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Innate Immunity in Asthma

Talal A. Chatila, MD, MSc.

Division of Immunology, Boston Children's Hospital, Department of Pediatrics, Harvard Medical School, Boston, MA, USA

It is appreciated that the marked increase in the prevalence of asthma over the last decades reflects changes in environmental exposures and living conditions associated with modern lifestyles¹. Of particular interest is the documentation of a protective effect of exposures associated with traditional farming, the impact of which has waned with increased urbanization and the advent of mechanized agriculture². In small family-based farms where children are reared in close proximity to farm animals and their sheds, Increased exposure to microbial products found in these environments, including lipopolysaccharides (LPS), has been associated with protection against asthma^{3,4}. It remains unclear how exposure to a traditional farming environment confers protection against asthma and whether such protection also applies in the context of large scale industrialized farming. In the current issue of the Journal, Stein et al advance our knowledge on both accounts⁵.

Stein et al took advantage in their studies of a special lifestyle attribute that differentiates two otherwise closely related farming populations in the US with contrasting incidence of asthma. The Amish and the Hutterites are reproductively isolated farming communities that are linked by ancestry, having originating in German speaking alpine regions. They also share a similar lifestyle, sharing most of the exposures commonly impacting the risk for asthma with one notable exception. Whereas the Amish have maintained a traditional farming practice that revolves around single family dairy farms and which eschews mechanization, the Hutterites practice large-scale, highly mechanized communal farming. The Amish exhibit low asthma prevalence of asthma and allergic sensitization, while those of the Hutterites are strikingly high in common with the US population at large^{6,7}. As such, these two communities are ideally matched for analysis of environmental exposure-related influences on asthma susceptibility.

By studying school children from the respective community, Stein et al confirmed the discrepancy in allergy and asthma incidence between their Amish and Hutterites study subjects. They also established the presence of distinct microbial composition and increased burden of LPS in dust samples collected in the houses of their Amish as compared to Hutterite subjects. After exposing samples of peripheral-blood lymphocytes from both populations to lipopolysaccharides, the samples from the Hutterites expressed more innate immunity-related cytokines than those from the Amish. PBL of Amish subjects also exhibited a genetic signature of increased gene transcripts associated with innate type

immune responses, including those involved in innate immune response to microbial products such as TNF and IRF7. Importantly, dust samples collected from Amish households suppressed the induction of airway inflammation in a mouse model of allergic asthma. This protection was abrogated in mice lacking in MyD88 and Trif, adaptor proteins that mediate signaling by microbial products via Toll-like receptors (TLR). In agreement with these findings are previous studies on protective bacterial species isolated from farm dust samples including the gram-negative bacterium *Acinetobacter lowffii*, whose application in the airways of mice triggers local and systemic inflammatory innate immune responses in a TLR-dependent manner⁸. Overall, the results of Stein et al are consistent with the protective effect of Amish dust being related to its distinct microbial composition.

What mechanisms account for the protective effect of chronic innate immune cell activation by farming-related microbial products? Studies have delineated a network of innate immune cells, including epithelial cells, type 2 innate lymphoid cells (ILC2), mast cells, dendritic cells and others, that are activated by allergens⁹. This network programs a pro-allergic adaptive immune response involving allergen-specific T helper type 2 (Th2) cells and IgE producing B cells that sustains disease activity. The studies of Stein et al support the notion that exposure to microbe-rich farm dust directs an alternative pro-inflammatory innate immune response involving transcriptional pathways and mediators, including NF- κ B and IRF7, that prevents the emergence of asthma. It should be pointed out that microbial products may also act via TLR and MyD88 to activate the formation of regulatory T cells that enforce tolerance at mucosal surfaces¹⁰. Thus both the innate and immune regulatory mechanisms may contribute to their immunomodulatory effects.

The studies by Stein et al leave several questions unanswered. It is unclear if continuous exposure is required to maintain the protective effect of farm dust against allergic asthma. In mice, pregnant mothers exposed to *A. lowffii* transmit protection against allergic asthma to their off-spring by mechanisms involving maternal TLR activation, suggesting an epigenetic effect acquired in utero⁸. Also unclear is whether the protective effect of microbial exposure requires live microbes that may colonize the airways or can be reproduced with purified microbial products. Answering these questions will facilitate harnessing the insights gleaned from the studies of Stein et al and others for therapy and prevention of asthma.

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Figure 1.

Farming Lifestyle, the Activation of Innate Immunity, and Protection against Asthma. Differences in the prevalence of asthma and allergic sensitization in Amish and Hutterite communities are linked to their distinct farming practices. The traditional farming practices in Amish communities protect against asthma by inducing a long-term, low-level, proinflammatory innate immune response. This protection involves the activation by microbial signals, acting through MyD88 and Trif and the production of tumor necrosis

factor (TNF) and interleukin-1. The Hutterites, who practice mechanized farming and are not exposed to the same microbial influences, are not protected.

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