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How a farming environment protects from atopy

Julie Deckers[1], **Bart N Lambrecht**[1,2,3], **Hamida Hammad**[1,2]

[1]Laboratory of Immunoregulation and Mucosal Immunology, VIB Center for Inflammation Research, Technologiepark 927, B-9052 Ghent (Zwijnaarde), Belgium [2]Department of Internal Medicine and Pediatrics, University Hospital Ghent, De Pintelaan 185 K12, B-9000 Ghent, Belgium [3]Department of Respiratory Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

Abstract

It is now well established that the exposure to certain environments like farms have the potential to protect from the development of allergies later in life. This protection is achieved when repeated exposure to the farming environment occurs early in life, but persists when children spend sufficient amount of time in contact with livestock and hay, and drink unpasteurized milk. The capacity of farm dust to protect from allergy development lies mainly in the microbe composition in the farm. These protective microbes can produce metabolites and colonize various barrier sites (skin, lung, intestine) in children, leading to persistent changes in the way their immune system and their barrier cells respond to environmental allergens.

Introduction

The prevalence of allergic diseases like allergic rhinitis, asthma and atopic dermatitis is on a steep rise since World War II [1]. Currently, more than 30% of children in Westernized countries have allergies [2,3]. The fact that this remarkable increase in the prevalence of allergies occurred within such a short time implies environmental influences above genetics. The Western lifestyle is associated with reduced environmental biodiversity and an altered host microbiome and we know now that this implies a lack of instructive signals for the developing immune system [4]. Therefore, exploring what environmental cues regulate human immune responses and unraveling mechanistic pathways is of major interest to develop prevention therapies that can halt the rise of allergic diseases. This review will summarize what has been explored until now and some recent advances to mechanistically explain how a farming environment protects against allergies.

Farming and atopy

The protective effect of a farming environment on transient wheeze and atopy is now generally established by multiple epidemiological studies [5]. Altogether, they revealed that

Correspondence to: Bart N Lambrecht.

Corresponding author: Bart N Lambrecht, Technologiepark-Zwijnaarde 71, 9052 Zwijnaarde, Belgium, Tel: +32 93313740, bart.lambrecht@ugent.be.

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several farm-related factors could contribute to protection from atopy (Figure 1). For instance, contact with livestock, particularly cows [6], has long been identified as a major contributing factor to protect from rhinitis, asthma and atopy [7,8]. The protective farm effect is stronger in children of full-time farmers compared to children of part-time farmers [8], and residential proximity to livestock can protect non-farmers' children from atopy but to a lesser extent than farmer's children [9]. This indicates that contact with livestock protects in a dose-responsive way. In fact, Amish farm children, who live in very close proximity to livestock, are even better protected from atopy than the European farm children [10]. This was not the case for Hutterite farm children, sharing genetic background with Amish children but live more distant from highly industrialized farms [10]. Early exposure to a farming environment appears to be crucial for the protective effect [11]. Actually, a life-long exposure to a farming environment is optimal to confer protection from atopy from childhood until adulthood [12]. Protection presumably starts at very early stage, when embryos are exposed to the farming environment via the pregnant mother [11,13-16]. However, many confounding factors, such as the health status of the mother, placental transfer of certain metabolites and whether or not the baby receives breast feeding, influence the newborn's risk to develop allergies this will not be discussed in this short review. Finally, children who grow up on farms are regularly nourished with unprocessed cow's milk, and this appeared to be a very important contributor to the protective effect [11,17,18]. The reduced risk of atopy in non-farmer's children living in close proximity to a farm could be explained by drinking raw cow's milk [19]. A whole body of evidence unveiled several active components in raw cow's milk and this is discussed in a recent review [20].

Farm-related exposures that confer protection against allergy

Several farm-related factors that are inversely associated with the risk to develop atopy, such as livestock and cowshed (straw, hay, manure), presumably instigate an altered environmental microbiome. Indeed, living on a farm is associated with an increased variety of environmental organisms, and this increased biodiversity protects against asthma [21]. Likewise, a recent study showed that a stronger protection was found in farms that clusters with other farms and therefore harbor a broader microbial diversity [19]. Amish home dust contained higher endotoxin levels and *Proteobacteria* and effectively suppressed asthma features in mice, compared to Hutterite home dust [10]. However, dust from Amish and Hutterite farms were both able to suppress asthma features in mice [22]. This, together with the fact that Hutterite children do not spend time around the farm before the age of 6, indicates that close contact to biodiversity and timing are crucial for protection. Because microbial diversity can be transferred from outside towards indoor [23], it will likely affect the host exposure to metabolites as well as the host microbiome itself (Figure 1).

Exposure to Microbial Metabolites and Plant Metabolites

Several metabolites have been studied in the context of allergic diseases and were shown to be either protective or rather a risk factor. The most commonly studied microbial agent is endotoxin or lipopolysaccharide (LPS), derived from Gram-negative bacteria. Multiple studies report an inverse relationship between endotoxin content in farmer's mattress- or home dust with the risk to develop hay fever, asthma or atopic sensitization [10,24-28].

Nevertheless, there was no or even a positive association between endotoxin in home dust and non-atopic or virus-triggered wheeze [24,29]. Additionally, increased endotoxin levels in home dust reduced lung function amongst asthmatics [30,31] and exacerbated exercise-induced asthma [26]. Similar contradictory findings were reported for β-glucan, a bacterial and fungal contaminant that causes a more severe, steroid-resistant asthmatic response to allergens *in vivo* [32-34]. While some reports found no association between p-glucan in home dust and the risk for atopy [28,35], others claim it is inversely correlated to moderate to severe asthma in adults [31]. Likewise, certain fungal species and extracellular polysaccharide from *Penicillum* and *Aspergillus* species in farmer's homes have been associated with a reduced risk for asthma [28,36,37]. Presumably, the dosing and timing of exposure to bacterial or fungal contaminants defines whether or not they counteract or exacerbate allergic diseases.

A farm environment is also enriched in non-microbial and/or plant-derived metabolites, which can also affect the risk for atopy. As such, farmer's children have elevated antibodies against N-glycolylneuraminic acid, derived from livestock, and this is inversely correlated with wheeze and asthma in non-atopic children [38]. Cowshed-derived N-glycolylneuraminic acid and grass arabinogalactan protect against allergic airway inflammation in mice [38,39].

Host Microbiome

Besides releasing metabolites, environmental microbes can also colonize and change the host microbiome at various barrier sites. Two recent studies showed that living on a farm causes increased microbial diversity in mattress dust, nose and throat [40,41]. Lower diversity in the nose, but not in the throat, was correlated with asthma. Additionally, the presence of *Moraxella* species in the nose and lower airways enhanced the risk for asthma but this was not the case in farmer's children [41,42]. Experimental evidence shows that intranasal administration of cowshed-derived bacterial strains, such as *Lactococcus lactis, Acinetobacter lwoffii* or *Staphylococcus sciuri* can protect from airway inflammation in mice [43,44].

Even though the nasal microbiome appeared to be important for protection, the association between mattress dust microbial diversity and asthma in farmer's children was more pronounced [40]. This indicates an involvement beyond the upper airways microbiome diversity. There is a well-established gut-lung axis and the important role of gut microbiome in the etiology of asthma has been reported before [45]. Until now, no study addressed how the gut microbiome in farmer's population could be involved in the protection from atopy. Nevertheless, oral exposure of mice to dust from homes with pets results in *Lactobacillus johnsonii* abundance in the gut and protects from allergic airway inflammation [46].

The skin is the largest barrier site and is also colonized by a microbiome which has been shown to have a major impact on immune regulation [47,48]. Hanski and colleagues showed that environmental biodiversity is reflected in skin microbial diversity and this was lower in atopic individuals [49]. Noteworthy, only the *Acinetobacter* genus was negatively associated with the risk for atopy [49]. *Acinetobacter lwoffii* colonization of the skin was later shown to suppress murine allergic airway inflammation induced by epicutaneous sensitization to OVA

[50]. Notably, a recent clinical trial observed that the use of *Bacillus-impregnated* bedding covers suppressed symptoms in patients with HDM-allergic rhinitis, despite similar allergen levels in mattress dust [51]. This might be a useful tool to validate how farm-related microbial exposures could protect against allergies in clinical trials.

Immunology and potential underlying mechanisms

Microbial communities at barrier sites instruct and skew the immune system from very early stage onwards. Chronic parasitic infections, which are like allergies mediated by Th2-cells, are regulated by regulatory T-cells (Tregs) [52]. Therefore, unraveling the mechanistic insights of the biodiversity hypothesis has been focusing on the loss Tregs to suppress allergic Th2 responses [53]. Children from farm-exposed mothers were shown to have increased numbers of Tregs until the age of 4,5 but this switched at the age of 6, indicating a crucial time window for Treg-mediated asthma protection [54-56]. Microbial colonization of murine neonatal lungs is required for generation of Tregs, which in turn reduce susceptibility to allergic sensitization in neonates [57]. Likewise, introducing bacterial metabolites (e.g. butyrate and Polysaccharide A) or non-microbial metabolites (e.g. N-glycolylneuraminic acid) in murine gut or nose induces Tregs that can counteract allergic airway responses [38,58-60].

Colonization of bacterial communities at barrier sites is also known to induce type 17 immune responses and one report showed that exposure to farm dust extract provoked such responses in agricultural workers and in mice [61]. Even though this could cause increased asthma severity [34], type 17 T-cells are also able to regulate type 2 immunity [62]. Likewise, microbiota-induced type 17 responses in the skin enhance innate barrier immunity and might thus also reduce susceptibility for atopic sensitization via the skin [47,48].

Sensitization to allergens is known to be initiated by an intimate crosstalk between barrier epithelial cells and dendritic cells (DCs) [63]. Farm children had less circulating DCs, particularly the type 2 conventional DCs (cDC2s) that were previously shown to be responsible for sensitization [64,65]. Cultured DCs that were stimulated with cowshed dust, expressed higher levels of co-stimulatory molecules CD86 and CD80, mainly produced IL-10 and were unable to sensitize mice to allergens [66,67]. Recent work showed that inhaled *Acinetobacter lwoffii* could protect neonatal mice from airway hyperresponsiveness by preventing HDM-induced expansion of cDC2s and monocyte- derived DCs in the lungs [68]. This reduction in DC numbers directly impacted IL-$13^{+}CD4^{+}$ T-cells, which were responsible for the increased susceptibility of neonates for allergic airway hyperresponsiveness [68]. This partially explains how a farming environment could particularly protect children at young age.

Additionally, there is growing evidence that innate immune responses play a major role in the protective effect of a farming environment. Farming was repeatedly reported with increased expressions of Toll-like receptors (TLR) or TLR-signaling molecules on circulating leukocytes [69,70] and SNPs in *TLRs* and/or *CD14* have been associated with farming [71,72]. TNF and IRF7, two key proteins in the innate response to microbes, appeared to be important network hubs from all the differentially expressed genes between

Amish and Hutterite circulating leukocytes, most of which showed higher expression in Amish versus Hutterite children [10]. This suggests a reinforced innate immunity in Amish children, which could possibly confer protection to allergens. Interestingly, a recent study designated TNF as a key to regulate endotoxin-mediated protection from asthma [73]. Simultaneous exposure to LPS and HDM induces TNF, which in turn upregulates T-bet expression in cDC2s that then skew immune responses towards Th1 [73]. Our previous work showed that endotoxin-mediated protection, occurred at the level of the bronchial epithelial cells [74]. Repeated intranasal exposures to endotoxin or farm dust, prior to HDM, induced the expression of *TNFAIP3* (coding for A20, a negative regulator of NFκB signaling) in bronchial epithelial cells, resulting in an increased activation threshold for allergens like HDM. Endotoxin-exposed epithelial cells did not produce Th2-skewing cytokines (GM-CSF, CCL20 and IL-33) upon HDM stimulation and therefore failed to instruct DCs to mount an allergen-specific Th2 response [74]. Intriguingly, a SNP in *TNFAIP3* locus was associated with protection from allergy but only in farm children [74] and *TNFAIP3* expression was also increased in peripheral blood cells of the Amish children compared to the Hutterite children [10]. Another clear genetic-environment interaction is SNP in the 17q21 locus, which encodes the genes *ORMDL3* and *GSDMB.* In fact, the risk for asthma caused by the 17q21 genotype is confined to children with virus-triggered wheeze in early life, whereas this genotype rather confers protection in farmer's children [75].

Conclusion

Despite the growing body of evidence showing that some particular farming environments are protective against allergy development, there are still many unanswered questions. It would be important to identify the "protective" factors contained in farm dust. Also, more murine and translational studies are required to identify the cell populations at the basis of protection from allergy, to be able to more precisely study the mechanisms underlying the protective effect of certain types of farms.

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Highlights

- Growing up in farms protect from developing allergies later in life
- Farm-induced protection is mediated by a gene-environment interaction
- Farm dust components confer protection by acting on both barrier and immune cells

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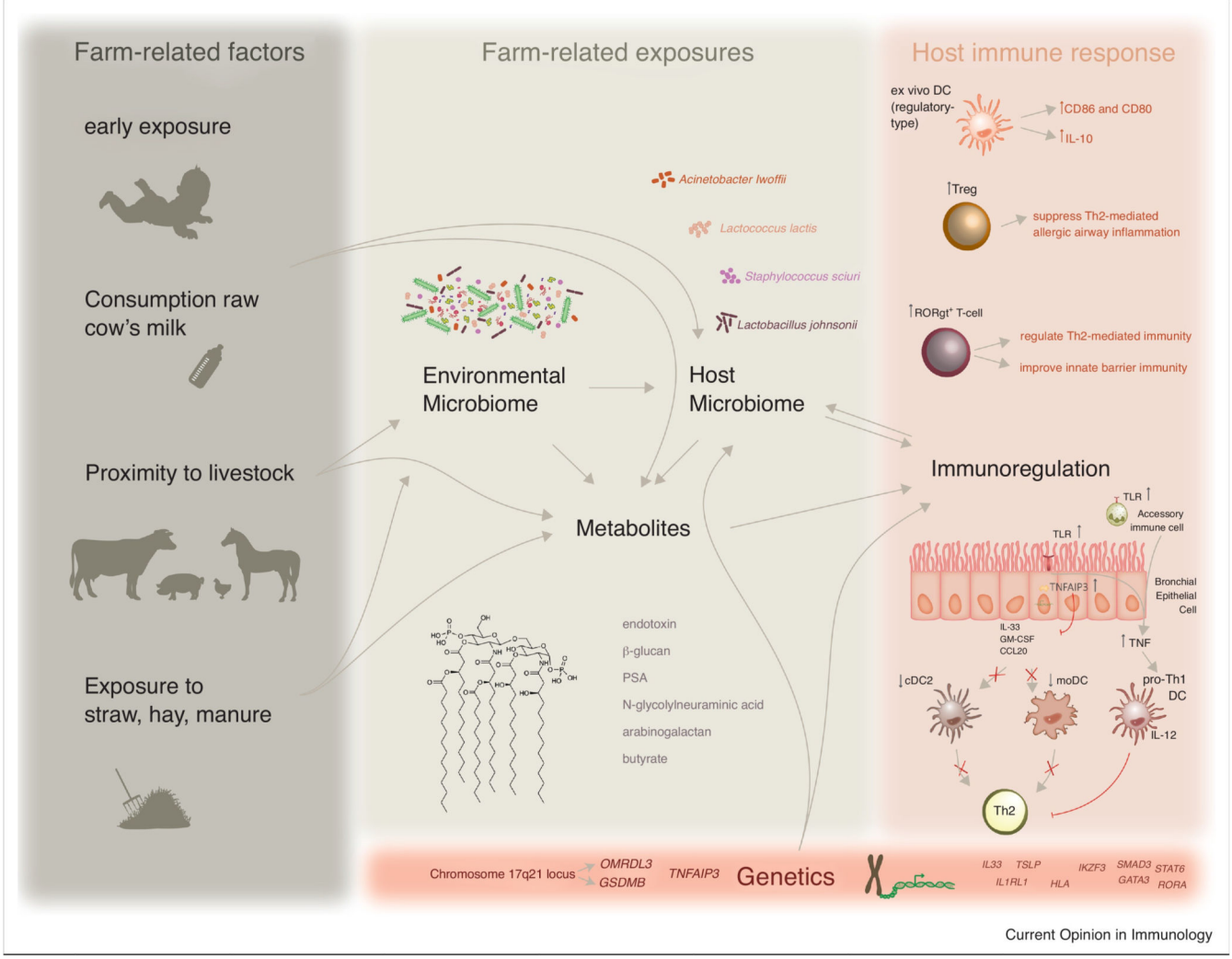

Figure 1. Early exposure to a farming environment protects from the development of allergy.

This type of environment is rich in microbes that can produce metabolites and colonize the host, leading to a microbiome change. This will in turn impact on immune cells and barrier epithelial cells, and modify the way they respond to allergens.

Table 1

Selection of recent evidence for farm-related exposures that affect allergy or asthma

Nature of exposure		Area of exposure	Effect on allergy or asthma	Subject of study	Reference
Microbial and non-microbial agents	Endotoxin	Mattress, Home dust	⇔	Subjects living on a farm or in rural area	10,25-29
		Murine airways		Experimental mouse model for asthma	76, 77
		Home dust	No relation or exacerbation	Patients with non-atopic (e.g. exercise-induced) or viral triggered wheeze	25,27,30
		Mattress, Home dust	Reduced lung function	Asthmatic patients (both atopic and non-atopic)	31-32
	β-glucan	Home dust	⇔	Children with asthma	32
		Home dust	Exacerbation	Children with asthma	32
		Murine airways		Experimental mouse model for asthma	33-35
	Extracellular polysaccharide	Home dust	⇔	Subjects living on a farm	29, 37,38
	N-glycolylneura-minic acid	Antibodies in Serum	⇔	Non-atopic children living on a farm	39
		Murine airways	⇔	Experimental mouse model for asthma	39
	Arabinogalactan	Murine airways	⇔	Experimental mouse model for asthma	40
Bacteria that colonize the host Acinetobacter lwoffii	*Moraxella species*	Human upper and lower	Exacerbation	Children that don't live on farm. Farmers' children are protected	42,43
	Lactococcus lactis	Murine airways	⇔	Experimental mouse model for asthma	44
	Staphylococcus sciuri	Murine airways	⇔	Experimental mouse model for asthma	45
	Acinetobacter lwoffii	Human skin colonization	Correlation with IL-10 in PBMCs	Healthy adolescents, living in an area with rich biodiversity	50
		Murine airways	⇔	Experimental mouse model for asthma	44, 69
		Murine skin		Asthma model induced by epicutaneous sensitization to OVA	51
	Lactobacillus johnsonii	Murine gut	⇔	Experimental mouse model for asthma	47
	Bacillus species	Mattress	⇔	Patients with allergic rhinitis	52

⇔Abbreviations:inverse relationship, OVA: Ovalbumin, IL-10: Interleukin-10, PBMCs: Peripheral Blood Mononuclear Cells