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Immunological and Inflammatory Responses to Organic Dust in Agriculture

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Abstract

Purpose of review—Agriculture represents a major industry worldwide, and despite protection against the development of IgE-mediated diseases, chronic exposure to agriculture-related organic dusts is associated with an increased risk of developing respiratory disease. This article will review the literature regarding new knowledge of important etiologic agents in the dusts and focus on the immunologic responses following acute and repetitive organic dust exposures.

Recent findings—Although endotoxin remains important, there is an emerging role for non-endotoxin components such as peptidoglycans from Gram-positive bacteria. Pattern recognition receptors including Toll-like receptor 4 (TLR4), TLR2 and intracellular nucleotide oligomerization domain-like receptors are partially responsible for mediating the inflammatory consequences. Repeated organic dust exposures modulate innate and adaptive immune function with a resultant adaptation-like response. However, repetitive exposures cause lung parenchymal inflammation, chronic disease, and lung function decline over time.

Summary—The immunological consequences of organic dust exposure in the farming industry are likely explained by the diversity of microbial motifs in dust that can elicit differing innate immune receptor signaling pathways. Whereas initial activation results in a robust inflammatory response, repetitive dust exposures modulate immunity. This can result in low-grade, chronic inflammation and/or protection against allergic disease.

Keywords

Farm; innate immunity; respiratory disease; adaptation; endotoxin; peptidoglycan; pattern recognition receptors

Introduction

Agricultural workers are at an increased risk of developing respiratory disorders including rhinosinusitis, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), and hypersensitivity pneumonitis. The resultant respiratory disease is predominately non-IgE mediated and marked by neutrophilic influx. As the agricultural industry has evolved, it is now recognized that livestock farmers as compared to crop farmers are at the highest risk

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of developing chronic bronchitis, COPD and lung function decline (1). This may be explained by the increase in large-scale, concentrated, closed, animal-feeding operations that can generate significant amounts of dust. Chronic inhalation of these complex organic dusts, rich with particulates and microbial-rich components, is implicated in disease development and severity (1). Although endotoxin remains an important inflammatory agent, peptidoglycans, Gram-positive bacteria cell wall components, (1→3)-β-D-glucans, and fungi are all emerging as potentially important players.

By focusing on the innate immune response to these various agents, there is new information on host genetic factors and potential novel targets. There has also been progress to better establish and understand the chronic inflammatory adaptation response, which describes the phenomenon whereby initial exposure to organic dust elicits an intense inflammatory response that subsequently wanes following repetitive exposures. Yet, repetitive exposure leads to chronic airway disease in agricultural workers. Finally, understanding the immunologic response to organic dust may also have implications in explaining the protective effect of agricultural exposures with allergy. This review will highlight these recent advances in organic dust-induced inflammatory consequences primarily focusing on industrial animal farming environments. This review will not discuss hypersensitivity pneumonitis, which was reviewed by Girard and Cormier in this journal last year (2). A schematic of the agents and immunologic consequences of organic dust exposure in the agriculture industry is shown (Figure 1).

Exposure Assessments and Disease Associations

To determine the etiology of airway disease manifestations in farmers, studies have investigated the relationships between quantifiable environmental agents with airway disease consequences. Generally, respirable particle counts, total dust, endotoxin, and ammonia levels are analyzed because of the relative ease in measuring these agents and their association with symptoms and disease. Whereas endotoxin (cell wall component of Gram-negative bacteria; lipopolysaccharide/LPS) is routinely measured and linked to airway inflammatory outcomes (3,4), there has been disagreement as to the association of endotoxin and disease in exposed workers. There can be high endotoxin exposure without symptoms (5,6) or low endotoxin exposure with a possible dose-response relationship (6). To date, endotoxin remains an important agent, but discrepancies in its association with disease continue to exist. Senthilselvan and colleagues reported that cross-shift changes in lung function among workers changed significantly in poultry layer operations (caged), which was associated with endotoxin concentration (7). However, endotoxin concentration was higher in the poultry broiler operations (floor), but no significant association was observed in lung function changes (7). A potential explanation may lie in respirable size fraction and its association with endotoxin. In floor-housed poultry operations, more endotoxin was found in larger size fraction (>9.8 μm) whereas in caged-housed operations, endotoxin was found to be greater at smaller size fractions (1.6–3.5 μm)(8).

To understand the real concentration and nature of airborne microorganisms, applied molecular approaches and gas chromatography-mass spectrometry (GC/MS) methods are being utilized (9). Phylogenetic analysis has revealed large number of sequences (>90%) related to Gram-positive anaerobic bacteria (10) and methanogenic archaea (11) in the bioaerosols from swine facilities. Mass spectrometry methods revealed high concentration of muramic acid, a marker of peptidoglycan (PGN) derived predominately from Gram-positive bacteria (i.e.~85% of cells wall), but also Gram-negative bacteria (i.e.~5% of cell wall), in settled dust samples from swine and dairy barns (12–14). Levels of muramic acid have been associated with inflammatory outcomes in humans following swine barn exposure in Europe (15,16). β-glucans have also been measured in agricultural environments and are recognized

as potentially modulating inflammatory responses (17,18). These studies highlight the complexity of the exposure setting, and also underscore the importance of broadening environmental sampling approaches beyond endotoxin and dust particulate to understand the full-range of biological agents responsible for disease development. This information could be important for establishing and setting occupational guidelines for the industry.

Role of Innate Immune Pattern Recognition Receptors

Because organic dusts from agricultural settings contain a high quantity of microbial rich components, targeting pattern recognition receptors (PRRs) that recognize specific microbial components has been a strategy to determine the role of specific inflammatory agents within dusts and to potentially reduce dust-induced airway disease. One family of innate immune receptors responsible for recognizing highly conserved microbial motifs is the Toll-like receptors (TLRs). Of the human TLRs, TLR4 forms a complex with CD14 and LPS-binding protein (LBP) to recognize and respond to endotoxin. Earlier work established that corn dust-induced airway inflammation could be significantly and dramatically reduced in endotoxin-resistant mice (19,20). However, the same is not true for animal farming dusts. In the TLR4-deficient mouse, animals were significantly protected from neutrophil airway influx following a one-day exposure to swine barn air (21). However, there was no difference in swine barn air-induced cytokine release or airway hyper-responsiveness (AHR) in TLR4-deficient animals as compared to controls (21). There is a role for TLR4 variants in humans exposed to swine barns. Humans with variant in TLR4 (299/399) were found to have decreased cross-shift change in lung function (FEV_1) following a high endotoxin swine barn exposure challenge, but no difference was observed after a low endotoxin swine barn exposure challenge (22). In a separate study, CD14 polymorphorisms (CD14/-159T and CD14/-1610G) were associated with increased prevalence of wheezing among farmers (23). These studies validate the role for endotoxin, but also highlight an important role for TLR4-independent pathways.

In further support of non-endotoxin components in swine facility organic dust playing important biological roles, dust extracts reduced of endotoxin retain significant ability to elicit inflammatory and biological responses in a variety of cell types (13,24–28). Given the abundance of Gram-positive bacteria in dusts, recent studies have focused on the TLR2 pathway because TLR2 recognizes lipoteichoic acid, lipoproteins, and peptidoglycans from Gram-positive bacteria. Swine facility organic dust exposure upregulated airway epithelial cell TLR2 (29), and blocking epithelial cell TLR2 resulted in a dampening of pro-inflammatory cytokine release after organic dust exposure *in vitro* (30). In addition, neutrophil influx, cytokine release, and lung parenchymal inflammation was significantly less in TLR2-deficient mice following single and repetitive organic dust intranasal inhalation challenges as compared to control animals (31). However, AHR and NO release were not reduced (32). Although a role for TLR2 gene variants in agriculture workers is not known, children of farmers with polymorphism in TLR2/-16934 were less likely to have asthma and allergic symptoms compared to children of non-farmers with same polymorphism (33). Thus, there is a critical role for the TLR2 signaling pathway, but it is noted that inflammatory outcomes were not completely eliminated, suggesting that TLR2-independent pathways are also important.

Another innate immune PRR group that senses microbial motifs is the NACHT-LRR protein family. Of this large family of intracellular proteins, there is a role for nucleotide oligomerization domain 2 (NOD2), which senses muramyl dipeptide, a component of virtually all types of bacterial-derived peptidoglycan. Organic dust extracts, as well as endotoxin and peptidoglycan, upregulated NOD2 expression in mononuclear phagocytes, which was dependent on dust-induced NF-κB activity as opposed to a TNF-α autocrine/

paracrine mechanism (34). In comparison, endotoxin and peptidoglycan products alone upregulate NOD2 expression via TNF-α in epithelial cells (35–37). Loss of NOD2 resulted in an enhancement of select mediator production from isolated lung macrophages following organic dust stimulation, and *in vivo*, there was small, but significant increases in airway inflammation in the NOD2-deficient mice following organic dust challenges (34). Although other groups have also reported that NOD2 may play a negative regulatory role following TLR2 signaling (38) and TLR4-signaling (39), there are also reports that in the absence of NOD2, pro-inflammatory cytokine production is reduced after stimulation with various TLR agonists (40,41), suggesting a positive regulatory role. Although not described in agriculture workers, NOD2 polymorphisms have been implicated in atopic diseases (42). Interestingly, NOD1, which senses muropeptides commonly found in Gram-negative bacteria, has been associated in several studies with asthma susceptibility and development (42–44).

Chronic Inflammatory Adaptation Response

Organic dust exposures in agricultural environments result in an intense inflammatory response that attenuates over time, but repetitive exposures can result in chronic respiratory disease. This chronic inflammatory adaptation response (45) is well recognized, but the mechanisms to explain it are not clear. Recent advances have improved our insight into this phenomenon. Sundblad and colleagues (46) assessed whether inflammatory responses to organic dust and endotoxin challenges were similar in pig farmers and smokers (both groups routinely exposed to organic material) compared to healthy nonsmokers (naïve group) with the hypothesis that tolerance/adaptation developed in the regularly organic dust exposed groups and that cross reactivity between different types of organic dust exposures existed. They confirmed that as compared to controls and consistent with the adaptation observation, pig farmers demonstrated an attenuation of symptoms, lung function, bronchial responsiveness, and markers of airway inflammation, but yet had markers of low-grade, on-going inflammation. However, the results were mixed with smokers because in some parameters smokers responded like controls, but in other parameters responded like the farmer group, suggesting that an indoor swine farming environment and tobacco smoke exposure do not activate identical adaptive mechanisms. Additionally, they observed that exposure in the pig barn was a much stronger pro-inflammatory stimulus than the inhalation of pure endotoxin (LPS), even though the doses of the LPS challenge were 200-fold higher than the doses inhaled in the pig barns. This latter observation is consistent with the concept that non-endotoxin components are playing an important role in the response to animal farming agricultural dusts.

Earlier work demonstrated that swine workers have increased levels of soluble L-selectin, which may be important in the adaptation response because soluble L-selectin decreases inflammatory cell migration (47). Recent studies have demonstrated that pig farmers as compared to controls demonstrate an increase in circulating neutrophils and IL-13- and IL-4-producing Th2 cells as well as diminished TLR2 expression on peripheral blood monocytes (48). Moreover, a relative monocytosis and a monocyte TNF-α hyper-responsiveness occurred after swine barn exposure (49). These findings suggested alteration in systemic innate and adaptive immune responses following organic dust challenges.

In cell culture models, repeat exposure of healthy human peripheral blood monocytes to organic dust and its components (endotoxin, peptidoglycan and endotoxin-reduced dust) resulted in a tolerant response with regards to TNF-α and IL-6, but not CXCL8/IL-8 and IL-10, which was partially mediated by protein kinase C (PKC) activity (24). Notably, in bronchial epithelial cells, organic dust-stimulated IL-6 and CXCL8/IL-8 release are strongly mediated by sequential activation of PKCα and PKCε following an autocrine/paracrine dust-induced TNF-α response (50). Repetitive exposure to organic dust modulates innate immune

host defense in macrophages and dendritic cells (DCs). Specifically, when monocytes are differentiated into macrophages in the presence of dust extracts, cell-surface marker expression (HLA-DR, CD80, CD86), phagocytosis, intracellular bacterial killing, and cytokine responsiveness are significantly impaired as compared to control macrophages differentiated without dust extracts (13). In addition, organic dust exposure altered monocyte differentiation to immature DCs and prevented maturation of immature DCs to mature DCs (25).

Animal models to understand the chronic adaptation inflammatory response have been developed. One model whereby rodents are placed in hanging cages within the swine barn demonstrated increased AHR, cellular influx, and cytokine release after one day of exposure and resolution of AHR and dampening of cellular and cytokine releases with repetitive exposures (51). Although chronic lung parenchymal changes were observed, changes were subtle (51). Other animal models utilizing intranasal or nebulization administration of dust extracts also demonstrated similar adaptation responses, but produce an overall exaggerated airway inflammatory response (20,32). Specifically, robust increases in airway inflammatory mediators and AHR following single exposure were significantly dampened following repetitive exposures (32). Importantly, there were semi-quantifiable increases in peribronchiolar and alveolar compartment inflammation with the development of discrete mononuclear cellular aggregates composed of T-cells, B cells, and mononuclear phagocytes (32). Together these studies suggest that the adaptation response observed in humans can be applied to animal models. Future directions should investigate manipulating these models to understand the cellular and molecular mechanisms responsible for the chronic inflammatory adaptation response.

Farming Exposures and Protective Effects

For over a decade, it has been recognized that children who grow up on the farm and farmers have less allergic (IgE-mediated) disease as compared to those who are not from farming communities (52). This observation is consistent with the hygiene hypothesis that suggests that lack of microbial exposure might be a risk factor for allergic disorders. The role for microbial agents modulating adaptive/T cell responses away from the classic allergic, Th2 phenotype, has been recently reviewed (53). As this current review highlights, organic dust exposure(s) modulate innate immunity, and it could be speculated that having an adapted/tolerant innate immune response might protect one from responding to allergens. There is evidence that exposure to farm environments can alter innate immunity in children and associated atopic disease. Maternal contact with farm animals and cats during pregnancy significantly protected children in the first 2 years of life from developing atopic dermatitis (54). Furthermore, elevated gene expression of TLR5 and TLR9 (trends were observed for other TLRs and CD14) in cord blood was associated with decreased atopic dermatitis (54). A separate study found that although allergic children had an exaggerated innate immune response at birth, by age 5 years these children had significant attenuations in their TLR2-9 ligand responsiveness compared to nonallergic subjects (55).

Agricultural exposures might also be protective against the development of cancer because a meta-analysis reported that occupational exposure to endotoxin in agriculture is protective against lung cancer (56). However, there might be important differences in gender because it was reported that between 1984 and 1998, after adjustment for smoking, there was significant excess proportionate lung cancer mortality among women in the United States working in agriculture (57). To further highlight a potential difference in gender in respiratory outcomes in agriculture work, upper, but not lower respiratory tract symptoms were found to be more frequent in women than in men employed in a variety of organic dust-producing industries (58).

CONCLUSION

Organic dust exposure in the farming industry, particularly large animal farming, is associated with the development of chronic respiratory diseases. The exact etiology of disease remains unclear, but emerging evidence shows that it cannot be ascribed to one or two agents alone. Targeting host defense response to pathogen-associated molecular patterns and/or common downstream proteins is one potential future strategy to dissect out the key components mediating disease in this complex environment as well as to prevent and reduce disease manifestations. Genetic factors in innate immune host defense are important, and future studies to understand gene-environment interactions are warranted. Utilization of newly developed cell culture and animal models to expand our understanding of the complex inflammatory adaptation response is necessary. The goal remains to identify key environmental factors and host defense responses that can ultimately be targeted to alleviate disease in exposed agriculture workers. Information from cohort studies, such as the young Danish farmer longitudinal study, should provide new information over the forthcoming years (59). Importantly, the creation of AGRICOH, a consortium of agricultural cohorts in nine countries, should provide a venue for affirming key observations with larger numbers of persons from diverse areas regarding immunologic and inflammatory responses to agricultural exposures (60).

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KEY POINTS

- Agriculture work is associated with increased risk of developing chronic respiratory disease despite a protection against the development of IgE-mediated diseases.
- The inflammatory consequences from organic dust exposure in the agriculture industry, particularly the animal industry, are likely explained by the diversity and synergy of microbial motifs with endotoxins and peptidoglycans as key components.
- Pattern recognition receptor signaling pathways involving TLR2, TLR4, and NOD2 are partially responsible for mediating inflammatory consequences to organic dust environments.
- Whereas the initial exposure to organic dust elicits a robust inflammatory response, there is a dampening, but not complete resolution, of airway inflammatory consequences, which is consistent with the so-called chronic inflammatory adaptation response.
- The creation of agricultural cohorts like the AGRICOH should provide a venue for affirming gene-environment observations with larger numbers of persons from diverse areas in regards to the immunologic and inflammatory responses to agricultural exposures.

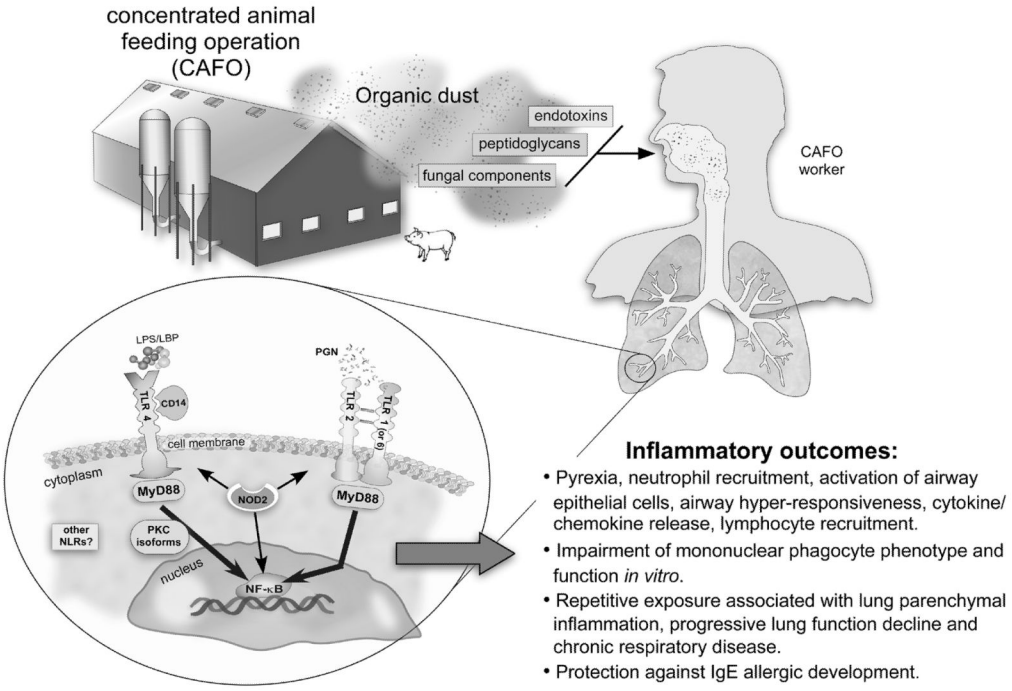

Figure 1.

An overview schematic is depicted of the agents and immunologic and inflammatory consequences of organic dust exposure in the agriculture industry. Large, concentrated animal feeding operations (CAFOs) can produce significant amounts of organic dust rich in microbial motifs (i.e. peptidoglycans, endotoxins, fungi) and particulates that can be easily respirable by exposed workers. These complex dusts are recognized by highly conserved innate immune receptor signaling pathways resulting in various immunologic inflammatory outcomes. Key: LPS: Lipopolysaccharide/endotoxin, LBP: LPS binding protein, PGN: peptidoglycan, TLR: Toll-like receptor, NLR: Nucleotide oligomerization domain-like receptors, NOD2: Nucleotide oligomerization domain 2, PKC: protein kinase C