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ORIGINAL PAPER

THE ROLE OF GUT MICROBIOTA IN IMMUNE HOMEOSTASIS

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Abstract. *The microbiota plays a fundamental role in the induction, education, and function of the host immune system. The gut microbiota has such profound effects on both the innate and adaptive immune system. Both environmental factors as well as host genetics influence the composition and homeostasis of gastrointestinal tract microbiome.*
Objectives Understanding the interaction of gut microbes with the host immune system is a timely and important health topic. The purpose of this systemic review was to collect and analyse current data of the association between gut microbiota, immune homeostasis, and Imuniplant in the management of disfunctional immune responses.
Materials and methods In this presentation we will focus our discussion on the exploration of the homeostatic relationship between the host immune system and the microbiota. Imuniplant modulation of the immune system has applications within the clinical setting, but can also have a role in healthy populations, acting to reduce or delay the onset of immune-mediated chronic diseases.
Results Alterations of these gut microbial communities can cause immune dysregulation, leading to autoimmune disorders. Imuniplant may restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration or prevention of gut inflammation and other intestinal or systemic disease phenotypes, possibly also as a genetic modulator (CARD14 gene).
Conclusion This presentation describes how Imuniplant and intestinal luminal conversion by gut microbes play a role in immune-mediated chronic diseases. Ongoing research in this field will ultimately lead to a better understanding of the role of diet and Imuniplant from Deniplant in immune function.

Keywords: gut microbiota, dysbiosis, immune homeostasis, Imuniplant

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Introduction

Homeostasis, a word of Greek origin "home = the same" and "stasis = stable", is achieved at all levels of organization (cellular, tissue and organ level), implies the stability of connections between the body and the environment through which its factors achieve certain changes in the body to stay alive and maintain its parameters within normal limits.

The gut microbiota and its metabolites have been shown to influence immune homeostasis both locally and systemically.

The human gut is an ecosystem consisting of a great number of commensal bacteria living in symbiosis with the host. The human intestinal tract harbors a complex community including 100 trillion of microbes, referred as intestinal microbiota. This diverse microbial ecosystem provides benefits to the host, essentially through its role in energy metabolism and immunity. The intestinal epithelium is the primary point of contact between our immune system and our environment (1).

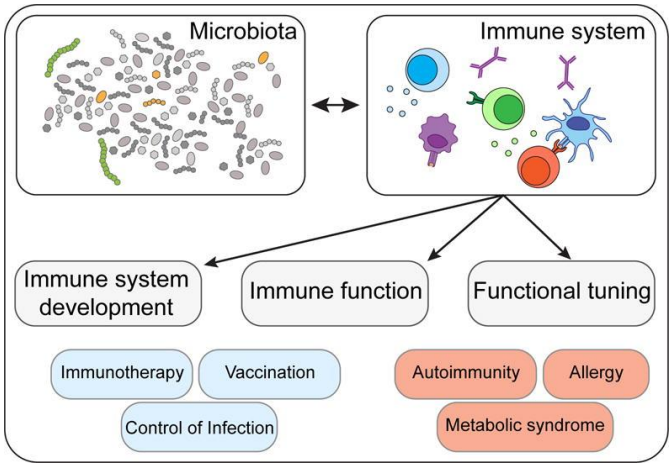

Figure 1. The microbiota plays a fundamental role in the induction, education and function of the mammalian immune system (1)

Several data confirm that gut microbiota is engaged in a dynamic interaction with the intestinal innate and adaptive immune system. The intestinal microbiota is involved in a variety of metabolic functions. Bacteria in the gut produce a number of nutrients, including amino acids, vitamin K, and several B vitamins. They also aid in the absorption of calcium, magnesium, and iron (2).

In addition, the intestinal microbiota has been shown to play an important role in energy metabolism, breaking down nondigestible carbohydrates, such as cellulose, pectins, and resistant starches (3).

An often overlooked function of gut bacteria is immune homeostasis. Bacteria in the gut influence local immunity in the intestines and can also profoundly influence systemic immunity in the body (4).

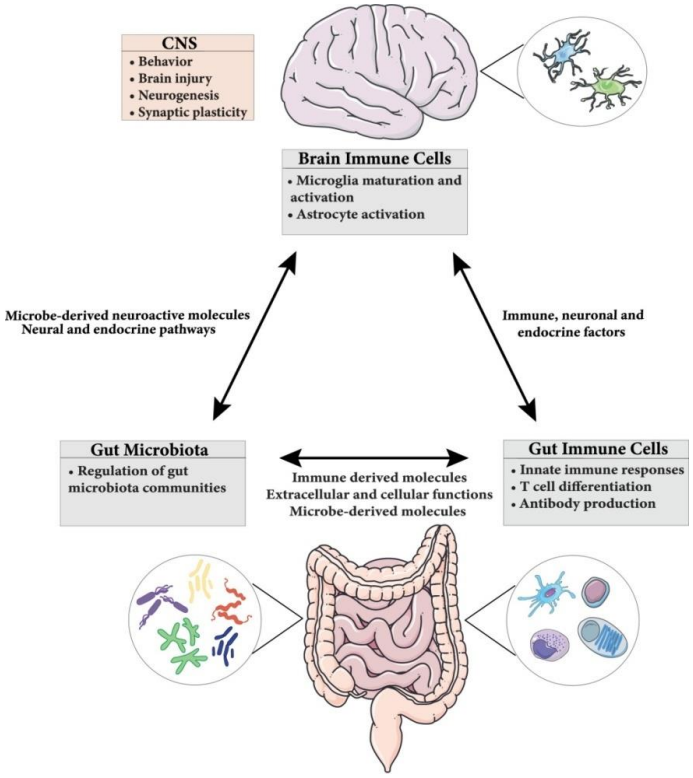

Fig. 2 Pathways of immune signaling regulating the microbiota-gut-brain axis (4)

Here we review the role of microbiota-immune interactions in the gut and the brain during homeostasis and disease and their impact on gut-brain communication, brain function, and behavior as well as the use of probiotics in central nervous system alterations.

Our first microbial colonization is obtained at birth and is determined by the method of delivery. Differences in intestinal microbiota have been noted between infants born vaginally and those delivered by Caesarean section (5).

The immune system has a vital role in the body and that is to protect it from foreign and harmful invaders. The gut microbiome - which is a collection of bacteria that reside in the gut - is being thoroughly studied in many specialities as it has such widespread effects on the body, ranging from cognitive function, behaviour, appetite, metabolism, immunity, and digestive health (the list goes on). The majority of these bacteria are located along the gastrointestinal tract, and can also be found on the skin, in the nose and ears (6).

The role of intestinal microbiota in the development of the immune system and immune responses has been well established. The relationship between microbiota and host immune responses is complicated, and their interactions occur not only in the intestine but also elsewhere in the body (7).

Accumulating evidence indicates that intestinal microflora has protective, metabolic, trophic and immunological functions and is able to establish a "cross-talk" with the immune component of mucosal immunity. The gut microbiota is acquired entirely from the mother during birth, and is subject to change under different environmental factors such as diet, age, travel, use of certain medications and disease conditions (8).

Furthermore, this microbiota can function as multicellular organ which influences hosts in a wide variety of biological processes in various ways, including gut physiology, nutrient production and absorption, host growth, metabolic functions, immune system function and inflammatory processes, energy balancing, and brain-behavior (9).

The relationship between gut microbiota and the immune system is one of reciprocity. Accumulating evidence indicates that gut microbiota-derived metabolites regulate the development and function of multiple types of immune cells, including both adaptive and innate cells.

The host immune system has evolved multiple means by which to maintain its symbiotic relationship with the microbiota. The microbiota contributes to development, maturation, and function of the immune system (10).

The gut microbiome, a term that describes the entire intestinal habitat, including resident microorganisms (the microbiota) and their metabolic byproducts, has a profound impact on systemic health ranging from immune development, metabolism, and protection from infection. The gut microbiota has a critical role in the maintenance of immune homeostasis. The role of microbiota-derived metabolites in regulating $CD4^+$ T cells is an area of intensive investigation. Effector $CD4^+$ T cells have an essential role in modulating immune-related inflammatory diseases (11).

Alterations in the intestinal microbiota and gut microbiota-derived metabolites have been recognized in many immune-related inflammatory disorders (12). These metabolites can be produced by gut microbiota from dietary components or by the host and can be modified by gut bacteria or synthesized de novo by gut bacteria (13). Some of these metabolites are involved in the pathogenesis of immune-related inflammatory diseases, such as inflammatory bowel diseases, diabetes, rheumatoid arthritis, and systemic lupus erythematosus (14).

The composition of the intestinal microbiota varies among individuals and throughout development, and is dependent on host and environmental factors. Imbalances in the gut microbiota, known as dysbiosis, can trigger several

immune disorders. Neutrophils are a crucial component of the innate immune system and a systemic influence of microbiota in the regulation of neutrophils has been demonstrated. Intestinal macrophages represent the largest population of tissue macrophages in the body. Macrophages can ingest and kill pathogens, produce proinflammatory and anti-inflammatory cytokines, and present antigens to T cells and are thus indispensable in maintaining immune responses. Increasing studies have indicated that gut microbiota-derived metabolites regulate macrophage function. Aberrations in the communication between the innate immune system and the gut microbiota might contribute to complex diseases.

The gut microbiota plays an important role in the development of $CD4^+$ T cells, both within and outside the intestine. IL-10 produced by effector T cells is an important self-regulatory mechanism for maintaining immune homeostasis. It has been established that the gut microbiota regulates the pathogenesis of various immune-related inflammatory diseases (15**).**

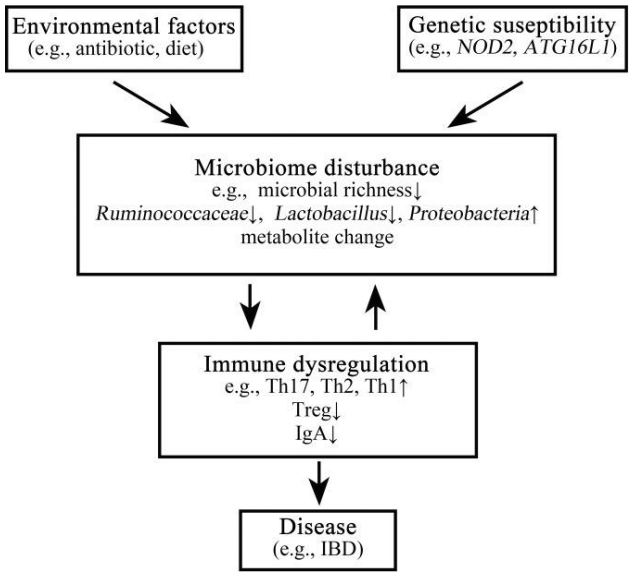

Fig. 3 Dysregulation of microbiome-immunity interaction in disease (16)

Among the microbial metabolites, short-chain fatty acids and microbial tryptophan catabolites have been shown to regulate B cell activation and antibody responses.

Interactions between the gut microbiota and the immune system are believed to impact on cancer immune surveillance (16).

Imbalances in the gut microbiota, known as dysbiosis, can trigger several immune disorders through the activity of T cells that are both near to and distant from the site of their induction.

Klebsiella pneumoniae and Proteus mirabilis worked in concert with other members of the endogenous microbial community to induce inflammation. It is not clear how the microbiota located in the gut can modulate systemic immune cells, which in turn regulate a non-gut disease. Antibiotic treatments, vaccinations and hygiene practices all can alter gut microbiota composition (17).

Many immune-related inflammatory disorders, such as inflammatory bowel diseases (IBDs), diabetes, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), have been associated with altered gut microbiota (18).

Inflammatory bowel diseases, which comprise Crohn's disease and ulcerative colitis, are chronic intestinal disorders with an increased prevalence and incidence over the last decade in many different regions over the world. The etiology of IBD is still not well defined, but evidence suggest that it results from perturbation of the homeostasis between the intestinal microbiota and the mucosal immune system, with the involvement of both genetic and environmental factors.

The crosstalk between gut microbiota and the immune system is intricate and is partially dependent on gut microbial metabolites. This process releases short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, which are essential to health and immunity. The intestinal microbiota also produces a number of other metabolites, including indoles, trimethylamine-N-oxide (TMAO), neurotransmitters, and secondary bile acids (19).

Understanding the interplay between gut microbiota-derived metabolites, the immune system, and diseases will help develop future therapeutics to treat various inflammatory diseases.

Antibiotic use was associated with the reduction of Bacteroides and Bifidobacterium and the outgrowth of Campylobacter, Streptococcus, Leuconostoc or yeasts such as Candida albicans in the intestinal microbial communities. Antibiotics might increase the risk of autoimmune disease by the microbiota-mediated immunomodulation (20).

Restoring immune homeostasis through the normalization of the gut microbiota is now considered a valuable therapeutic (21).

Dietary habit is one of the major factors influencing the diversity of gut microbiota. Diet-based alteration in nutrient availability may constitute another feasible microbiome-modulating approach, given the strong influence of diet on gut microbiome composition and function (22).

Dietary compounds, which represent a source of energy and metabolites for gut bacteria, are also appreciated to be important actors in the etiology of inflammatory bowel disease, for example by altering gut microbiota composition and by regulating the generation of short chain fatty acids.

A massive effort during the past decade in studying microbiome-immune interactions has led to better understanding of their molecular basis (23).

An unbalanced diet that is low in fresh fruits and vegetables is already associated with accelerated aging and the early onset of disease. The highest levels of betaine are found in those with a high intake of food sources rich in betaine, such as quinoa, spinach, fortified cereal products, bran, and beets. Since fruit and vegetable intake is lower in some socioeconomic groups, the researchers believe this may partly explain their low betaine levels. The researchers focused their study on the microbiota captured by circulating white blood cells in the body. They found that those who were biologically older had significantly more pathogenic bacteria, while those with younger biological age had more salutogenic bacteria (bacteria that support human health and well-being), key to good physiological function. These academics also believe that the abundance of pathogenic bacteria found in those with a low socioeconomic status, combined with their lower levels of good nutrients like betaine, may explain why people in these groups are biologically older than their counterparts. from higher socioeconomic levels. The microbiota also influences the immune system. The protective mucus at the interface between the intestinal mucosa and the intestinal lumen is where most of the interactions between the host and microbes take place, and the exchange of molecules between the mucous layer and the epithelium facilitates the communication between the intestine and the immune system regarding the recognition of self from non-self structures.

The objective was to demonstrate role of Imuniplant in the management of disfunctional immune responses. Imuniplant modulation of the immune system has applications within the clinical setting, but can also have a role in healthy populations, acting to reduce or delay the onset of immune-mediated chronic diseases. Ongoing research in this field will ultimately lead to a better understanding of the role of diet and Imuniplant from Deniplant in immune function. A dysfunctional immune system can cause a whole range of pro-inflammatory conditions like impaired gut function, weakened responses to new infection as well as a high metabolic burden. Imuniplant may restore the composition of the gut microbiome and introduce beneficial functions to gut microbial communities, resulting in amelioration or prevention of gut inflammation and other intestinal or systemic disease phenotypes. This presentation describes how Imuniplant and intestinal luminal conversion by gut microbes play a role in immune-mediated chronic diseases.

Imuniplant tea is a natural immunomodulator of the human microbiome.

Removing dysbiosis from the microbiota can prevent and eliminate pain; regulates cellular metabolism; regulates the central nervous system; modulates the activity of important neurotransmitters; physically and mentally energizing; remineralizing; increases fatigue resistance.

In 2019 it was established the Center for Biomedicine (www.deniplant.ro/biomedicina) to combine the two sciences, biology and medicine, where we try to find the link between autoimmune diseases, metabolic, neurological, genetic and human microbiome. Here we try to elucidate the causes of disease and to find new ways to diagnose and fix them by modulating natural microbiome. One of the issues studied was the relationship between hives and microbiome, we presented it in the paper.

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Conclusions

It is not entirely clear how bacteria and possibly other microbiome constituent species affect the immune system. Research has shown that intestinal bacteria have an important role to play in maintaining homeostasis and regulating immune function. Several reports provide direct evidence that demonstrates the pivotal role of the gut microbiota in regulating the development of antigen presenting cells. The intestinal epithelium is the primary point of contact between our immune system and our environment. Gut microbiota interacts with both innate and adaptive immune system, playing a pivotal role in maintenance and disruption of gut immune quiescence. Alterations of the gut microbiota may cause dysregulated mucosal immune responses.

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