

What the 21st century does not know about asthma—yet

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The 2007 update of the “Guidelines for the diagnosis and treatment of asthma,” summarized in the November 2007 issue of this Journal, eloquently and completely covers our current understanding of the pathogenesis, diagnosis, and management of asthma. It summarizes what my generation learned during the incredibly productive last half of the 20th century, but we must not become complacent. There is still much to learn, and there are many questions that the guidelines, which are based on current evidence, do not discuss, such as

1. Why do a few individuals have asthma but most do not?
2. Why does asthma develop when it does? Is there more we could do to prevent it?
3. Why do many patients recover from asthma spontaneously? Why do they recover when they do? Could we develop strategies to increase recovery?
4. Why do mature individuals more often have asthma that is intrinsic rather than allergic? What are the environmental/genetic relationships? These patients do not have the family correlation seen in patients with allergic asthma.
5. What are the intracellular pathways of the spectacular (and underinvestigated) variety of airway remodeling called nasal polyps? How are these pathways related to intrinsic asthma and aspirin idiosyncrasy?
6. Why is the airway obstruction incompletely reversible in so many elderly patients, even at the time of diagnosis?
7. Why is the severe obstruction that closes segmental bronchi with mucus plugs localized? What is the cause of localized hypertrophy of the submucosal mucus glands?

Answers to the preceding questions obviously are incomplete at present. The 21st century has begun several lines of investigation that promise some answers and new solutions to these questions. This article will discuss one of them: the role of response to molecules that activate innate immunity.

The guidelines stress that asthma results from interaction between environmental agents and expression of specific genetic alleles and that these interactions are very complex. A large part of the complexity lies in the intercellular and intracellular signaling cascades of the response to environmental agents. The 20th century established 2 categories of environmental agents: allergens and respiratory viruses. Since the turn of the century, interest has been focusing on a third category: agents that stimulate innate immunity. The term *innate immunity* refers to

an immediate inherent defense against infecting organisms that does not require a specific *acquired immune* response. The term was originally applied to defense against viruses and bacteria activated through Toll-like receptors, but it has recently been extended to a second process of defense against multicellular pathogens through protease-activated receptors (PARs). Innate immunity inflammatory responses are the same as the inflammation generated by antigen-antibody reactions. They produce the same cytokines, chemokines, and adhesion molecules and recruit granulocytes to attack the organisms. Innate immune responses can also be activated internally by endogenous stimuli and are involved in wound healing, cancer metastasis, and autoimmune diseases. Of course, they are also involved in allergic diseases. Toll-like receptor stimulation produces T_H1 cytokines, and PARs produce T_H2 cytokines, with the PAR inflammatory response closely resembling atopic IgE-mediated allergy (Table I).

These 2 pathways can coexist and interact; in particular, LPS increases the PAR response. Although exposure to endotoxin in infancy protects against asthma, exposure in later life increases it, and chronic exposure causes chronic obstructive pulmonary disease.¹ There is considerable evidence that exposure to environmental agents that stimulate PARs can cause asthma. Proteases, both endogenous proteases from the coagulation cascade, mast cells, and respiratory epithelial trypsin and exogenous proteases from parasites, insects, mites, molds, pollens, and other aeroallergens, can stimulate a tissue response that includes attraction and activation of eosinophils and neutrophils, degranulation of eosinophils and mast cells, increased response of afferent neurons, smooth muscle contraction, mucus secretion, angiogenesis, fibrosis, and production of IgE to antigens that otherwise would not do so.^{2,3} The expression of PAR-2 is increased on the epithelial cells of patients with asthma, but it is not known whether this increase occurs before or after asthma develops.⁴ Mast cell tryptase is a potent activator of PAR-2, but the response depends on differences between α and β tryptase and on glycosylation of the PAR-2 receptor molecule. Furthermore, in keeping with the central role of mast cells in asthma, activation of mast cell PAR-2 causes degranulation and cytokine release.

Airborne endotoxin and other agents that activate Toll-like receptors and serine and cysteine proteases that activate PARs produced by organisms growing in indoor environments, especially in damp or water-damaged buildings, offer a very plausible answer to the first 4 questions asked at the beginning of this article. Such exposures could explain pathogenic mechanisms of the increased incidence and prevalence of asthma in damp houses, schools, and office buildings. Dampness is not necessary for growth of mites and cockroaches, and because the proteases are in the fecal excretions, they presumably become airborne after they dry. Similarly, allergens and digestive proteases from molds that do grow in damp spots are excreted into the surrounding media from hyphae much more than from spores and remain in the dust to become airborne after the area dries.⁵ Finally, mouse droppings might be a source not only of endotoxin but also of trypsin, one of the activators of PAR-2.

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TABLE I. Brief summary of innate immunity of the lung

	T_H1-like	T_H2-like
Stimuli	Endotoxin, bacterial and viral RNA and DNA, and fungal β (1-3) glucans	Serine and cysteine proteases
Receptors	Toll-like receptors, especially Toll-like receptor 4	PARs, especially PAR-2
Airborne sources	Gram-negative bacteria and fungi	Mites and molds
Target organisms	Viruses, bacteria, and molds	Helminths, arthropods, and molds
Primary airway responding cells	Macrophages/monocytes	Epithelial and mast cells
Cytokines generated	TNF- α , IFN- γ , IL-6, IL-10, and IL-12	IL-4, IL-13, IL-5, GM-CSF, and IL-6
Chemokines generated	IL-8	Eotaxins
Adhesion molecules generated	ICAM-1	ICAM-1 and VCAM-1
Leukocytes activated and attracted	Neutrophils, monocytes, and lymphocytes	Eosinophils, monocytes, and lymphocytes
Granulocytes activated	Neutrophils	Eosinophils and mast cells
Increased immunoglobulin production	IgG	IgE
Tissue effects	Loss of alveolar elastic tissue and goblet cell hyperplasia	Bronchial hyperreactivity, basement membrane collagen production, smooth muscle hypertrophy, bronchial gland secretion and hypertrophy, angiogenesis, and increased noxiocception

Clinical studies are needed that include measurement not only of endotoxin but also of proteases in the environment. Standardized methods for measurement of endotoxin are available. Assays for serine and cysteine proteases are also available but have not yet been standardized and adapted for widespread use. Sample collection methods need evaluation, too. Theoretically, airborne concentrations would be most relevant, but should the sample be collected in the room for 24 hours or in a personal sampler? Some particles, such as mite allergens, settle so fast that dust samples actually correlate with disease better than air samples. Similar information about size and settling rate is needed about particles that stimulate innate immunity. Furthermore, methods of collecting settled dust and expressing the results need evaluation. What is the best apparatus? Is the molecule uniformly distributed in the building, and if not, where should the sample be collected? Should the results be expressed as concentration per gram of dust or concentration per square meter of area sampled?

After standardized methods of sampling have been shown to correlate with asthma, methods for controlling exposure need to be devised and evaluated. Some of these agents, particularly gram-negative bacteria and molds, are related to damp or water-damaged areas, and therefore the environment should be checked for excess moisture and corrected. Attention needs to be paid to modern building techniques that prevent areas of high humidity. Other innate immune stimulants occur in dry buildings. Measurement and control of mite and cockroach exposure is effective treatment for patients with specific IgE.^{6,7} Is it also effective for nonatopic asthmatic patients? Widespread clinical laboratory availability of assays for endotoxin and proteases in the environment could be as helpful in patient care as currently available assays for IgE antibodies. Such assays for mite, cockroach, and several occupational allergens have established levels that elicit symptoms.

The development of nasal polyps is associated with the germination of molds on the respiratory mucosa.⁸ Fungal protease activation of PARs on mast cells, epithelial cells, and connective tissue is the presumptive link between mold growth and polyp formation (see question 5 above). Perhaps molds germinating in the bronchi not only cause allergic bronchopulmonary aspergillosis but also are relevant to the pathogenesis of intrinsic asthma. Thirty years ago, while evaluating criteria for the diagnosis of allergic bronchopulmonary aspergillosis, I found that sputum

cultures for *Aspergillus* species were more than 90% sensitive but poorly specific. Almost half of the control patients with chronic asthma had positive sputum cultures. This observation needs to be followed up. If some patients with asthma have fungi or bacteria growing in a bronchus, it could account for the segmental location of mucoid impaction and the development in older asthmatic patients of bronchiectasis and segmental fibrosis, one of the reasons for irreversible obstruction (see questions 6 and 7 above). In this regard chronic combined exposure to both endotoxin and proteases could be the reason that older individuals often have irreversible obstruction from chronic obstructive pulmonary disease, even at the onset of asthma.⁹

In addition to the environment, the genetics of Toll-like receptor and PAR expression and signal transduction pathways need to be examined to account for why only a selected few individuals have asthma or polyps in response to these environmental agents. Hints include the observation that different forms of mast cell tryptase have different effects on PAR-2, and the PAR-2 response requires glycosylation.

There are, of course, many other productive areas of research to keep the investigators of the 21st century as occupied and productive as those of the 20th century.

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