization occurs after birth, mainly due to the mother's microbiota. This first colonization is influenced by many things, for example, the method of childbirth, which affects the composition of the primary microbiota in different places of the body. It is well known that maternal antibodies transmitted with breast milk protect newborns from pathogens. A recent study showed that the commensal microbiota of pregnant mice provides protective immunity during breastfeeding, mediated by antibodies [21,22,23,24].

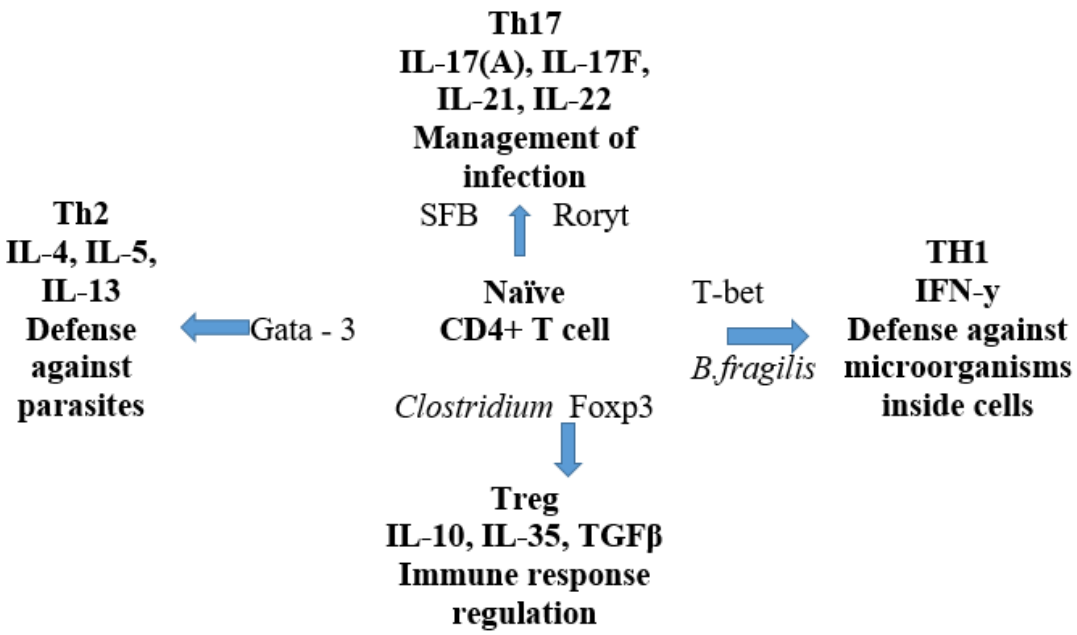

Figure 1. Differentiation of CD4+T cells occurs in commensal bacteria.

Naive CD4+T cells can be divided into four main cell classes: Th1, Th2, Treg and Th17. The induction of a transcription factor specific to each type is necessary for the differentiation of each type. As shown in the figure, after differentiation, each type secretes a specific type of cytokines. Th2 cells regulate parasitic infections, and Th1 cells play an important role in the destruction of intracellular pathogens. Th17 mainly fights infection, while Treg controls the immune response. The figure shows bacteria that are known to cause T-cell differentiation.

CD4+ T cells play an important role in the adaptive immune system. Intestinal CD4+ T cells are mainly found in the lymphoid tissue of the intestine. T helper cells 1 (Th1), Th2, Th17 and regulatory T cells (Treg) make up the four main groups of T cells that can manifest themselves when stimulating naive CD4+. The expression of various transcription factors and cytokines distinguishes these different subgroups of CD4+ T cells [23,24,25]. The gut microbiota is involved in the development of CD4+ T cells inside and outside the intestine. Thus, the number of CD4+ T cells in lymphoid tissue in mice with a genetic defect is significantly reduced. Animals with a genetic defect also do not have lymphoid zones in the spleen and mesenteric lymph nodes. Mice with a genetic defect also have a Th1/Th2 imbalance: their immune system reacts more to the Th2 response. Recent studies have even found that certain types of bacteria are associated with the development of certain subtypes of T cells. Thanks to its polysaccharide A (PSA) molecules, *Bacteroides fragilis* contributed to the development of the Th1. 18 systemic response. On the other hand, segmented filamentous bacteria (SFB) have been found to be strong inducers of Th17 LP cells [25,26,27,28].

Discussion. Microbiomes are a variety of microorganisms that live in the intestines, skin and other mucous membranes of humans. Due to the rapid development of culture-independent methods of genomic analysis, groups of genomes of bacteria and other microorganisms present in this ecosystem, such as fungi, viruses and parasites, are being actively studied. Recent microbiome studies have shown that the gut microbiome not only monitors what is happening, but also actively influences many body processes, such as circadian rhythms, reactions to nutrition, metabolism and immunity [1,5,6,8,14]. However, changes in the gut microbiome caused by environmental factors such as antibiotic use, diet, or changes in geographical location, as well as disruptions in the interaction of the host microbiome or the immune system, can cause systemic proliferation of commensal microorganisms, susceptibility to pathogenic invasion, and aberrant immune responses. The interaction of the microbiome and the immune system contributes to the development of a number of "non-communicable" diseases of the gastrointestinal tract, such as

celiac disease and inflammatory bowel diseases; They are also associated with extra-intestinal diseases such as tumors, rheumatoid arthritis, metabolic syndrome and neurodegenerative diseases. The gut microbiota and host immunity interact with each other in a complex, dynamic and changeable form [15,16,17,20]. Consequently, many more questions need to be answered in this area. A deeper understanding of the relationship between microbiota and the body has allowed the creation of microbiota-based therapies such as bacterial modulation and fecal microbiota transplantation. These methods provide the best clinical effect in the treatment of *C. difficile* infection., diabetes, inflammatory bowel disease and other diseases. Thus, we have more opportunities to treat diseases and improve our health by influencing microbial symbionts [25,2627,28].

Conclusions. Overall, this review highlights how strongly the gut microbiota affects all parts of the human immune system. This affects not only the gastrointestinal system, but also the formation and functioning of systemic immune cells. Intensive research on manipulations with the gut microbiome in the treatment of many diseases gives hope that they can influence the development of the human immune system at different stages, such as pregnancy, infancy, childhood and even adulthood, helping to prevent the development of certain diseases or treat those that have already developed.

There is an urgent need for antitumor therapy to stratify and precisely regulate tumor immunotherapy by accurately studying the gut microbiota, since the gut microbiota is more genetically diverse and manageable. Thus, further study of the effect of the gut microbiota on adaptive immunity in pathological tumor conditions and tumor treatment methods is of great importance and promising. Since adaptive immunity is a complex system, the main task will be to understand the relationship between the microbiota and various types of immune cells that affect the immune system and even tolerance, such as lymph, stroma, endothelium and epithelium cells.

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