

Endotoxin and the lung: Insight into the host-environment interaction

Jaspal Singh, MD,^a and David A. Schwartz, MD, MPH^{a,b} Durham, NC

Understanding the pathophysiology and basic mechanisms of asthma and chronic obstructive pulmonary disease (COPD) has been an intense source of investigation over the years. For decades, research in these fields has focused on the control of inflammation. However, new evidence has emerged demonstrating that airway inflammation is just the surface of a more complex pathobiological relationship between the disease and its host. Specifically, the relationship is a unique interaction of one's genetic background and the environment. The airway response to inhaled endotoxin serves as an effective model for studying the pathobiology of asthma as well as the importance of host genetic susceptibility. In this review, we provide a brief overview on the role of endotoxin in asthma and COPD, highlighting a few of the major discoveries, but also discussing future directions. (*J Allergy Clin Immunol* 2005;115:330-3.)

Key words: Endotoxin, LPS, asthma, allergy, COPD, hygiene, T_H1 , T_H2 , genetics, genomics, polymorphisms, innate immunity, TLR

Over the years, numerous investigators have used endotoxin's effects to model and study airway diseases. Surprisingly, endotoxin is not only an effective model of airway disease; environmental endotoxin may itself cause airway disease. After all, endotoxin is ubiquitous in the environment and induces a wide spectrum of acute and chronic airway manifestations. To the contrary, there is also evidence that exposure to environmental endotoxin early in life may be protective from the development of allergy and/or asthma. Such heterogeneity in the response to endotoxin has raised important insight into the host-environment interaction. But how does endotoxin play all these roles? Key elements appear to be the dose and timing of the exposure and the genetic influence on one's immune system. In this article, we review the epidemiology and biology of endotoxin-induced airway disease, highlight-

Abbreviations used

BAL: Bronchoalveolar lavage

COPD: Chronic obstructive pulmonary disease

ing the role of genetic determinants in this complex interaction, and discuss the future research needs. Perhaps understanding the effects of endotoxin on airways, specifically in relation to the development of asthma and COPD, we will gain better insight into the relationship between the host, one's environment, and the development of clinical disease.

ENDOTOXIN IS UBIQUITOUS IN THE ENVIRONMENT

Endotoxins are LPS fragments that coat the outer membrane of gram-negative bacteria. Significant amounts of endotoxin have been uncovered in settled dusts and ambient air of occupational and domestic environments, although in highly variable quantities. Common occupational sources of exposure include livestock, grain dust, and textiles, but significant concentrations also occur in the household from pets, carpeting, and indoor ventilation systems.¹ Several investigators have also found endotoxin in tobacco smoke² and particulate matter in air pollution.³ Although our lungs are constantly exposed to endotoxins in the environment, the host response to inhaled endotoxin varies. The role of endotoxin in airway disease pathogenesis remains to be defined precisely.

AIRWAY RESPONSE TO LPS

Inhalation of LPS can cause a host of airway responses including symptoms of chest tightness, myalgias, fevers, chills, and dyspnea. The corresponding physiological responses include airflow obstruction, enhanced airway hyperreactivity, and a reduction in alveolar diffusion capacity. At the cellular level, recruitment of resident macrophages and neutrophils has been demonstrated in

From ^athe Department of Medicine at Duke University Medical Center and ^bthe Durham Department of Veterans Affairs Medical Center.

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Reprint requests: Jaspal Singh, MD, Duke University Medical Center, Durham, NC 27710. E-mail: Jaspal.Singh@duke.edu.

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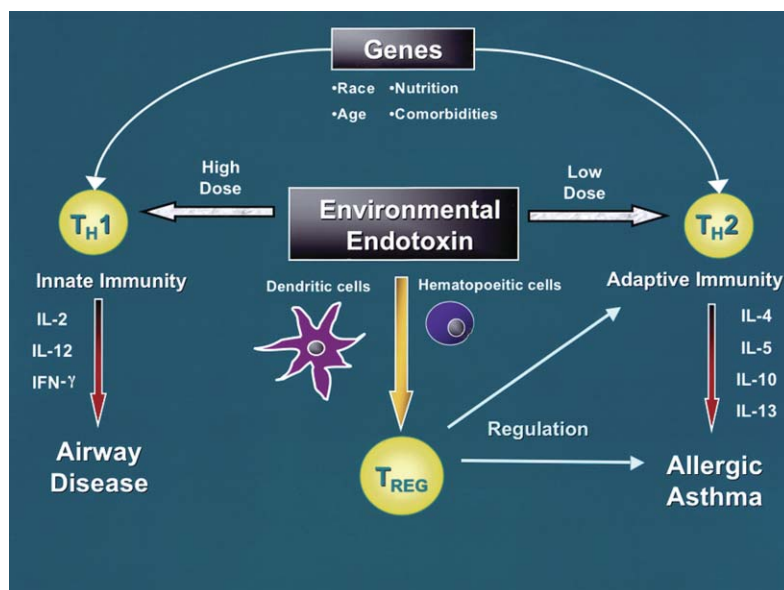


FIG 1. Environmental endotoxin, depending on dose and timing, can result in predominantly either an adaptive or innate immune response. Endotoxin directly and indirectly stimulates lung resident (dendritic) and recruited (hematopoietic) cells, which in turn interact with T_{reg} cells. The T_{reg} cells modulate the adaptive immune system to develop clinical allergy and/or asthma. Individual genetic predilection, modified by other factors of host susceptibility, mediates this complex interaction.

bronchoalveolar lavage (BAL) fluid; likewise, increased concentrations of inflammatory mediators (eg, IL-1, IL-6, IL-8, TNF- α) have been recovered from BAL fluid after inhalation or local instillation of LPS.⁴ With acute exposure to inhaled endotoxin, murine models demonstrate not only histologic inflammation but also airway hyperresponsiveness and neutrophilic cellular response in the BAL fluid.⁵ Thus, it appears that inhaled endotoxin induces a physiologic and inflammatory airway reaction that phenotypically resembles an acute asthma flare. However, unlike an asthma flare, the pathophysiologic response to inhaled LPS or to dusts containing LPS can be reproduced in subjects without asthma.⁶

Notably, inhaled endotoxin is more than simply an experimental model of asthma. It plays a major role in the clinical development of asthma for a wide range of exposed individuals. In patients with mild atopic asthma, exposure to air containing low levels of endotoxin (250 ng/m³) for 4 hours before bronchial challenge with allergen significantly increased both bronchial reactivity and airway eosinophilia.⁷ Such airway obstruction was achieved with lower doses of inhaled endotoxin in subjects with asthma versus normal subjects, indicating an important issue of host susceptibility.⁶ Similarly, occupational exposure to endotoxin causes a greater fall in FEV₁ in atopic than in nonatopic workers.⁸ Environmental endotoxin exposure induces airway hyperreactivity, and there may be distinct effects on individuals with atopy or pre-existing asthma.

Chronic exposure to endotoxin may also be associated with the development of chronic obstructive lung disease. In mice, chronic intratracheal exposure to LPS elicits lung

pathologic changes similar to human COPD-associated inflammation.⁹ In rats, acute exposure to intratracheal LPS alters lung histology even after 16 days beyond the acute exposure, with a resulting increase in extracellular matrix, differentiation of myofibroblasts, and altered secretion of surfactant by newly differentiated type II pneumocytes.¹⁰ Textile workers who developed byssinosis (thought now to be caused mainly by chronic occupational endotoxin exposure) developed severe obstructive airway disease.¹¹ Similarly, swine confinement workers developed symptomatic chronic airflow obstruction; corresponding histology revealed thickening of the airway basement that was similar to COPD.¹² Understanding such mechanisms of injury will lead to new insight in the pathogenesis of chronic airway diseases.

EPIDEMIOLOGY OF ENDOTOXIN-INDUCED AIRWAY DISEASE

The prevalence of asthma and COPD in various populations is clearly affected by the environment. Tobacco exposure has been linked to the number of asthma exacerbations, and smoking may even retard efficacy of asthma medications¹³; similarly, the development of COPD has been unequivocally linked to smoking. Given the presence of endotoxin in tobacco smoke,² it is conceivable that the airway inflammation of these diseases is also mediated by endotoxin. In the absence of cigarette smoke, several studies have established that significant endotoxin levels also occur in the domestic environment and that levels of exposure may

relate to disease severity.¹⁴ Subjects with asthma with high levels of home endotoxin exposure had increased dyspnea and treatment scores as well as increased medication usage.¹⁵ A recent epidemiologic survey of the homes of children with asthma in Puerto Rico found very high levels of environmental endotoxin and correlated these with increased health care utilization and use of asthma medication.¹⁶ Clearly, endotoxin induces and exacerbates airway disease, but the source, dose, and timing of endotoxin that elicit disease remain to be discerned.

HYGIENE HYPOTHESIS: CAN EXPOSURE TO ENDOTOXIN BE BENEFICIAL?

Several studies suggest that chronic low levels of exposures to endotoxin during infancy may reduce the risk of developing atopy and even asthma. The controversial hygiene hypothesis has been extensively reviewed by Liu.¹¹ Some epidemiologic studies have observed a lower prevalence of allergic rhinitis, asthma, and inhalant allergen sensitization in persons who have grown up around higher concentrations of endotoxin or had significant respiratory infections (eg, measles, tuberculosis). The number of childhood febrile infections in the first year of life by parental self-report was also associated with decreased risk of the development of asthma and atopy.¹⁷ Early participation in daycare and older siblings (presumably exposing children to more microbial pathogens) appear to reduce the risk of atopy and asthma.¹⁸ Increased endotoxin levels in house dust correlated with lower levels of allergic sensitization in German children,¹⁹ and higher levels of endotoxin in a child's mattress were associated with a lesser incidence of hay fever and atopic sensitization.²⁰ In young mice, presensitization with ovalbumin attenuates the hyperresponsiveness to inhaled LPS.⁵ All of these studies highlight a potential mechanism whereby chronic exposure in early life may be protective from the eventual development of asthma and atopy. As intriguing as these studies are, many of these data are merely associations. Furthermore, other epidemiologic studies do not support this association. In fact, epidemiologic findings have been published that suggest that individuals exposed to endotoxin early in life may be at higher risk of developing asthma. For instance, crowding in the home²¹ and increased public hygiene is associated with the development of asthma. Moreover, a recent study has shown that higher levels of domestic endotoxin may be a risk factor for the development of asthma in children.²² Nevertheless, there is evidence that environmental endotoxin exposure in early life may prevent the development of asthma and atopy.

The biological basis for the potential protective effect of early low dose endotoxin exposure is a shift in the balance between T_H1 and T_H2 immune cells.¹¹ However, recent findings indicate that both T_H1-mediated and T_H2-mediated immunity can produce airflow obstruction and airway inflammation.²³ Endotoxin and presumably other innate

immune stimuli may primarily affect the function of T_{reg} cells that control the biological activity of T_H1 and T_H2 lymphocytes. Thus, under some circumstances (dose-dependent and development-dependent), innate immune stimuli, through their effect on dendritic and T_{reg} cells, may profoundly affect the development of allergies, asthma, and other immune-mediated diseases (Fig 1).

In considering the effects of endotoxin and other innate immune stimuli on the development of allergic diseases, one could conceivably consider stimulating the innate immune system to control or regulate adaptive immunity. In fact, this is actively being pursued by several immunologists and may represent a novel approach to control asthma and other forms of airway disease.

GENOMICS OF ENDOTOXIN RESPONSE

Is it possible that the immune dysregulation behind asthma (and endotoxin exposure) mostly occurs at the genetic level? Although the genetic associations are inconsistent, numerous familial aggregation, twin, and large genetic cohort studies show that a genetic predisposition to asthma indeed exists.²⁴ Given our current understanding of the innate immune receptor/signaling pathway,²⁵ several potential candidate genes emerge that may play an important role in controlling the response to innate immune stimuli. For instance, a polymorphism of Toll-like receptor 4 (Asp299Gly) is observed in approximately 10% of individuals in the general population and has been associated with a blunted response to LPS *in vitro* and with diminished airway response to inhaled LPS.²⁶ A recent study found that the TLR4 polymorphism is more prevalent in Swedish children with asthma, especially those with atopic asthma, suggesting that an inability to respond to endotoxin places one at higher risk of T_H2-mediated diseases.²⁷ Although a large family-based cohort study did not find TLR4 polymorphisms to be associated with asthma or atopy,²⁸ another recent study found that individuals with the TLR4 polymorphism appeared to have an increased risk of being atopic.²⁹ Concordantly, the presence of CD14 (a ligand for the TLR4 receptor) can modify the response to inhaled LPS,³⁰ whereas a genetic polymorphism for CD14 may determine severity of atopy.³¹ In addition, a genetic variation of the TLR2 gene was associated with the development of asthma in children of European farmers.³² Polymorphisms of genes involved in the TLR pathway (eg, *IRAK-4*, *NEMO*, *Csp-12*) that are involved in other human diseases are also being investigated regarding their contribution to asthma susceptibility.³³ Overall, it appears that a genetic predisposition to asthma exists and that fundamental mechanisms of the innate immune system may be involved.

CONCLUSION

The environment is constantly evolving at a speed faster than our genetic makeup is accustomed to change. As environmental toxins, gases, and particles accumulate

with changes in our surroundings, it is no wonder that diseases that are influenced by the environment continue to proliferate despite medical technologic advances. How will the human genome, which has evolved over a period of thousands of years, adapt to these environmental alterations that are of relatively recent origin? If the adaptation to innate immune stimuli is an indication, it is clear that there is a dynamic interplay of the human genome, the environment, and the risk of developing clinical disease. Because the lung is intimately connected to the environment, adaptive mechanisms have developed that modulate the toxicity of inhaled environmental pollutants. Further investigation of these environmental defense mechanisms may lead to new insights into asthma and other forms of lung disease.

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