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Environmental protection from allergic diseases: From humans to mice and back

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Allergic diseases have a strong environmental component, illustrated by the rapid rise of their prevalence in the Western world. Environmental exposures have been consistently shown to either promote or protect against allergic disease. Here we focus on protective exposures and the pathways they regulate. Traditional farming, natural environments with high biodiversity, and pets in the home (particularly dogs) have the most potent and consistent allergy-protective effects and are actively investigated to identify the environmental and host-based factors that confer allergy protection. Recent work emphasizes the critical protective role of microbial diversity and its interactions with the gut/lung and skin/lung axes — a cross-talk through which microbial exposure in the gut or skin powerfully influences immune responses in the lung.

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Introduction

Allergic diseases such as asthma, atopic dermatitis and allergic rhinitis have a strong environmental component, eloquently illustrated by the rise of their prevalence in the Western world over the last few decades [1,2]. Several environmental factors have been consistently shown to increase allergic disease risk in isolation or in the context of gene–environment interactions [3,4], but remarkably other environmental exposures have been repeatedly found to confer protection against these diseases. These exposures, and the allergy-protective pathways they regulate, are the focus of this review.

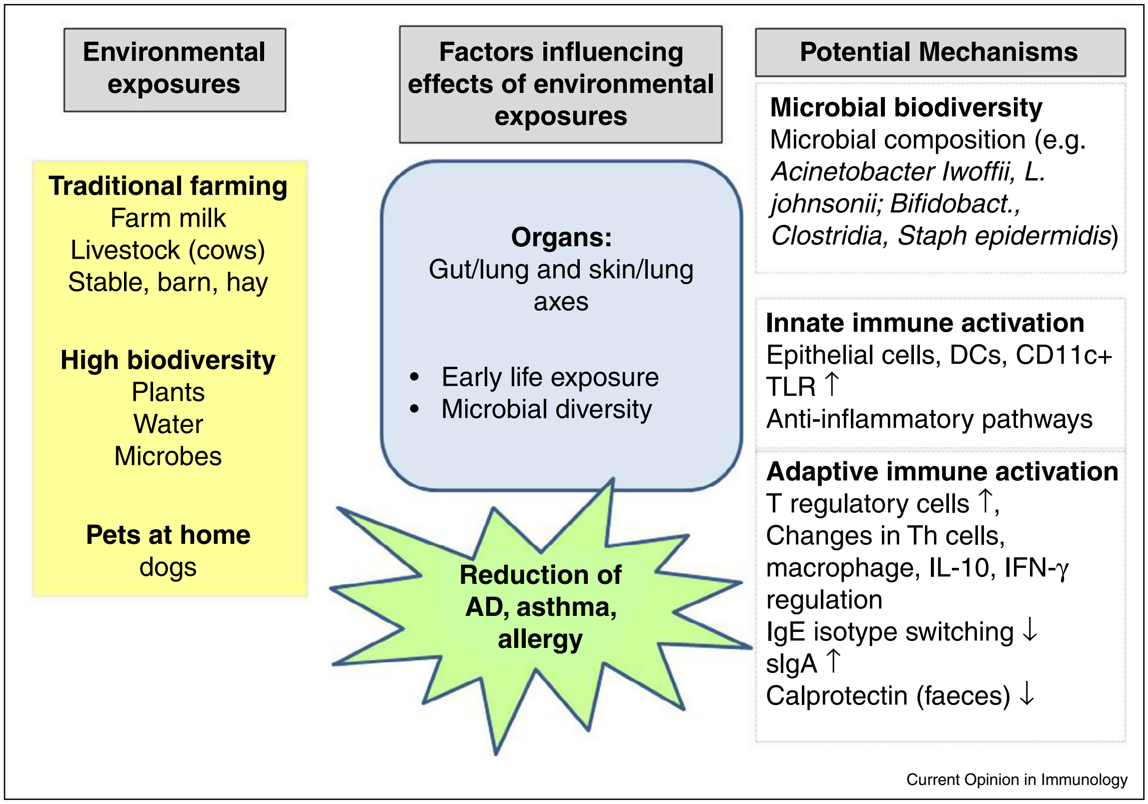
Among the exposures known to protect human populations from allergy and asthma, traditional farming [5], natural environments with high biodiversity [6••], and pets in the home (particularly dogs) [7] appear to have the most potent and consistent effects. Therefore much research in both humans and mice is currently dissecting the environmental and host-based factors that confer allergy protection under these conditions. As we will see, despite the distinct characteristics of these protective environments, a unifying theme is emerging from this research: the strong nexus between protection from allergic disease and microbiota in the environment and/or the host. In combination with population-based studies that identify the most relevant questions, mouse models are playing a critical role in shaping this novel paradigm because even with the caveats necessary when translating results across distant species, they provide a powerful tool to go beyond associations and characterize causal pathways. Seminal studies in specific pathogen-free or germ-free mice that illustrate the connection between allergic disease and microbiota have been recently reviewed [8]. Here we will discuss recent work that specifically highlights the complex relation between the environment and protection from allergic disease.

The farm effect

A strong association between traditional farming and protection from IgE-mediated allergic diseases including asthma, hay fever, atopic dermatitis and atopic sensitization has been consistently shown throughout the world [5], particularly for prenatal exposure [9•]. Moreover, recent data from the PASTURE birth cohort enrolled in rural areas of Austria, Finland, France, Germany, and Switzerland demonstrated that not only asthma, but also rhinitis, respiratory tract infections, otitis, fever and C-reactive protein levels at 12 months were reduced by about 30% following raw milk consumption in early life [10], thus significantly extending the scope of the protection conferred by farm exposure. Interestingly, whereas the overall farm effect can be explained by specific exposures (cows, straw, and farm milk for asthma, and fodder storage rooms and manure for atopic dermatitis), the link between the farm effect and hay fever and/or atopic sensitization is still partially missing [11].

To decipher the mechanisms underpinning the farm effect, human studies have explored the impact of farm exposure on immune system maturation (Figure 1). Farm-related exposures were associated with modified expression of innate immune receptor genes in early life

Figure 1



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Underlying potential mechanism of allergy protection through environmental exposure (traditional farming/high biodiversity/pets at home).

[9•] and increased T regulatory (Treg) cells at age 4 years but also already at birth [12•,13]. At age 4 years, Treg cells in part explained the asthma-protective effect of farm milk exposure [12•]. The role of diet is looming large in these studies. Indeed, a recent comparison of urban (Guangzhou) and rural (Shoaguan) China confirmed that the prevalence of self-reported asthma (6.6% vs 2.5%), rhinitis (23.2% vs 5.3%) and eczema (34.1% vs 25.9%) was significantly higher in urban subjects, and showed that the schoolchildren's diet is affected by the country's urbanization and in turn affects asthma risk. High vegetable and low milk intake protected against childhood asthma [14]. Introduction of an increasing diversity of foods within the first year of life was positively associated with increased Treg markers and protection from the development of food sensitization, food allergy and asthma up to 6 years also in children from the PASTURE/EFRAIM study. One possible protective mechanisms involving Treg cells is the inhibition of isotype switching to IgE: a decrease in C_ε germline transcripts was associated with increased food diversity [15•]. Furthermore, serum IgA levels were positively associated with contact to farm animals or cats during pregnancy, and inversely associated with atopic dermatitis up to 2 years, independent of breastfeeding duration [16]. It is noteworthy that not only the Treg but also the Th17 lineage appears to be targeted by prenatal farm exposure. Expression of Th17 cell markers in cord blood per se was not influenced by maternal farming. Yet, after stimulation of the cord blood cells with LpA, the main component of endotoxin, we found that Th17 and Treg cell markers were positively correlated only in non-farming children, potentially suggesting a stimulus-specific TH17/Treg mRNA correlated effect in children with low exposure or, alternatively, no effect in previously exposed children [17].

Several mouse studies demonstrated that inhalation of farm-derived dust extracts or selected microbes can prevent allergen-driven airway hyperresponsiveness (AHR) and lung eosinophilia [18–22]. While suggestive, those studies are difficult to interpret because the lack of true negative controls prevents determining how specific these inhibitory effects were. Significant progress may be fostered by a different, novel approach that compares and contrasts traditional and modern farm environments and populations with closely comparable genetic makeups. Indeed, differences in asthma prevalence between farm and non-farm children are recapitulated in 2 U.S. farming populations, the Indiana Amish and the South Dakota Hutterites. Both are founder populations with