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A STUDY ON MICROBIOME CONTRIBUTIONS TO IMMUNE DYSFUNCTION AND DISEASE PATHOGENESIS

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ABSTRACT

Both the functioning of the immune system and general health are strongly influenced by the human microbiome, which is comprised of a wide variety of microbial communities that occupy different parts of the body. The microbiome is responsible for the training and development of significant components of the innate and adaptive immune systems of the host, whereas the immune system is responsible for orchestrating the preservation of essential aspects of the symbiotic relationship between the host and the microorganism being studied. In a host that is genetically vulnerable, it is hypothesized that abnormalities in the interactions between microbiota and the immune system under certain environmental conditions contribute to the pathogenesis of a wide variety of immunological-mediated illnesses. The dysfunctional relationship that exists between the microbiome and the host has been related to a number of illnesses, including malignancies, metabolic deficits, autoimmune disorders, and infectious diseases. A deeper understanding of the ways in which the immune system interacts with other systems inside the body has led to the opening of new research pathways, one of which is the study of the microbiome. Through the investigation of the complex interaction that exists between the microbiome and immunological dysfunction, this research sheds light on the role that the microbiome plays in the development of a number of immune-mediated disorders.

Keywords: Microbiome, Immune system, Dsyfunction, Dysbiosis, Microbial

I. INTRODUCTION

Throughout life, the billions of microbes that call different parts of the human body home (the microbiome) modulate immune responses. In a complex and ever-changing way, the microbiome affects immune function. Both directly and indirectly, commensal microorganisms affect immune cell development, cytokine production, and the balance of pro- and anti-inflammatory responses via microbial metabolites. For example, certain bacterial species increase immunological tolerance by inducing regulatory T cells (Tregs), whereas other bacterial species cause tissue damage in autoimmune diseases by stimulating inflammatory responses. The immune system must be able to generate efficient responses against infections while tolerating innocuous antigens and preserving tissue integrity, and these interactions are critical for achieving and maintaining immunological homeostasis.

The role of dysbiosis, or an imbalance in the microbiome's composition or function, in immunological dysfunction and disease etiology is becoming more and more apparent. Changes in the composition of the gut microbiome may cause inflammatory bowel disease

(IBD) and other inflammatory bowel diseases by weakening the intestinal barrier and triggering persistent inflammatory reactions that target commensal bacteria. In autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, dysbiosis has also been linked to the breakdown of immunological tolerance mechanisms that are impacted by the microbiome, leading to abnormal immune responses that target host tissues.

In addition to autoimmune and inflammatory diseases, metabolic disorders, and malignancies are all affected by the microbiome. Obesity, insulin resistance, and dyslipidemia are the hallmarks of metabolic syndrome, which has been associated with certain microbial traits that foster persistent low-grade inflammation and metabolic dysfunction. The microbiome has a role in cancer by influencing immune surveillance and tumor responses. New research indicates that microbial communities in many places, including the gut, may modulate systemic immune responses, which in turn affects how well cancer progresses and how well treatments work.

The study of the microbiome and its relationships with the immune system in both healthy and sick states has been greatly enhanced by recent developments in computational biology and high-throughput sequencing. Through the use of these technologies, complex microbial community structures have been uncovered, and microbial signatures linked to various diseases have been established. Also, experimental models like gnotobiotic and germ-free mice have shown important connections between changes in the microbiome and immunological dysfunction, which might lead to new treatments.

There are substantial clinical implications and scholarly interest in understanding the microbiome's roles in immunological dysregulation and disease etiology. The use of probiotics, prebiotics, dietary changes, and fecal microbiota transplantation (FMT) to target the microbiome is an exciting new area of personalized medicine. The goals of these methods are to improve immunological function, reduce symptoms of immune-mediated diseases, and restore microbiome harmony. Nevertheless, there are still obstacles to overcome in order to turn the results of microbiome studies into practical treatments. These include, among other things, the fact that people's microbiomes react differently and the need of conducting thorough clinical trials to confirm the effectiveness and safety of any potential treatments.

II. MICROBIOTA AND INNATE IMMUNE CELLS INTERACTION

An efficient regulator of microbiota composition is a-defensins (DEFA), which are secreted by Paneth cells and other epithelial cells. These cells govern the microbiota. A decrease in the amount of IL-17A+ CD4+ T cells in the lamina propria has been associated with a decrease in segmented filamentous bacteria (SFB), which in turn may cause a change in mucosal responses towards an inflammatory phenotype in DEFA-deficient animals. Loss of human defensin gene expression Patients are more likely to develop Crohn's disease of the ileum when Paneth cells affect the luminal microbiota with human a-defensin (HD)5 and HD6. The ileum of Paneth cells is an important site for the expression of the antimicrobial lectin RegIII, which stands for regenerating gene family protein III. Bacterial gut colonization and pathogenic infection cause a rise in RegIII expression, which in turn causes inflammation, kills Gram-positive bacteria,

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and limits the activation of adaptive immunity. Only the mucosal surface is able to facilitate RegIII diffusion. So, it physically isolates the microbiota from the surface of the epithelial cells. The colonization of mucosa by Gram-positive bacteria, namely Bacteroidetes and Firmicutes phyla, was enhanced in RegIII-deficient animals.

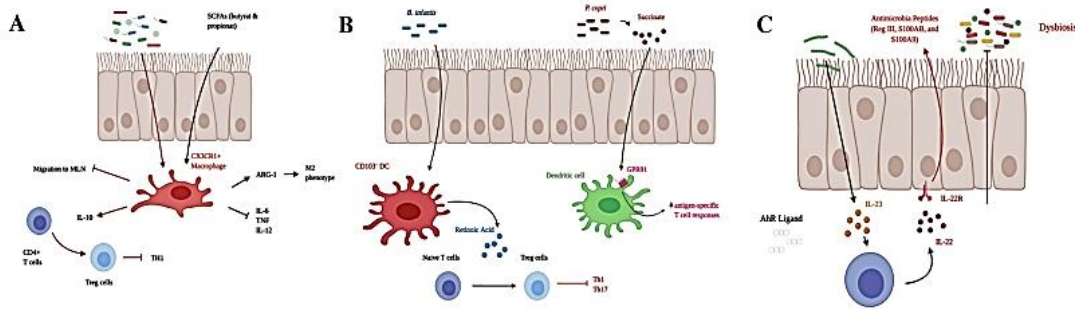

Figure 1: Crosstalk between microbiota and innate immune cells

Intestinal homeostasis and adaptive immunity to microbiota are both significantly influenced by lamina propria macrophages. In both the small and large intestines of the mouse, CX3CR1þ macrophages establish an interconnected network along the whole vascular lamina propria of the mucosa during the steady-state. These cells are like a protective barrier that stops germs from entering the bloodstream. In dysbiosis, there is a disruption in the normal network of macrophages, which allows more germs to pass from the lamina propria into the circulation. Tolerance to the gut microbiota is induced by CX3CR1þ macrophages via the production of IL-10 and antigen function, which limits Th1 responses and encourages the formation of Treg cells (Fig. 1A). In the tolerogenic intestinal environment, microbiota play a role by restricting the movement of CX3CR1þ macrophages that have been trapped by antigens from the luminal to the mesenteric lymph nodes. Colonic macrophages' production of pro-inflammatory cytokines including IL-6, TNF, and IL-12 may be modulated by SCFAs released by commensal bacteria, namely butyrate and propionate, by blocking the activity of histone deacetylases (HDACs). Another mechanism by which butyrate activates macrophages is via increasing production of arginase 1, which in turn increases polarization of the M2 phenotype. Macrophages help defend the body from viral infections by responding to Clostridium orbiscindens' polyamine desaminotyrosine (DAT) in the stomach with type 1 interferon responses.

The microbiota also controls how neutrophils are made and how they function. The pro-inflammatory actions of neutrophils vary due to their diversity. As we become older, our neutrophils become more active and respond to priming signals sent by innate immune receptors such Toll-like receptors (TLRs), natural killer cells (NLRs), and pathways involving MyD88. Depletion of microbiota is linked to a dramatic and specific decrease in neutrophils in the blood and bone marrow, which in turn slows the ageing process of neutrophils. As neutrophils age, a functionally active fraction of neutrophils may be generated by a number of chemicals produced from microbiota, including LPS and peptidoglycan.

Intestinal dendritic cells (DCs) collect bacteria samples directly from the gut lumen by projecting dendrites beyond the epithelium. Immunoglobulin A (IgA) and local protective mucosal immune responses are induced by these DCs, whereas unneeded systemic immune responses are suppressed. Mesenteric lymph nodes are restricted by these DCs. Intestinal CD103+ DCs may be influenced in frequency and function by commensal bacteria and the compounds they produce. The commensal gut bacteria Bifidobacterium infantis increases the number of CD103+ dendritic cells and upregulates the enzyme retinaldehyde dehydrogenase, leading to an increase in regulatory T cells and a reduction in Th1 and Th17. Several commensals, including Prevotella species, generate succinate, which in turn enhances the antigen-specific T helper cell responses by signaling GPR91 (G-protein coupled receptor 91) in DC (Fig. 1B).

The innate lymphocyte cells known as innate lymphoid cells (ILCs) mirror the characteristics and roles of the CD4+ T helper subsets and are found mostly on the surface of the immune system's protective barrier. Intestinal homeostasis and the regulation of epithelial cell responses are both significantly impacted by the IL-17 generating RORgtþ ILC3. At steady condition, the main source of IL-22 in the intestinal tissue is RORgt þ ILC3. Since epithelial cells in the colon are the primary loci of IL-22R expression, this molecule may be able to inhibit bacterial invasion by inducing the synthesis of anti-microbial peptides such RegIIIg, RegIIIb, S100AB, and S100A9. As shown in Figure 1C. The aryl hydrocarbon receptor (AhR) detects components obtained from the microbiota, such as indole-3-lactic acid, which is produced after the breakdown of dietary tryptophan. It is a ligand-dependent transcription factor. IL-22 production, ILC maturation, immunity to infections like Citrobacter rodentium in mice, and AhR expression on RORgt þ ILCs are all essential. Commensal bacteria have the ability to control RORgt þ ILCs directly by the generation of tryptophan metabolism, which they may activate after hyperpolarization (AhP). Indirect regulation of ILCs by commensal bacteria is possible via modification of responses by myeloid cells or epithelial cells. While things are running well, commensal bacteria encourage the synthesis of IL-1b in intestinal macrophages, which have the ability to produce IL-22 from RORgt þ ILCs (Fig. 1C).

Alterations to the microbiota's make-up are another potential consequence of ILCs. Commensal SFB and Alcaligenes species linked to colitis may flourish due to ILC3's decreased IL-22 production. Alterations to the microbiota in inflammatory bowel disease (IBD) patients may be caused in part by IL-22, although elevated IL-22 production may exacerbate dysbiosis via other processes, such as changing the amount of antimicrobial peptides. The permeability and translocation of nonpathogenic microorganisms across the intestinal epithelial cells are enhanced by IFN-g and tumor necrosis factor, which are generated by T-betþ ILCs (Fig. 1C).

III. DYSREGULATION OF MICROBIOME-IMMUNITY INTERACTION IN DISEASE

Complex immune-mediated illnesses may arise in genetically predisposed people due to aberrant interactions between the microbiota and the host's immune system (Fig. 2). Cancer, inflammatory bowel disease (IBD), cardiometabolic disease (CMD), and systemic autoimmune

disease (SAD) are some of the best researched instances of these. Further human research are needed to confirm the proposed modulatory role of the microbiomeimmunity relationship in other'multifactorial' illnesses, such as neurodegenerative disorders. Notably, it is still not known if the microbiome is the direct cause of immunological dysregulation in the majority of the aforementioned human illnesses.

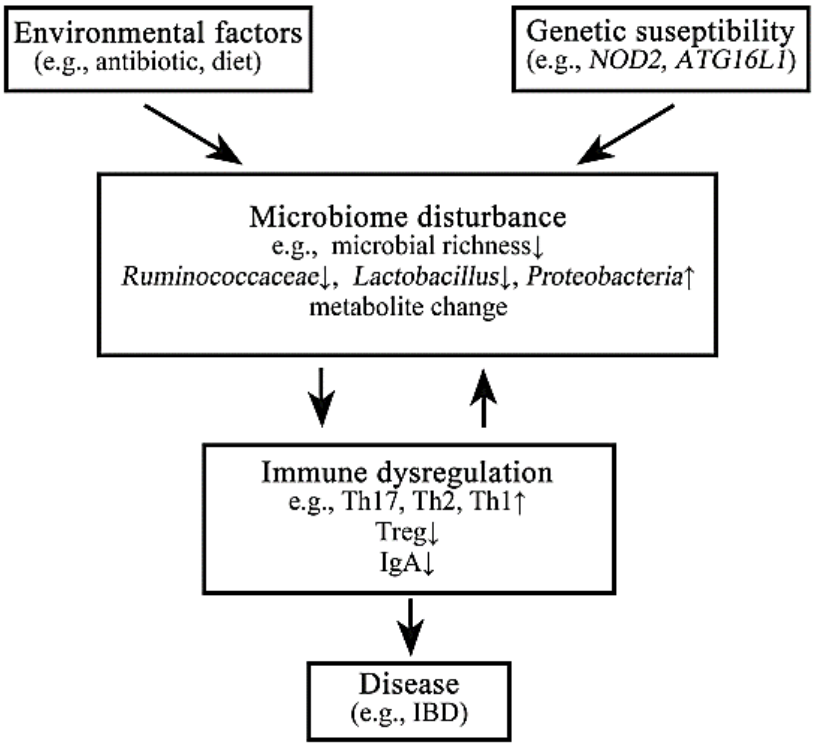

Figure 2: Dysregulation of microbiome-immunity interaction in disease

An increasing number of people throughout the world are living with inflammatory bowel disease (IBD), which mostly includes Crohn's disease (CD) and ulcerative colitis. Gut microbiome alterations are crucial to the pathophysiology of inflammatory bowel disease (IBD), according to many lines of evidence. Included in this are changes to the metabolite profiles associated with the microbiome as well as a decrease in bacterial diversity and an increase in the abundance of certain bacterial taxa, such as Gammaproteobacteria and Enterobacteriaceae, and a decrease in the abundance of Bacteroides, Firmicutes, Clostridia, Lactobacillus, and Ruminococcaceae. Translocation of bacterial symbionts into the mucosal layer occurs when the strictly controlled intestinal barrier is broken down. This process fuels abnormal host immune responses and tissue destruction. Therefore, it is thought that AMP secretion, epithelial cell junctions, and mucus layer abnormalities all contribute to the development of inflammatory bowel disease (IBD).

IV. MICROBIOTA IN DIAGNOSIS AND TREATMENT

Recognizing microbiota as agents of illness treatment and diagnostics should follow the discovery of diverse functions for bacteria in particular diseases. The use of prebiotics is one

of many potential modes of microbial participation in therapy that are now under investigation. A significant clinical burden in healthcare, recurrent CDI is a major nosocomial diarrheal illness (CDI). Fecal microbiota transplantation (FMT) has been used as a therapy for CDI. Microbiota-based medicines aim to address CDI, which is now known to be associated with an imbalance in the gut flora. FMT refers to the practice of transferring feces from a healthy patient to one who is experiencing gut dysbiosis. The use of colonoscopy to administer FMT has shown promising results in the management and prevention of CDI. The recipient's microbiota is restored when it reduces proinflammatory cytokines like IL-6 and TNF-α and increases antiinflammatory bacteria like Lactobacillaceae and Ruminococcaceae. More research on FMT is needed to see whether it is safe and if it may affect other disorders. An intriguing link between the microbiome and allergies has recently emerged, suggesting that bacteria influence the immune system and lead to allergic reactions. A combination of prebiotics, probiotics, and synbiotics may be all that's needed to alleviate some allergies; these three types of microbes work together to control the resident microbiome, which in turn increases variety and normalizes the gut flora. Simple dietary changes to increase diversity of the gut microbiota may be effective treatments.

Despite the potential benefits of probiotics and prebiotics, little is known about the diseases they may cause since they are not unique to any one bacteria. Another possible therapy strategy is the use of bacteriophages to target harmful bacteria or bacteria that are overrepresented in disorders related to the microbiome. Research has shown that bacteriophages have the ability to focus on certain bacteria in the gut microbiota and eliminate them, while also affecting bacteria that are not intended to be targeted. Because microbiota in the gut and elsewhere are so highly interdependent, it is reasonable to assume that there will be an off-target cascade of effects in the microbiome.

The gut microbiome may influence the body's reaction to vaccinations because of its strong ties to immune system development and response in the intestines. Therefore, microbiota might be an avenue to explore for improving vaccination effectiveness. While Pseudomonadales, Enterobacteriales, and Clostridiales have been linked to reduced vaccination responses, Bifidobacteria have been shown to have a positive correlation with CD4+ T cell response to certain vaccines, including bacillus Calmette-Guerin, oral polio vaccine, tetanus toxoid, and hepatitis B vaccine. To improve immunological memory and provide greater protection against viral infections, more research into the relationship between microbiota and vaccination effectiveness is necessary. As our knowledge of the ecological principles governing the system expands, treatments that include the microbiome will also develop.

V. CONCLUSION

From metabolic syndromes and cancer to autoimmune illnesses and inflammatory disorders, the microbiome and the immune system interact in complex ways that impact health outcomes. Disruptions in the composition and function of microbes, known as dysbiosis, are crucial in initiating and worsening immunological dysregulation, which in turn contributes to the development and progression of illness.

Applying this information in the future might lead to the creation of new treatment approaches that improve immune function and restore the balance of microbes. Possible strategies to influence the microbiome to enhance immunological tolerance, decrease inflammation, and improve clinical outcomes include fecal microbiota transplantation (FMT), dietary changes, probiotics, and prebiotics. The complexity of microbial interactions within host ecosystems, the need for rigorous clinical validation of therapeutic interventions, and variability in microbial responses among individuals are some of the challenges that must be addressed in order for microbiome research to be translated into clinical practice.

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