EDITORIAL

Innate Immunity in Asthma

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It is appreciated that the marked increase in the prevalence of asthma over the past few decades reflects changes in environmental exposures and living conditions associated with modern lifestyles.[1] Of particular interest is the documentation of a protective effect of exposures associated with traditional farming, the influence of which has waned with increased urbanization and the advent of mechanized agriculture.[2] On small family-based farms where children are reared in close proximity to farm animals and their sheds, increased exposure to the microbial products found in these environments, including lipopolysaccharides, 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. Stein et al. now advance our knowledge on both accounts in this issue of the *Journal*.[5]

In their study, Stein et al. took advantage of a lifestyle attribute that differentiates two otherwise closely related U.S. populations in which the incidence of asthma is dissimilar. The Amish and the Hutterites are reproductively isolated farming communities that are linked by ancestry, having originated in German-speaking alpine regions of Europe. They also share a similar lifestyle that includes environmental exposures that often affect the risk of asthma, with one notable exception — whereas the Amish have maintained a traditional farming practice that revolves around single-family dairy farms and eschews mechanization, the Hutterites practice large-scale, highly mechanized communal farming. The prevalence of asthma and allergic sensitization among the Amish is low, but among the Hutterites the prevalence of both conditions is strikingly high, similar to that in the U.S. population at large.[6,7] As such, these two communities are ideally suited for analysis of the influence of environmental exposures on susceptibility to asthma.

By studying children from these two communities, Stein et al. confirmed the discrepancy that exists in the communities' incidences of allergy and asthma. The researchers also established the presence of a distinct microbial composition and an increased burden of lipopolysaccharides in dust samples collected from the houses of the Amish as compared with those of the Hutterites. After exposing samples of peripheral-blood lymphocytes from both populations to lipopolysaccharides, the samples from the Amish expressed more innate immunity-related cytokines than those from the Hutterites. The peripheral-blood lymphocytes of Amish children also exhibited a genetic signature characterized by higher levels of the gene transcripts associated with innate-type immune responses, including those involved in the innate immune response to microbial products such as tumor necrosis factor and IRF7. In addition, 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 MyD88 and Trif, adaptor proteins that mediate signaling by microbial products through toll-like receptors (TLRs). In agreement with these findings are previous studies on protective bacterial species isolated from farm-dust samples, including the gram-negative bacterium *Acinetobacter lwoffii*, whose application to the airways of mice triggers local and systemic inflammatory innate

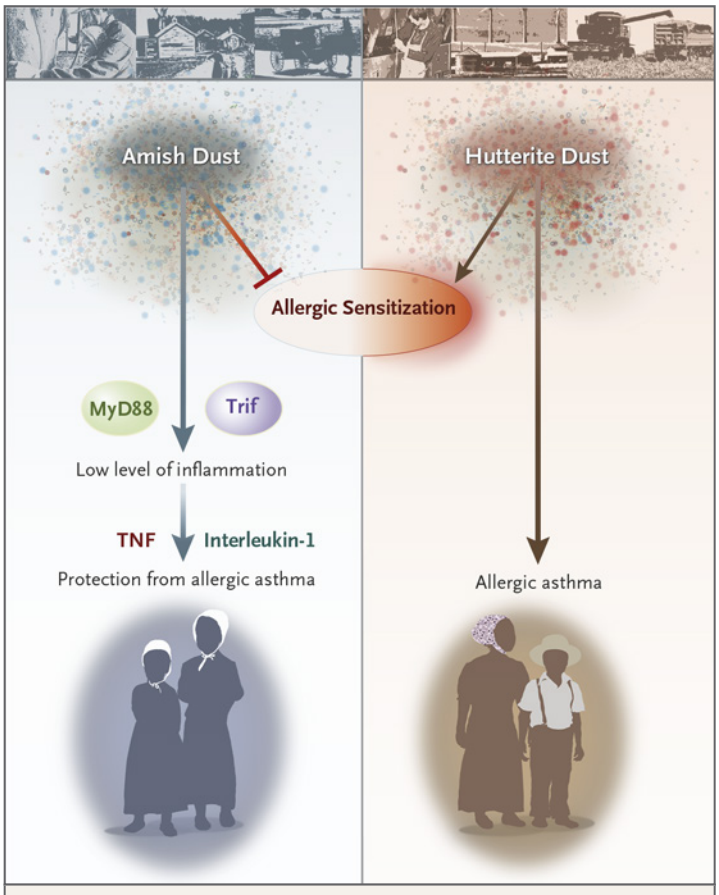

Figure 1. Farming Lifestyle, the Activation of Innate Immunity, and Protection against Asthma.

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.

immune responses in a TLR-dependent manner.[8] Overall, the results of the study by Stein et al. are consistent with the idea that the protective effect of Amish dust is related to its distinct microbial composition.

What mechanisms account for the protective effect of long-term, innate, immune-cell activation by farming-related microbial products (Fig. 1)? Studies have delineated a network of innate immune cells, including epithelial cells, type 2 innate lymphoid cells, mast cells, dendritic cells, and others, that are activated by allergens.[9] This network programs a proallergic adaptive immune response involving allergen-specific type 2 helper T cells and IgE-producing B cells that sustains disease activity. The findings of Stein et al. support the notion that exposure to microbe-rich farm dust directs an alternative, proinflammatory, innate immune response involving transcriptional pathways and mediators, including nuclear factor κB and IRF7, that prevents the emergence of asthma. It should be pointed out that microbial products may also act through TLRs and MyD88 to activate the formation of regulatory T cells that enforce tolerance at mucosal surfaces.[10] Thus, both long-term, low-level activation of innate immune cells and possibly T-cell–related immune regulatory mechanisms may contribute to the protective effects of the Amish farm dust against asthma.

Stein et al. also leave several questions unanswered. It is unclear whether continuous exposure to farm dust is required to maintain its protective effect against allergic asthma. In mice, pregnant mothers exposed to *A. lwoffii* transmit protection against allergic asthma to their offspring through mechanisms that involve maternal TLR activation, which suggests that an epigenetic effect may be acquired in utero.[8] It is also unclear whether the protective effect of microbial exposure requires live microbes that may colonize the airways or can be reproduced with purified microbial products. The answers to these questions will help to harness the insights gleaned from the studies of Stein et al. and others for the purpose of treating and preventing asthma.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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