Mechanisms of allergic diseases

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Mechanisms of occupational asthma

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: *Authors:* Piero Maestrelli, MD, Piera Boschetto, MD, Leonardo M. Fabbri, MD, and Cristina E. Mapp, MD

Activity Objectives

1. To identify the structure-activity relationship for causal agents of occupational asthma (OA).

2. To understand the role of environmental and genetic factors in OA development.

3. To understand the pathophysiology of immunologic and nonimmunologic OA.

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Inhalation of agents in the workplace can induce asthma in a relatively small proportion of exposed workers. Like nonoccupational asthma, occupational asthma is probably the result of multiple genetic, environmental, and behavioral influences. It is important that occupational asthma be recognized clinically because it has serious medical and socioeconomic consequences. Environmental factors that can affect the initiation of occupational asthma include the intrinsic characteristics of causative agents as well as the influence of the level and route of exposure at the workplace. The identification of host factors, polymorphisms, and candidate genes associated with occupational asthma may improve our understanding of mechanisms involved in asthma. High-molecular-weight compounds from biological sources and low-molecular-weight chemicals cause occupational asthma after a latent period of exposure. Although the clinical, functional, and pathologic features of occupational asthma caused by low-molecular-weight agents resemble those of allergic asthma, the failure to detect specific IgE antibodies against most low-molecular-weight agents has resulted in a search for alternative or complementary physiopathologic mechanisms leading to airway sensitization. Recent advances have been made in the characterization of the immune response to low-molecular-weight agents. In contrast, the mechanism of the type of occupational asthma that occurs without latency after high-level exposure to irritants remains undetermined. (J Allergy Clin Immunol 2009;123:531-42.)

Key words: *Workplace exposure, asthma, airway hyperresponsiveness, antigen, chemical, genetics, mechanisms, inflammation*

Occupational asthma (OA) is a type of asthma due to causes and conditions attributable to a particular work environment rather than to stimuli encountered outside the workplace.[1] OA has become one of the most common forms of occupational lung disease in many industrialized countries, having been implicated in 9% to 15% of cases of adult asthma. There is general agreement that 2 types of OA can be distinguished. First, immunologic OA appears after a latency period of exposure necessary for acquiring immunologic sensitization to the causal agent. It

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Terms in boldface and italics are defined in the glossary on page 532.

Abbreviations used

GST: Glutathione *S*-transferase
HDI: Hexamethylene diisocyanate
HMW: High molecular weight
LMW: Low molecular weight
NAT: *N*-acetyltransferase
NK2R: Neurokinin 2 receptor
OA: Occupational asthma
TDI: Toluene diisocyanate
WTC: World Trade Center

GLOSSARY

ACID ANHYDRIDES, COLOPHONY, DIISOCYANATES, PERSULFATE SALTS: Low-molecular-weight substances involved in occupational asthma. Diisocyanates and acid anhydrides are in vapor form. Isocyanates are found in paints, plastics, adhesives; acid anhydrides are found in epoxy resins; colophony (abietic and resin acids) is obtained from conifers and used in the electronic industry; and persulfate exposure occurs in hair dressers.

APOPTOSIS: Apoptosis, also referred to as *programmed cell death*, typically induces very little inflammation because of a lack of cell lysis and discharge of intracellular constituents. Apoptosis can occur because of intrinsic damage signals such as reactive oxygen species that activate "apoptosome" complexes, which in turn activate caspases, or because of extrinsic death signals such the binding of Fas-ligand and TNF to their receptors with subsequent activation of caspase-8. Assays such as a terminal deoxynucleotide transferase-mediated dUTP nick end labeling can detect the presence of DNA strand breaks typical of apoptotic cell death.

α-HELIX: The α-helix is the most common helical secondary structure found in proteins. Properties include a radius that allows for favorable van der Waals interactions and side chains that are staggered to minimize steric interference.

CHITINASE: Chitinases are digestive enzymes that break down glycosidic bonds in chitin. Despite the absence of chitin, mammals synthesize chitinases. Murine asthma models initially demonstrated the role of chitinases in T_H2 airway inflammation. Subsequent human studies have demonstrated increased pulmonary and peripheral expression of chitinase 3-like1, in patients with severe asthma and airway remodeling.

EPIGENETICS: Used to describe studies of stable and heritable (or potentially heritable) changes in gene expression that do not involve changes in DNA sequence. Epigenetic mechanisms such as DNA methylation, histone deacetylation, and other modes of chromatine remodeling, ensure that genes are expressed or silenced with respect to developmental stage and cell type. The changes may remain through cell divisions for the remainder of the cell's life and may also last for multiple generations. Epigenetic traits exist on top of or in addition to the traditional molecular basis for inheritance.

γ/δ T CELL: γ/δ T cells represent a small subset of T cells that possess a distinct T-cell receptor, made up of 1 γ-chain and one δ-chain, on their surfaces. γ/δ T cells are less common than α/β T cells, recognize antigens such as heat shock proteins and mycobacterial lipids without requiring MHC I or II presentation, and are found as intraepithelial lymphocytes in the skin and gut mucosa. γ/δ T cells are capable of producing T_H2-associated or T_H1-associated cytokines and ILs.

GLUTATHIONE *S*-TRANSFERASE (GST): The GST is a family of enzymes that comprises a long list of cytosolic, mitochondrial, and microsomal proteins capable of multiple reactions with a multitude of substances, both endogenous and xenobiotic. GSTs catalyse the conjugation of reduced glutathione via the sulfhydryl group, to electrophilic centers of a wide variety of substances. This activity is involved in the detoxification of endogenous compounds as well as in the metabolism of xenobiotics. Polymorphisms within genes of the GST family are associated with risk of developing both nonoccupational and occupational asthma.

IgG_4: IgG subclass that is essentially equivalent in concentration to IgG_3 in human serum, can be decreased in conjunction with IgA in patients with IgA deficiency, and does not activate complement. Successful immunotherapy can be associated with decreasing levels of IgE and increasing levels of IgG_4.

IL-5, IL-13, IFN-γ: IL-5 promotes the survival, activation, and chemotaxis of eosinophils. IL-5 receptor shares a common β-chain with the IL-3 receptor. IL-13 promotes the production of IgE and induces the production of IL-5. IFN-γ is produced by T_H1 cells stimulated by IL-12. It decreases the production of T_H2 ILs.

IL-10: IL-10 is an anti-inflammatory cytokine. It can be produced by CD25-positive regulatory T cells; can be elevated in viral infections such as rhinovirus, respiratory syncytial virus, enterovirus, and influenza; and is associated with dampening immune response. IL-10 suppresses eosinophilia by inhibiting IL-5 and GM-CSF and is elevated after successful immunotherapy.

KERATIN 18: Keratin 18 is a type 1 cytokeratin. Cytokeratins are structural proteins found in epithelial cells. Autoantibodies to cytokeratin-8, cytokeratin-18, and cytokeratin-19 can be found in patients with toluene diisocyanate–induced asthma.

LEUKOTRIENE (LT) C_4, B_4: Leukotrienes are naturally produced eicosanoid lipid mediators. In cells that express LTC_4 synthase, such as mast cells and eosinophils, LTA_4 forms the cysteinyl LT, LTC_4, which can be converted by ubiquitous enzymes to LTD_4 and LTE_4. In cells equipped with LTA_4 hydrolase, such as neutrophils and monocytes, LTA_4 is converted to LTB_4, which is a powerful chemoattractant for neutrophils acting at BLT_1 and BLT_2 receptors on the plasma membrane of these cells. Both LTC_4 and LTB_4 are potent bronchoconstricting agents. The variability in clinical response to cysteinyl LT receptor antagonists is caused, in part, by to differences in promoters in genes such as 5-lipoxygenase.

N-ACETYLTRANSFERASE (*NAT*): An enzyme that catalyses the transfer of acetyl groups from acetyl-Co enzyme A to arylamines. *N*-acetylation polymorphisms could be used as genetic markers because slow *N*-acetylators are susceptible to develop asthma.

NEUROKININ RECEPTOR: A class of cell surface receptors for tachykinins that prefers neurokinin A (NKA, substance K, neurokinin alpha, neuromedin L); neuropeptide K (NPK); or neuropeptide gamma over other tachykinins. Neurokinin-2 (NK-2) receptors have been cloned and are similar to other G-protein–coupled receptors.

SUBSTANCE P: Substance P is a neuropeptide, an undecapeptide that functions as a neurotransmitter and as a neuromodulator. It belongs to the tachykinin family. Tachykinins such as substance P and calcitonin gene-related peptide can be released by mast cells and act mediators for vascular dilation and permeability. Calcitonin gene-related peptide is elevated in bronchoalveolar lavage and bronchial biopsies in patients with allergic asthma after challenge with Fel d 1.

VASCULAR ENDOTHELIAL GROWTH FACTOR: Vascular endothelial growth factor is a subfamily of growth factors. It is a proangiogenic factor, is increased compared with antiangiogenic factors such as endostatin in patients with asthma, can be produced by chymase-positive mast cells in the airway, and is associated with airway remodeling that can lead to airways dysfunction.

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