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Commentary

Gut microbiota-immunity interaction and personalized immune response

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Commentary

As presented in our previous article [1], the human immune system is built upon a genetic framework passed down through countless generations. Traditional dietary habits rooted in specific ethnicities have fostered profound immune diversity, enabling adaptation to harsh environmental conditions and ultimately ensuring survival. Consequently, it's evident that each individual's immune characteristics are uniquely shaped by a combination of racial background, environmental exposure, and dietary practices.

Over the past few decades, growing scientific understanding has revealed the significant influence of both symbiotic and parasitic microorganisms on immune function. Therefore, when exploring immune diversity at an individual level, gut microbiota emerges as a crucial factor. Notably, the gut microbiota consistently plays a leading role, largely due to the continuous interaction between humans and the food and water they consume. In this commentary, the author would like to offer a deeper perspective on the intricate molecular signaling pathways that mediate the interaction between the gut microbiota and the immune system, as well as the role of dietary habits - determined by racial characteristics and cultural environment - in shaping personalized immune responses through gut microbiota modulation.

Molecular Signaling Interactions Illustrating the Relationship between Gut Microbiota and the Immune System

The gut microbiota and the host immune system maintain a dynamic and reciprocal relationship, primarily coordinated through molecular signaling mechanisms. These interactions are essential for immune system maturation, tolerance to commensal organisms, and defense against pathogens. At the molecular level, various signaling pathways facilitate this crosstalk, including microbe-associated molecular patterns (MAMPs), bacterial metabolites, and host pattern recognition receptors (PRRs).

One of the primary signaling mechanisms occurs through PRRs on immune and epithelial cells [2]. PRRs are specialized proteins expressed by cells of the innate immune system that recognize conserved molecular structures on pathogens or damage-associated molecules. PRRs such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) detect conserved bacterial components known as pathogen-associated molecular patterns (PAMPs) [3], including lipopolysaccharides, peptidoglycan, and flagellin [4]. For example, TLR4 recognizes lipopolysaccharides from Gram-negative bacteria [5], activating NF-κB [6] and inducing the production of pro-inflammatory cytokines like interleukine-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [7], which regulate both innate and adaptive immune responses.

Beyond direct recognition, gut bacteria secrete metabolites that signal to the immune system. A prime example is short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, produced

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through dietary fiber fermentation [8]. These SCFAs bind to G protein-coupled receptors (GPCRs) like GPR43 and GPR109A on immune cells, influencing T cell differentiation and promoting anti-inflammatory responses [9,10]. Notably, butyrate also acts as a histone deacetylase inhibitor (HDACi), altering gene expression and fostering the development of regulatory T cells (Tregs) [11], which are essential for maintaining immune tolerance.

Secondary bile acids, modified by gut bacteria, impact nuclear receptors like Farnesoid X Receptor (FXR) and Pregnane X Receptor (PXR), modulating inflammatory responses and maintaining epithelial barrier integrity [12]. Similarly, tryptophan metabolites produced by certain gut bacteria can activate the aryl hydrocarbon receptor (AHR) on epithelial and immune cells, contributing to barrier function and cytokine regulation [13]. Furthermore, intestinal epithelial cells (IECs) serve as both physical and immunological barriers. They express PRRs and respond to bacterial signals by releasing antimicrobial peptides (AMPs), cytokines, and chemokines that coordinate immune cell recruitment and bacterial control [14]. Bacterial signals also regulate tight junction proteins, maintaining barrier integrity and preventing pathogen translocation [15]. In pathological conditions like dysbiosis, disruptions in bacterial communities lead to aberrant signaling [16]. Overactivation of PRRs due to pathogen overgrowth can result in chronic inflammation, while reduced SCFA production may impair Treg differentiation and tolerance [17]. In summary, molecular signaling between the gut microbiota and the immune system represents a finely balanced communication network. These interactions are crucial for shaping immune development, maintaining tolerance, and ensuring effective responses to pathogens. Disruptions in these signaling pathways are closely linked to the pathogenesis of inflammatory, autoimmune, and metabolic diseases, highlighting the therapeutic potential of targeting microbiota-immune signaling in disease management. Having established the importance of signaling pathways in the relationship between the microbiota and the immune system and disease pathogenesis, we will now explore how diet may modulate these microbial communities.

The Role of Dietary Habits in Shaping Personalized Immune Responses through Gut Microbiota Modulation

As mentioned earlier, the human immune system is intimately connected to gut microbiota. One of the most influential factors determining the composition and function of this microbial community is diet. Emerging research has demonstrated that individual dietary habits not only shape the gut microbiota but also drive personalized immune responses through its modulation [18-20]. This intricate relationship underscores the critical role of nutrition in immunity, inflammation, and disease prevention.

Diet as a critical factor determining the composition of the gut microbiota impacting the immune system

The gut microbiota comprises trillions of microorganisms, including bacteria, fungi, archaea, and viruses, with bacteria dominating. The composition of this microbiota is influenced by various factors such as genetics, environment, age, and notably, diet. Among these, diet is the most modifiable and has immediate and long-term effects on microbial diversity and function [21,22]. Diets rich in fiber, fruits, and vegetables – prevalent in the Mediterranean diet – promote the growth of beneficial bacteria like *Bifidobacterium* and *Faecalibacterium*, which are associated with anti-inflammatory functions [23-26]. Conversely, the Western diet, often high in fat, refined sugars, and low in fiber, is linked to reduced bacterial diversity and the expansion of potentially pathogenic bacteria like *Bilophila wadsworthia* [27].

At the biochemical level, dietary components are metabolized by gut bacteria into bioactive molecules that regulate immune function. Dietary fiber is fermented by specific bacteria into SCFAs like acetate, propionate, and butyrate [28,29]. These SCFAs bind to GPCRs (GPR43, GPR41) on immune and epithelial cells, promoting anti-inflammatory responses and enhancing Treg differentiation [30,31]. Butyrate, in particular, has been shown to maintain gut barrier integrity, reduce pro-inflammatory cytokine production, and promote the expression of forkhead box P3 (Foxp3), a key transcription factor for Tregs [32]. Thus, a high-fiber diet indirectly fosters a more balanced and tolerant immune response through bacterial metabolites.

Another pathway through which diet shapes immunity is via bacterial metabolism of dietary tryptophan [33,34]. Bacterial-derived indole compounds activate the AHR on gut immune and epithelial cells, promoting IL-22 production, enhancing barrier function, and reducing inflammation [35]. Individual differences in dietary tryptophan intake and bacterial composition can lead to variations in AhR activation, contributing to personalized immune responses.

Personalized microbial profiles and immune phenotypes

Each individual possesses a unique gut microbial signature largely influenced by long-term dietary patterns [36]. For example, vegetarians and vegans tend to have higher levels of fiber-fermenting and SCFA-producing bacteria compared to omnivores [37]. These differences can lead to distinct immune profiles, including differential cytokine production, T cell activation, and innate immune training.

Furthermore, early-life nutrition has long-lasting effects on gut microbiota development and immune system programming. For example, breastfeeding promotes the growth of *Bifidobacterium spp.*, supporting immune tolerance and reducing allergy risk [38]. Formula-fed infants often have more diverse gut microbiota but less immune regulation [39], suggesting that diet-related microbial patterns established in infancy can influence long-term immune processes.

High-fat diets, particularly those rich in saturated fats, are associated with gut dysbiosis and increased intestinal permeability [40,41]. This "leaky gut" allows bacterial products like lipopolysaccharides (LPS) to translocate into circulation, promoting systemic inflammation—a phenomenon known as metabolic endotoxemia [42]. LPS activates Toll-like receptor 4 (TLR4) on immune cells, triggering NF-κB signaling and the release of pro-inflammatory cytokines like IL-6 and TNF-α. Thus, these diets can induce dysbiosis and barrier dysfunction, predisposing individuals to chronic low-grade inflammation, contributing to obesity, diabetes, and autoimmune disorders.

Racial and cultural dietary patterns reflect immune diversity

As we can see in **Figure 1**, traditional and ethnic dietary patterns also influence the gut microbiota and, consequently, immune characteristics. Populations consuming high-fiber, plant-based diets (e.g., rural African or South Asian communities) tend to have more

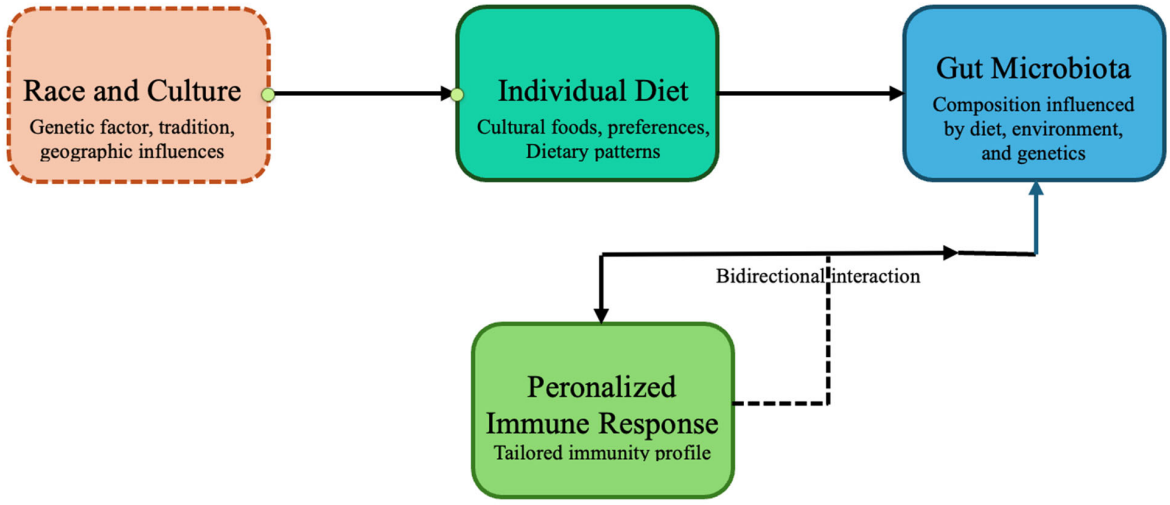

Figure 1. The diagram illustrates the interaction between individual diet (defined by genetic treats and cultural environment) and gut microbiota to create personalized immune responses: (1) Genetic factors, traditions, and geographical influences create the foundation of individual differences. (2) Cultural food practices, preferences, and dietary patterns emerge from racial and cultural backgrounds. These include variations in consumption of fermented foods, plant diversity, and fiber content. (3) Diet directly shapes the microbiome's composition, which is influenced by bacterial diversity, metabolite production (like SCFAs mentioned in the text), and signaling pathways. (4) The gut microbiota ultimately shapes a personalized immunity profile through specific cytokine patterns, regulatory T cell function, and barrier immunity mechanisms.

The diagram also shows a bidirectional interaction between the gut microbiota and immune system, highlighting that this isn't a one-way relationship but rather a constant feedback loop where immune responses can also shape the microbiota.

This chain of interactions forms the scientific foundation for precision and personalized medicine approaches, as individual variations at each step contribute to unique health profiles and responses to interventions.

diverse microbiota with anti-inflammatory properties compared to those consuming Western diets [43,44]. These differences may underline observed variations in immune responses to infections and vaccinations across ethnic groups. For example, variations in gut microbiota composition have been linked to differences in rotavirus vaccine efficacy between children in developing and developed countries [45,46]. This suggests that microbiota-driven immune programming can modulate responses to immune challenges in a diet-dependent manner.

Personalized nutrition for immune modulation

Given the intimate link between diet, gut microbiota, and immunity, personalized nutritional approaches are gaining attention as a means to optimize immune health. Studies have shown that individuals respond differently to the same dietary interventions due to variations in their baseline gut microbiota. Zeevi *et al.* [47] demonstrated that personalized diets based on gut microbiota profiles were more effective in controlling postprandial glucose levels than standard dietary advice. In the context of immunity, future precision nutrition strategies may involve gut microbiota profiling to tailor diets that enhance beneficial bacterial functions, promote immune tolerance, and reduce disease risk [48,49].

In summary, dietary habits are powerful modulators of gut microbiota composition and function. Through the production of immunomodulatory metabolites, gut microbes translate dietary signals into molecular cues that shape host immunity. Thus, individual dietary patterns contribute to the uniqueness of the gut microbiota, leading to personalized immune responses.

As we deepen our understanding of the microbiota-immune interface, it becomes increasingly clear that diet is not merely a source of nutrients but a key determinant of immune resilience and disease susceptibility. Integrating microbiome science into nutritional recommendations holds great promise in restoring gut microbiota balance and modulating immune responses, including in cases of autoimmune-related immune dysfunction. Short- and long-term dietary changes should be leveraged as a form of personalized nutritional therapy, particularly for addressing immune-related diseases.

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