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Essay

Probiotics and Intestinal Microbiome: A Review of Literature

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Abstract: Probiotics, prebiotics, and synbiotics modify various aspects of local and systemic immune function in multiple experimental models. However, their impact and mechanisms of action are not known across all products or noticed in every population studied, and impacts on *in vitro, ex vivo*, or other measures of immune function do not necessarily result in an impact on infection and illness *in vivo*. Studies have discussed that intestinal microbiota has an essential role in enhancing the immune system against viruses. The regulatory impact of the intestinal microbiota on viral infection is connected with local and systemic immune responses and plays a part in congenital and adaptive immune responses. The microbiota composition critically modulates the production of virus-specific CD4 and CD8 T cells and antibody responses following influenza virus infection. The intestinal microbiota has an important role in the stabilizing of immune homeostasis by augmenting the integrity of the barrier functions of the gut mucosa, which is a crucial aspect of systemic immunity. In conclusion, the intestinal microbiota can influence organismal immunity locally and systemically, proximally, and distally. Studying the possible mechanism by which the intestinal microbiota maintains host immunity can provide a clearer understanding of the occurrence and development of diseases.

Keywords: Probiotics, Prebiotics, Synbiotics, Intestinal Microbiome, Microbiota, Review

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Review

Historically, the approaches that were popular for targeting and modifying the gut microbiota have involved introducing new bacteria into the community and supporting substrate to feed good community members [1]. The previous approach relies on probiotics, known as "live microorganisms that, when taken in appropriate amounts, reflect a health benefit on the host" [2]. On the contrary, the latter approach depends on prebiotics, defined as "substrates [e.g., nutrients] that are selectively used by host microorganisms [e.g., gut microbes] offering a health benefit" [3]. Though there are few ready prebiotics at present, several oligosaccharides, polysaccharides, and other compounds are considered "candidate prebiotics" [3], because their usage by gut microbes is considered to provide a health benefit. Synbiotics are a mixture of probiotics and prebiotics. Probiotics, prebiotics, and synbiotics modify various aspects of local and systemic immune function in multiple experimental models [4, 5]. However, their impact and mechanisms of action are not known across all products [i.e., bacterial strains, or prebiotic type] or noticed in every population studied, and impacts on *in vitro, ex vivo*, or other measures of immune function do not necessarily result in an impact on infection and illness *in vivo*. As such, proof for synthesis and recommendations for utility require

attention to the form of the intervention itself, needed outcomes, and target population [6].

Studies have discussed that intestinal microbiota has an essential role in enhancing the immune system against viruses [7, 8]. The regulatory impact of the intestinal microbiota on viral infection is connected with local and systemic immune responses and plays a part in congenital and adaptive immune responses [9, 10]. The intestinal microbiome may prevent or upgrade viral infections, essentially *through* bacterial components, and metabolites, and control the immune response of the host [11, 12].

Recently, the most popular experimented probiotics include *Lactobacillus, Bifidobacteria, Escherichia coli, Enterococcus*, etc. Although probiotics' mechanism greatly focuses on the GIT, the action of probiotics is not restricted to the primary infection site. Probiotics can affect the whole body through immune regulation. Probiotics and their metabolites are phagocytosed by small cells to form endosomes in gut-associated lymphoid tissues. These antigens are suddenly produced and held by Dendritic cells (DCs), which can transfer them to local lymph nodes which results in the activation of naive T and B cells to differentiate into various effector subpopulations. This promotes the increase of the relevant cytokines and different immune responses [12].

Pleiotropism of probiotics form enhancement of biological barriers in the GIT and regulating the balance of intestinal microbiota. Probiotics have antimicrobial action, maintain intestinal epithelial cell function, prevent adhesion and growth of pathogens through a space-occupying effect, boost competitive antagonism, secrete antimicrobial substances as bacteriocins, augment the activity of digestive enzymes, and synthesize organic acids [12, 13]. Probiotics enhance the expression and production of mucous glycoproteins through intensified tight junction proteins synthesis between epithelial cells, thereby enhancing epithelial integrity and mechanical barrier function, and inhibiting the displacement of the intestinal microbes and endotoxins. Besides, Probiotics can repair the damaged barrier function through reconstruction of the tight junction complex via increased expression and redistribution of zonula occludens (ZO-2) proteins of the tight junction and protein kinase C (PKC) [13, 14]. The administration of probiotics inhibits cytokine-induced epithelial destruction, which is also assigned to mucosal barrier enhancement. Moreover, probiotics reinforce mucous secretion and provide better barrier function and pathogen exclusion. Probiotics also prevent pathogen adherence by promoting qualitative alterations in intestinal mucins [14, 15]. Excitedly, the bacterial component also degenerates into an AMP, which gives anti-pathogenic characteristics to the host. This provides an example of the great beneficial pleiotropic effect of large surface proteins. Besides, probiotics also activate the production of defensins from epithelia, the small peptides act against bacteria, fungi, and viruses. Additionally, these peptides maintain the barrier function of the gut. Probiotics prevent the binding of the pathogen through steric hindrance at pathogen receptors of the enterocyte. Certain metabolites of probiotics regulate signaling and metabolic pathways in various cells. Different components of the probiotic metabolome (e.g., hydrogen peroxide, amines, organic acids, and bacteriocins) interact with many targets in host metabolic pathways that adjust inflammation, angiogenesis, metastasis, cellular proliferation, differentiation, and apoptosis [15].

Short-chain fatty acids (SCFAs) are the most essential metabolites of the intestinal microbiota, involving acetic acid, propionic acid, and butyric acid. SCFAs decrease the growth and binding of pathogenic microorganisms, enhance the integrity of the epithelium, and further improve systemic host immunity by decreasing the intestinal pH, resulting in increasing the production of mucin [13, 14]. SCFAs induce G protein-coupled receptors (GPCRs) and prevent histone deacetylase (HDAC) to provide their biological functions [15]. Per a study by Trompette *et al*. [12], SCFAs also modulate the hematopoietic function of Ly6c(-) patrolling monocytes, prompt the function of CD8 T cells, and induce GPR41 to supply protection against influenza virus infection [16]. Besides SCFAs, there

are multiple other metabolites of the intestinal microbiota that are recorded to be related to host immunity. Pyruvate and lactate, which are released by the intestinal microbiota, help to improve immune responses by activating the growth of GPR31-mediated CX3CR1+ dendrites in the gut [17]. Research by Steed *et al*. [17] discussed that desaminotyrosine (DAT), a metabolite of the intestinal microbiota, prevents influenza infection by increasing type I IFN signaling in macrophages [18].

Toll-like receptors (TLRs) are pattern recognition receptors (PRRs). In innate immunity, TLRs identify pathogen-associated molecular patterns (PAMPs). TLRs can place bacterial flagellin and single-stranded viral RNA to regulate antiviral and antibacterial immune responses [19, 20]. Influenza virus infection markedly raises the mRNA expression of TLR7 in lung immune cells. Antibiotic-induced dysregulation decreases the expression of genes included in the TLR7 signaling pathway, while probiotic administration maintains the initial expression upregulation of genes, such as TLR7 [21]. Moreover, the microbiota composition critically modulates the production of virus-specific CD4 and CD8 T cells and antibody responses following influenza virus infection [22]. The intestinal microbiota has an important role in the stabilizing of immune homeostasis by augmenting the integrity of the barrier functions of the gut mucosa, which is a crucial aspect of systemic immunity [23, 24]. Furthermore, the beneficial intestinal microbiota plays an essential role in modulating TLR 7 signal transduction, which was found to alleviate common mucosal immune system (MIS) destruction caused by antibiotic treatment in mice [21]. However, if microbiota is disrupted for any reason, a reduction in the non-pathogenic dominant microbiota members declines the extent of colonization resistance, resulting in colonization and overgrowth of the opportunistic pathogens in the vacant nooks. A well-known example of this issue is the infection with *Clostridium difficile* which can cause pseudo-membranous colitis, sepsis, and death in severe cases [24].

Furthermore, a lot of researchers are studying how the gut microbiome affects immunity in different parts of the body, such as the lungs, brain, and liver. For example, disturbance in the microbial community in the lungs, involving the airways, can change the composition of the intestinal microbiota. In addition, some gastrointestinal diseases are also combined with changes in the respiratory tract [25]. The transfer of immunomodulatory signals and the transduction of metabolites between the lungs and gut form the gut-lung axis [26]. The intestinal and respiratory mucous membranes supply physical barriers to microbial penetration, and the colonization of the normal microbiome is resistant to pathogens. Bacterial travel from the gastrointestinal tract to the lungs has been noticed in sepsis and acute respiratory distress syndrome, in which barrier integrity is damaged [27, 28]. The gut-brain axis is related to the two-way information network between the intestinal microbiota and the brain. In the intestine, segmented filamentous bacteria can maintain the functions of B and T lymphocytes [29]. T lymphocyte receptors (TLRs) are also widely spread on neurons [30]. Therefore, gut epithelial cells transfer viral and bacterial metabolites to the inner environment, neurons respond to microbial components, and the nervous system interacts with these bacterial and viral components. The equilibrium of the intestinal Microbiota may change the modulation of the inflammatory response and may participate in regulating emotion and behavior [31, 32]. Though the liver is exposed to gut-derived microbial metabolites and components, intestinal dysbiosis is included in liver disease, inflammation, and fibrosis [33]. The gut-liver axis is also connected with autoimmune liver diseases, like primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) [34].

In conclusion, the intestinal microbiota can influence organismal immunity locally and systemically, proximally, and distally. Studying the possible mechanism by which the intestinal microbiota maintains host immunity can provide a clearer understanding of the occurrence and development of diseases [35].

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