

# Mechanism for impaired allergic inflammation in infants may explain hygiene hypothesis

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The hygiene hypothesis may explain why asthma and other allergic airway diseases have dramatically increased over the past decades in

industrialized countries. The hypothesis suggests that decreased exposure to microbial products in our cleaner homes and environments—due to improved sanitation or no longer growing up on farms—is the main driver of increased allergic airway disease.

But how could less exposure to infectious agents or parasites lead to more [asthma](#)? Research published in the journal *Immunity* by Beatriz León, Ph.D., and colleagues at the University of Alabama at Birmingham suggests an answer. León and colleagues describe a mechanism in a mouse model of asthma that supports the hygiene hypothesis—they found that infant [mice](#) need a higher exposure to a bacterial endotoxin, compared to [adult mice](#), to avoid developing asthma-like reactions to house dust mites.

Without the higher levels of the microbial lipopolysaccharide, or LPS, the infant mice developed allergic airway disease after repeated exposure to house dust mite, or HDM, allergen, and this window of susceptibility for allergic airway disease was open only while the mice were the equivalent ages of human infants and toddlers. The UAB researchers have detailed the mechanism underlying this window of susceptibility, which may then inform research into human disease.

"When we know the mechanism, then we perhaps can intervene," said León, assistant professor in the UAB Department of Microbiology.

About 10 percent of U.S. school-aged children now have asthma, and almost all began developing the disease in very early childhood, before age 5. Asthma is marked by inflammation, spasms of the muscles around the airways and excess mucus secretion that obstruct the airways and make breathing difficult. The most common form, atopic asthma, is triggered by inhaled allergens like house dust mites, animal dander, fungal spores, and plant or tree pollen.

In the mouse model, airway exposure to HDM triggers the disease. Interestingly, it was known that if HDM was given simultaneously with a dose of bacterial LPS—one of the most immunogenic substances known—the mice did not develop asthma-like disease.

León and the UAB researchers took that observation further. They found that the amounts of LPS needed to prevent HDM asthma differed greatly between very young mice and adult mice. A low dose of LPS, in combination with the HDM, was sufficient to prevent asthma in adult mice; but that low dose did not prevent asthma in infant mice. Instead, very young mice needed 10 times as much LPS to prevent the HDM asthma. These different thresholds for suppression of disease by LPS led the researchers through a long series of experiments to unravel the mechanism causing this difference.

The story is complex because immune responses in mammals involve a complicated chain of cell-to-cell contacts among immune cells, migration of some of those immune cells throughout the body, and intricate "cross-talk" among cells using small protein signaling compounds called cytokines that interact with cell receptors.

The end point for HDM asthma is the activation of naïve T-cells into pathogenic T helper 2 cells that cause inflammation in the airways. However, the researchers found that the different infant and adult responses to LPS was not due to any difference between the T-cells of the infants or adults. Instead, the different response was located upstream.

In adult mice challenged with HDM and a low dose of LPS, migratory dendritic cells—[immune cells](#) that process the antigens from allergens or infectious microbes and present them to T-cells—was associated with upregulation the transcription factor T-bet in the dendritic cells, which caused production of the signaling compound interleukin-12. As a

consequence of the interleukin, naïve T-cells interacting with the migratory dendritic cells in the adult mice upregulated the transcription factor T-bet, and that step precluded differentiation of the T-cells into inflammatory T helper 2 cells and thus prevented a subsequent pathogenic allergic response.

In contrast, the migratory dendritic cells from infant mice failed to upregulate T-bet and interleukin-12 in low-LPS conditions. Thus, the naïve T-cells interacting with the migratory dendritic cells in infants failed to receive the suppressive interleukin-12 signals and did not upregulate T-bet. Without the T-bet, the T-cells fully differentiated into pathogenic T helper 2 cells.

The different responses of the migratory dendritic cells turned out to be due to another cell signaling protein—[tumor necrosis factor alpha](#). Adults rapidly produced that cytokine in response to the low-dose LPS sensitization, while infant mice had an impaired ability to produce the tumor necrosis factor alpha in response to LPS. The source of the tumor necrosis factor alpha was not specified in the UAB study, but indirect evidence points to some type of white blood cells in the lung.

"Collectively," León said, "our data demonstrate that LPS prevents T helper 2-dependent allergic responses with different thresholds in adults and infants; as such, a high content of LPS in airborne house-dust is required to mediate protection from allergic airway disease, specifically during infancy. Our data, therefore, provide a plausible mechanism underlying the higher susceptibility to allergic airway inflammation observed in children raised in uber-clean and sanitized environments."

**More information:** Holly Bachus et al. Impaired Tumor-Necrosis-Factor- $\alpha$ -driven Dendritic Cell Activation Limits Lipopolysaccharide-Induced Protection from Allergic Inflammation in Infants, *Immunity* (2019). [DOI: 10.1016/j.immuni.2018.11.012](https://doi.org/10.1016/j.immuni.2018.11.012)

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