Maturation of a hypothesis

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Recent findings of associations between markers of exposure to microbial products that do not directly cause disease and the risk of having asthma and allergies have significantly changed and enriched our understanding of the so-called hygiene hypothesis.

This hypothesis was originally presented as the proposed increased burden of atopy that Western societies paid for a dramatic decrease in infectious diseases during the first years of life.[1] This enunciation, provocative and trail-blazing, as it was, suggested a more or less direct relation between the occurrence of acute episodes of infectious disease and the subsequent development of allergies. Many researchers thus studied associations between the incidence of such episodes and subsequent asthma and allergies, but the results were contradictory.[2–5] It became clear that some acute infections in early life could be protective, but this may depend on other factors that went unmeasured.

More recently, studies performed in rural and urban areas of developed countries have considerably widened the scope of the original hygiene hypothesis. Surveys in rural communities have consistently found that children living on animal farms have considerably less burden of atopic diseases than those living in the same communities but away from farms.[6–8] Moreover, children who frequently visit farms but do not live on them also have a lower prevalence of allergies.[8] More in-depth studies of the indoor environment in animal-farm homes suggest that the endotoxin content in these homes is much higher than that in rural homes away from animal farms.[9] A recent study in an urban environment in the USA suggests that exposure to indoor endotoxin (as measured in house dust samples) is inversely associated with the risk of developing allergic sensitization in infants and young children, and is also associated with a higher proportion of interferon-γ-producing T cells in circulation.

A broader approach is thus needed for our understanding of the environmental factors that may influence the development of the immune system. Endotoxin contains lipopolysaccharides (LPS) that form part of the cell wall of Gram-negative bacteria. A very sensitive mechanism that responds to LPS is present in vertebrate immune systems. This receptor system constitutes the first, non-adaptive response to external microbial stimuli. It activates a complex intercellular signaling mechanism and triggers the production of a set of immune mediators by antigen presenting cells. It is possible that these mediators, when produced by co-stimulation with perennial exposure to endotoxin, may deviate or modify the original responses to allergens in such a way that drives them away from T helper cell (Th)-2-type responses mediated by immunoglobulin E (IgE).

Based on these premises, and in collaboration with Holt, we speculated that polymorphisms in the receptor system for LPS could influence the risk of allergies. We have thus screened the genes involved in this receptor system for LPS, starting with CD14 gene, which codes for one of the main components of the endotoxin receptor system.[10] We reported a C $\rightarrow$T variation at position –159 of the promoter region of the gene (CD14/–159). We found that, both in Caucasians and Hispanics, one-half of all chromosomes contain one or the other allele (C or T). Carriers of the T allele in homozygote form had significantly higher levels of the circulating soluble form of CD14. We also found that skin-test-positive homozygotes for the T allele had significantly lower levels of total serum IgE, and atopic carriers of the T allele had significantly lower numbers of positive skin tests than carriers of the C allele. Similar findings have been reported by two other research groups,[11,12] although not all researchers have been able to confirm our findings.[13,14] It thus appears that, at least in some populations and at some ages, polymorphisms that increase the expression of CD14 may be associated with lower levels of IgE. A potential explanation for this finding could be that increased sensitivity to endotoxin and other microbial products that interact with CD14 could increase interleukin-12-mediated and interleukin-10 responses to these products, with increased likelihood of development of Th1-type responses or modified Th-2 responses and thus with less likelihood of atopic diseases.

These findings may allow us to assess the role of genetic variants in genes of the receptor system for endotoxin as determinants of susceptibility allergies in individuals who are exposed to different levels of endotoxin. Our final goal is to design prevention strategies based on exposure to innocuous surrogates of endotoxin in individuals who may be more susceptible to the preventive effects of bacterial products because of their specific genetic background.

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