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Commentary

Asthma & the Gut: Bridging the Unseen Connection

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The human microbiome plays a significant role in the development, manifestation, and mitigation of asthma and allergic diseases. Asthma, a chronic disease affecting millions worldwide, is strongly associated with immune dysfunction, particularly hyperactivation of the T-helper 2 arm of adaptive immunity. Emerging evidence implicates microbiota in shaping immune responses, with key findings in both the respiratory and gastrointestinal tracts [1].

The gut microbiome is the largest and most diverse microbial ecosystem in the human body, hosting trillions of microorganisms that play a pivotal role in immune regulation, metabolism, and systemic health. Unlike microbiomes in the airways or skin, it impacts the entire body via pathways like the gut-lung and gut-brain axes, influencing diseases such as asthma and allergies [2]. Its metabolites, like short-chain fatty acids, regulate inflammation and immune tolerance [3]. This systemic influence highlights its superior importance in maintaining overall health compared to the localized effects of other microbiomes.

The microbiome of asthmatic airways differs significantly from that of healthy individuals, displaying higher bacterial diversity and load. Notably, the Proteobacteria phylum is enriched in asthmatic airways, including species like *Haemophilus* and *Neisseria.* These bacteria produce lipopolysaccharides with strong endotoxic properties, which can exacerbate inflammation and drive asthma severity. Studies also highlight altered microbial communities in corticosteroid-resistant patients compared to corticosteroid-sensitive ones, suggesting that microbial composition influences treatment responses [4].

There is a correlation with disease severity where the enriched airway microbiota in asthma is associated with increased bronchial hyperresponsiveness, mucus production, and airway obstruction. These microbial imbalances may disrupt immune homeostasis, enhancing inflammatory responses. Targeting airway microbiomes offers a potential pathway for managing asthma severity and corticosteroid resistance. In this sense, human microbiome molecular detection techniques, like 16S rRNA sequencing, reveal the complexity and diversity of microbial ecosystems in humans [5]. Microbial communities significantly influence immune function and metabolic processes. 16S rRNA profiling and metatranscriptomics are key methods in microbiome research, each with unique strengths. 16S rRNA profiling is cost-effective and widely used for identifying bacterial diversity but lacks functional insights and excludes non-bacterial microbes [6]. In contrast, metatranscriptomics captures microbial activity and functional pathways across all microorganisms but is more expensive, technically demanding, and computationally intensive [7]. The choice depends on study goals: 16S is ideal for taxonomic surveys, while metatranscriptomics excels in exploring microbial functions and dynamic responses to environmental conditions. A big challenge for 16S rRNA techniques may reside in the protein-coding center that has been widely known quite early since the pre-genomic era [8].

The gut microbiome is crucial for immune system development, particularly during early life. Early colonization by diverse, beneficial microbes supports immune tolerance and prevents allergies [9]. Disruptions to this process, such as antibiotic use, C-section delivery, or reduced microbial exposure, are linked to increased asthma risk. These factors can lead to gut dysbiosis, impairing the induction of regulatory T cells and the production of anti-inflammatory molecules like Short-Chain Fatty Acids (SCFAs), which are vital for maintaining immune balance [10,11].

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The hygiene hypothesis suggests that reduced microbial exposure in modern environments contributes to rising asthma and allergy prevalence [12]. Early-life factors, like formula feeding or sterile environments, limit gut microbiota diversity, skewing immune responses toward inflammation [13]. Evidence links early gut dysbiosis to later respiratory issues, suggesting that interventions promoting gut microbial diversity could mitigate asthma risk and enhance immune resilience [14]. SCFAs are produced by gut bacteria regulate immune cells and reduce inflammation.

Environmental exposures during early life significantly shape the human microbiome and influence asthma risk. Studies highlight that microbial diversity in the home, particularly from pet ownership or rural environments, is protective against allergic diseases [9]. Children exposed to dogs or cats in infancy experience greater exposure to diverse bacterial species, including beneficial taxa such as *Lactobacillus* and *Bifidobacteria*, which are also associated with gut health [13]. These exposures promote immune tolerance by stimulating regulatory T cells and reducing inflammatory responses, thereby decreasing the likelihood of asthma development [15]. The hygiene hypothesis suggests that reduced microbial exposure in modern, sanitized environments contributes to increased asthma prevalence [12]. Studies in inner-city environments reveal that children exposed to richer and more diverse bacterial communities in household dust during their first year of life are less likely to develop asthma or wheeze by age three [15]. Conversely, environments lacking bacterial diversity and enriched with fungal species are linked to a higher risk of asthma [16]. This evidence underscores the importance of microbial-rich exposures in early life for promoting immune system resilience and reducing asthma risk.

The current health challenge emphasizes that microbiome-targeted strategies hold significant promise for preventing and managing allergic asthma, particularly during early life when the microbiome and immune systems are most adaptable [4]. Early microbial colonization influences immune tolerance, suggesting interventions like probiotic supplementation could help restore microbial balance. Specific bacteria, such as *Lactobacillus johnsonii*, have shown protective effects against respiratory infections and allergen-induced airway inflammation, supporting their therapeutic potential [17].

Emerging evidence highlights the potential of dietary modifications, such as increased fiber intake, to promote gut microbial diversity and reduce inflammatory responses via short-chain fatty acids [18]. Targeting the gut microbiome holds therapeutic promise through dietary fiber-derived SCFAs, probiotics, and microbiota modulation to regulate inflammation and immunity, particularly in diseases like asthma [2,3]. Further, interventions aimed at restoring the gut and airway microbiome during early life or after disruptions (e.g., antibiotic use) may prevent asthma onset [14]. As microbiome research evolves, integrating precision medicine with microbiome-based therapies could lead to innovative treatments that target specific microbial imbalances, improving asthma outcomes while minimizing reliance on traditional medications.

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