Pathogenesis and Disease Mechanisms of Occupational Asthma

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• Airway remodeling • Oxidative stress • Genetic susceptibility

CLASSIFICATION OF OCCUPATIONAL ASTHMA

A generally accepted definition proposed in an authoritative text, *Asthma in the Workplace*,[1] has defined occupational asthma (OA) as "variable airflow limitation and/or airway hyperresponsiveness due to exposure to a specific causal agent present in a particular work environment and not to stimuli encountered outside the workplace." This definition of OA does not include workplace activation or exacerbation of preexisting asthma symptoms, which is called work-aggravated asthma. OA can be further subclassified into 2 different types:

- OA appearing after an asymptomatic latent period (during which immune sensitization is thought to develop), including (1) IgE-associated OA typically triggered by high–molecular weight (HMW) protein antigens and (2) IgE-independent OA typically triggered by low–molecular weight (LMW) chemicals (isocyanates, red cedar dust). This type is sometimes called immunologic OA.

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- OA that appears after single or multiple workplace exposures to nonspecific irritants at a high concentration. The term reactive airways dysfunction syndrome (RADS) has been coined to describe this type of OA. This type is sometimes called nonimmunologic OA. RADS is covered in detail in another article by Brooks and Bernstein elsewhere in this issue.

CLINICAL MANIFESTATIONS OF OA

Symptoms and Degree of Severity

The clinical manifestations of OA are similar to those found in nonoccupational asthma, and patients present with varying degrees of disease severity. Patients with mild condition may experience only episodic dry cough, chest tightness, and increased breathing effort at work. In more severe cases, symptoms can include wheezing, cough, chest tightness, shortness of breath, and dyspnea that persist away from the work environment. Some individuals may develop bronchitis, nocturnal awakening, or concomitant symptoms of rhinoconjunctivitis.[2]

Airway Hyperresponsiveness

Nearly all individuals with asthma with active symptoms exhibit airway hyperresponsiveness (AHR), an exaggerated response to bronchoconstrictor stimuli, which can be assessed by pharmacologic testing (eg, methacholine inhalation challenge) or nonpharmacologic means (eg, exercise challenge). In the general population, only about 50% of individuals with AHR have symptoms of respiratory disease,[3] but it does appear to be a risk factor for asthma because it may precede development of asthma.[4,5] Although preexisting AHR does not consistently predict development of OA caused by a sensitizer, a link between AHR and active symptoms of OA is firmly established. Workers with OA often exhibit decreases or resolution of AHR corresponding with reduced or disappearance of symptoms after cessation of exposure to causative agents in the workplace.[6]

Patterns of Asthmatic Responses

Three patterns of asthmatic response in workers with OA have been defined from decreases in forced expiratory volume in the first second of expiration with time after antigen challenge during specific inhalation challenge (SIC) testing.[7] The isolated immediate or early-onset asthmatic reaction, which begins immediately and lasts for 1 to 2 hours, is characterized by smooth muscle contraction and/or edema and is not usually associated with inflammatory cells or increased AHR. Dual-phase asthmatic responses are characterized by both an early- and late-phase bronchoconstriction interrupted by a recovery interval with the late response occurring 3 to 12 hours after challenge. The isolated late-phase asthmatic response is almost always elicited by chemical sensitizers and, rarely, if ever associated with measurable specific IgE.[8] All late-phase responses to specific sensitizers are associated with infiltration of eosinophils, basophils, and/or neutrophils and increased AHR.

Chronic irreversible airflow obstruction observed in some workers with OA is believed to be associated with airway remodeling. Changes reflecting airway remodeling include loss of ciliated epithelial cells, increased mucous secretion by goblet cells, basement membrane thickening due to subepithelial fibrosis with fibroblast and myelofibroblast activation, and hypertrophy of airway smooth muscle cells.[6]

WORKPLACE SUBSTANCES PROVED TO BE CAUSATIVE AGENTS OF OA

Compendia of more than 250 specific causative agents can be found in other publications or on special Web sites,[9–12] and these agents can be generally subdivided based

on size as HMW (>10,000 Da) or LMW (<1000 Da). HMW allergens are macromolecules capable of inducing a specific IgE antibody response and are usually associated with workplace sensitization to animals, plants, and/or microorganisms. For some of the HMW agents, major and minor allergens have been purified, characterized, and recombinantly cloned/expressed (eg, wheat proteins, cow dander). Of some 189 reported HMW allergens, 56% have been confirmed by bronchial provocation tests.

HMW allergens that cause OA may possess functional characteristics (eg, proteolytic activity) that promote their allergenicity.[13,14] Other HMW allergens (eg, house dust mites) possess pattern recognition receptors capable of stimulating innate immune responses via toll receptors, which may enhance their sensitizing potential.[15] Although most HMW occupational allergens are proteins, complex polysaccharides, such as those contained in vegetable gums, may also cause OA.

Approximately 78 LMW chemicals have been described as causes of OA. Prominent LMW sensitizers include diisocyanates, acid anhydrides, amines, metals, therapeutic drugs, and reactive dyes.[12] Structural modeling of these chemicals suggests that certain characteristics, particularly the presence of functional groups containing 2 or more reactive nitrogen or oxygen and the ability to conjugate with lysine, may be critical to OA pathogenesis.[16] The reactive functional groups of isocyanate and other LMW asthma-causing chemicals are known to covalently bind to self-macromolecules, especially airway proteins such as human serum albumin, causing conformational changes, including formation of new antigenic determinants capable of triggering immune sensitization.[17]

IMMUNE MECHANISMS THAT DRIVE THE INFLAMMATORY PROCESSES OF OA

IgE-Mediated Mechanisms

Specific IgE-mediated sensitization to a workplace antigen accounts for 90% of cases of OA.[18] In type I IgE-mediated hypersensitivity reactions, IgE antibodies bind to and cross-link mast cell receptors, leading to degranulation and release of mediators that elicit asthmatic reactions in susceptible individuals. Respiratory sensitization occurs by inhalation of the substance, uptake by antigen-presenting cells such as dendritic cells that process antigens, and migration of these cells to regional lymph nodes where antigen is presented to $CD4^+$ T helper (T_H) cells that initiate an immune response. The nature of the immune response is influenced by the cytokine milieu at the site of lymphocyte stimulation. Depending on host factors and the antigenic epitopes, T_H cells differentiate into subpopulations of effector cells that produce different cytokines. The 2 most polarized subsets are T_H1 and T_H2 cells. Interferon-γ is the principle effector cytokine produced by T_H1 cells, which promotes isotype switching of B cells to immunoglobulin isotypes associated with phagocyte-dependent host reactions. T_H2 cells produce 3 cytokines, interleukin (IL) 4, IL-5, and IL-13, shown to critically influence asthma pathogenesis in mouse models,[19] and the levels of all these are increased in asthmatic patients.[20] IL-4 is essential for differentiation and expansion of T_H2 cells by upregulating the transcription factor GATA-3 in naive T cells.[21] IL-4 (together with IL-13) also promotes isotype switching from IgM to IgE production[22] and promotes expression of both high- and low-affinity Fcε receptors.[23] IL-5 regulates airway eosinophilia in asthma by promoting eosinophil differentiation, recruitment, activation, and survival.[24] In addition to promoting isotype switching to IgE, IL-13 also acts on airway epithelial cells and smooth muscle cells to affect airway remodeling and development of AHR.[25] Despite the evidence linking these 3 cytokines to the pathogenesis of allergic bronchial asthma, clinical trials using neutralization of these cytokines for asthma immunotherapy have provided disappointing results.[26–28] It seems probable that

human asthma involves a greater variety of phenotypic subtypes than those discovered in mouse models. There is substantial evidence implicating contributions of several other T_H subsets, including T_H9, T_H17, T_H25, as well as T_H1, T_H3, regulatory T cells, and invariant natural killer T cells to inflammatory processes contributing to asthma aggravation and pathogenesis.[29]

The main feature of chronic OA caused by the prototypic LMW chemical sensitizer, toluene diisocyanate (TDI), is airway inflammation.[30] Bronchial biopsy studies in workers with TDI asthma reveal a mixed infiltrate of activated T cells, eosinophils, neutrophils, and macrophages. Despite specific IgE being detectable in only a minority of cases of diisocyanate-induced asthma (DA), the histopathologic findings are indistinguishable from those observed in individuals with allergic asthma.[31–33] Bronchial biopsy results of workers after inhalation challenge with diisocyanates, however, failed to demonstrate expression of messenger RNA for IgE ε chains and IL-4, which is further evidence against a role for IgE in this type of OA.[34]

Cell-Mediated Immune Mechanisms

Alternative mechanisms have been invoked to explain chemically induced OA. Cell-mediated immunity or delayed-type hypersensitivity has been postulated as a possible mechanism for isocyanate asthma; however, scientific evidence for this hypothesis is lacking. Anecdotal cases of concomitant contact dermatitis and OA as a result of chemical causes of OA (eg, ammonium persulfate in hair dressers) have been reported.[35] In addition, delayed patch testing responses were not identified in a study of workers with DA.[36] In one small study, hexamethylene diisocyanate (HDI)-conjugated epithelial cell proteins stimulated proliferation of peripheral mononuclear cells from workers with DA but not HDI-exposed nonasthmatic subjects.[37] However, in vitro lymphocyte proliferative responses to diisocyanate antigens have not been rigorously validated as predictors of DA.

Innate Responses

Nonadaptive immune responses could play a role in chemically induced OA. Isocyanates may have intrinsic effects resulting in production of proinflammatory cytokines. For example, peripheral mononuclear cells challenged in vitro with diisocyanate-albumin conjugate antigens show enhanced release of histamine-releasing factors and β-chemokines, particularly monocyte chemoattractant protein 1 (MCP-1).[38] Furthermore, in vitro enhancement of diisocyanate-albumin conjugate–driven MCP-1 production by blood cells was found to be strongly associated with DA and served as a diagnostic marker, identifying 79% of workers with DA, with 91% specificity.[33] Wisnewski and colleagues[39] demonstrated that human peripheral blood mononuclear cells stimulated in vitro with HDI-albumin or control albumin antigens showed marked changes in gene/protein expression that seemed to be specific for the isocyanate moiety. Significant changes were noted in lysosomal genes, as well as increased expression of chemokines, including migration inhibitory factor and MCP-1, which attract mononuclear cells, chitinases (pattern recognition receptors), and oxidized low-density lipoprotein (CD68). Other investigators studied the gene expression profile of macrophages derived from the THP-1 human cell line and cultured with solubilized HDI and identified altered expression of genes involved in detoxification, oxidative stress, cytokine signaling, and apoptosis.[40] Thus, there is ample evidence suggesting that isocyanate chemicals stimulate nonadaptive immune responses that contribute to respiratory sensitization, airway inflammation, and clinical expression of OA.

Skin Exposure and OA

Although the respiratory tract has been the focus of most studies on OA, evidence is accumulating that the skin may also play an important role in pathogenesis as an exposure route for initiating immune sensitization.[41–50] This hypothesis of pathogenesis is similar to that of the atopic march and is supported by the identification of structural genes as determinants of severe atopic dermatitis, a condition associated with heightened asthma prevalence.[51–54] It is theorized that once immune sensitization occurs via the skin, secondary respiratory tract exposure to exceedingly low levels (which do not trigger responses in nonsensitized workers) elicits airway inflammation and asthma.[48]

Despite being long overlooked as a potential exposure route contributing to OA, the skin exposure is well recognized as a mechanism for inducing immune sensitization, including production of allergen-specific IgE molecules.[55,56] Uptake of small reactive chemicals as well as large protein molecules is well documented and thought to involve specific dendritic cell populations that reside in the epidermal as well as the dermal layers of skin.[57–59] Once skin dendritic cells become activated by allergen (to express appropriate receptors), a chemokine gradient directs them to draining lymph nodes.[60,61] The outcome of skin exposure varies for different chemicals. For example, skin exposure to some occupational chemicals induces strong T_H2-skewed responses, whereas others induce T_H1 skewed responses.[62–64] Exposure dose further influences the outcome of skin exposure, which may be nonlinear and/or paradoxically limited at higher doses.[45,47]

Increasing recognition of the potential for occupational skin exposure to contribute to OA has spawned the development of animal models to further investigate potential pathogenic mechanisms. Several different reports have confirmed the ability of major occupational allergens to induce systemic immune sensitization and exacerbate subsequent inflammatory responses to respiratory tract inflammation in animal models.[41,45–47,50] In many of these studies, skin exposure has been found to be more potent than respiratory tract exposure for eliciting primary immune sensitization, providing further support for an important role in disease prevention.

NONIMMUNOLOGIC MECHANISMS

Although the immune system clearly plays an important role in OA, it has been suggested that this response is a secondary phenomenon, rather than the underlying cause of disease.[65,66] It is theorized that the primary defect in asthma may relate to impaired barrier function of the epithelium, which allows greater access of environmental allergens, microorganisms, and toxicants, which in turn trigger allergic-type inflammation.[67–70] Impaired barrier function may be because of internal (genetic) or external (occupational exposure) factors that modulate the normal epithelial damage-repair cycle of the human airways.[71] A similar process has been shown to account for certain types of allergic skin disease (described earlier), supporting the overall concept of barrier defect–driven inflammation at epithelial cell surfaces.[72]

Epithelial Injury-Repair Cycle

The airway epithelium constitutes the interface between the internal milieu of the lung and the external environment. As the first point of contact for respirable particles, vapors, and aerosols, the airway epithelium is most susceptible to their damaging effects. As mentioned earlier, some compounds that cause OA are enzymes (eg, detergents/baking allergens) capable of directly disrupting cell-cell or cell-matrix interactions, whereas other occupational allergens are intrinsically cytotoxic (diisocyanates,

anhydrides).[13,16,73–75] Damage to the airway epithelium stimulates cell turnover through a process that involves several autocrine growth factors as well as signals from the adjacent mesenchyme.[76,77] Epidermal growth factor, fibroblast growth factor, transforming growth factor β, and their corresponding receptors, have emerged as critical mediators in this process.[78–80] Increased expression of these and other growth factors (insulinlike growth factor, platelet-derived growth factor, nerve growth factor, vascular endothelial growth factor) is observed in the airway epithelium of patients with active asthma.[68,81,82] Continuing cycles of epithelial damage and repair, as might be caused by occupational exposures, may create a chronic wound scenario, which may increase the potential for the development of allergic sensitization.[68,83,84]

The Epithelial-Mesenchymal Trophic Unit

Opposing layers of epithelial and mesenchymal cells constitute trophic units in which the resident cells counterregulate each other's differentiation via secreted factors.[85–87] The area between these 2 cell layers contains extracellular matrix and a network of nerve fibers.[85] Dysregulation of the epithelial-mesenchymal trophic unit, in response to specific inhaled exposures, has been documented in nonhuman primate studies and postulated to explain pathologic changes associated with asthma, which occur at very early stages of disease.[88–90] The effects of specific occupational exposures on epithelial-mesenchymal interactions in vivo remain unstudied; however, in vitro studies suggest a possible influence on critical epithelial signaling components.[91,92]

Remodeling of the Airway Wall

It has been postulated that when epithelial injury and repair becomes a chronic cycle, the structure of the airway wall may become remodeled, further increasing the opportunity for tissue penetration by allergens/toxins/viruses.[93,94] Structural changes observed in OA include hyalinization/thickening of the laminar reticularis, increased numbers of myofibroblasts, and hypertrophy/metaplasia of smooth muscle and mucous cells, which may persist despite cessation of exposure.[95–98] In animal models, profibrotic cytokines, especially IL-13, mediate many of these changes.[99,100] The appearance of remodeling during the natural history of OA remains unclear. However, in patients with environmental asthma, such architectural changes occur early in the course of disease and may precede inflammatory changes.[101,102]

Toxicity

Many of the compounds that cause OA are cytotoxic at relatively low doses, including the LMW chemicals, isocyanates, acid anhydrides, acrylates, and certain metals.[74,103–105] The immune response to these compounds has generally been studied independent of their toxicity; however, an interrelationship between these effects may exist. The danger signals elicited by certain occupational exposures (or coexposures) may play an important role in the development of specific immune responses.[106–109]

Oxidative Stress

Several different studies provide evidence of increased oxidative stress during asthma, both locally within the airways as well as systemically.[110–112] Exhaled breath condensate and bronchoalveolar lavage samples from affected individuals have been shown to contain increased levels of 8-isoprostane and other well-established markers of oxidative stress.[113,114] Peripherally, additional biomarkers of oxidative stress (superoxide anion generation, lipid peroxidation, total nitrates/nitrites, total protein carbonyls, and total protein sulfhydryls) may be increased, concomitant with

decreased levels of specific antioxidants (superoxide dismutase, catalase activity, glutathione, and glutathione peroxidase activity).[112,115,116] It remains unclear if increased levels of oxidative stress observed in asthmatic individuals is a cause of disease or rather a result of ongoing inflammation in the airways, which itself produces reactive oxygen species. Regardless of the source, oxidative stress is thought to aggravate asthmatic airway inflammation via multiple mechanisms, including proinflammatory mediators, and effects on smooth muscle and mucous secretion.[117–119]

The molecular mechanisms by which oxidative stress affects cellular responses are beginning to be deciphered. At low levels of oxidative stress, the transcription factor Nrf2 is released to the nucleus where it induces expression of more than 200 genes with antioxidant response elements in their promoters.[120] When oxidative stress exceeds the protective capacity of Nrf2-induced genes, additional intracellular cascades (MAPK pathway, nuclear factor $\kappa\beta$) may be triggered, leading eventually to the expression of proinflammatory cytokines, chemokines, and adhesion molecules.[117,121]

Certain exposures (diesel exhaust, ozone) are well recognized for their ability to induce oxidative stress and have been shown to act as adjuvants for the development of allergic-type respiratory responses in animal models.[122–126] Recent studies suggest that other important occupational exposures (isocyanates, chlorobenzene, cerium, and silicon oxide constituents of nanoparticles) may also induce oxidative stress.[74,127–131]

Thiol Redox Homeostasis

Thiols, especially glutathione, play a major role in protecting the airway against oxidant damage.[132,133] Airway fluid thiol levels are normally maintained at high levels (>100 μm), more than 10-fold more than systemic blood levels and are intimately connected to redox-sensitive (proinflammatory) intracellular signaling cascades.[134] In vivo animal models and in vitro studies with human cells have demonstrated that isocyanate chemicals have marked effects on airway thiols.[135,136] Glutathione may be an especially critical target because its levels are known to modulate T_H1 versus T_H2 priming by dendritic cells and subsequent asthmatic response in animal models.[137,138] Human genetic studies that associate glutathione-dependent enzyme polymorphisms (GST-P1, GST-M) with occupational and environmental asthma further support a potentially important role for airway thiols in asthma pathogenesis.[139,140]

Neurogenic Inflammation

The airway wall is entwined with fibers from neurons, some of which penetrate the basement membrane, reaching into the epithelial cell layer, where they sense external signals via specific receptors, and secrete factors capable of eliciting inflammation and bronchoconstriction.[141] Critical mediators include neuropeptides, substance P (SP), neurokinins (NKs), calcitonin gene-related peptides (GCRPs), and vasoactive intestinal peptides, which trigger responses from immune, vascular, and smooth muscle cells via specific receptors.[142–144] Further cross talk between neuronal and immune cells may be modulated through the epithelial-derived enzyme neutral endopeptidase (NEP), which breaks down proinflammatory neuropeptides.[145] Epithelial NEP activity can be further affected by occupational and/or environmental exposures.[146,147] Thus, neuronal cells produce potent mediators that may interact with other cell types to influence exposure-induced asthmatic responses.

A single neuronal receptor, TRPA1, which recognizes a wide variety of noxious stimuli, including occupational allergens (diisocyanates), environmental irritants (cigarette smoke, chlorine), and endogenous compounds (reactive oxygen/nitrogen species, arachidonic acid derivatives), has now been molecularly cloned.[148,149] In

animal studies, TRPA1 expression colocalizes with SP, NK, and GCRP in nerve fibers in the airways, and TRPA1 knockout mice exhibit reduced inflammation in an ovalbumin asthma model.[150,151] However, species differences in TRPA1 activation, as well as general innervation of the lung, are well noted, limiting translation of animal studies on airway neuroinflammation to human asthma.[141,152]

GENETIC SUSCEPTIBILITY FACTORS FOR OA

OA syndromes, such as nonoccupational asthma, are likely polygenic disorders. Identification of specific genes that contribute to OA has been challenging because study populations are relatively smaller than those needed for genetic association studies. Genetic studies in OA to date can be categorized as those associated with immunoregulation and innate immunity and those associated with T_H2 immunity and antioxidant enzyme genes.

Genes Associated with Immunoregulation and Innate Immunity

Candidate gene studies have been reported investigating associations between HLA class II antigen alleles or haplotypes and isocyanate-induced OA. Bignon and colleagues[153] evaluated HLA class II DQA1, DQB1, DPB1, and DRB alleles and reported that confirmed DA was associated with DQB1*0503 and the allelic combination DQB1*0201/0301. The DQB1*0501 allele and the DQA1*0101-DQB1*0501-DR1 haplotype seemed to be protective because their levels were increased among healthy exposed controls and decreased in DA. These findings were confirmed in a second study.[154] Single amino acid substitutions at residue 57 of aspartic acid in DQB1*0503 was significantly increased in workers with DA and negatively associated with a valine substitution at DQB1*0501.[155] However, these findings were not reproducible in a smaller US study, a European study of DA, or a similar Korean study.[156,157] In the Korean study, HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype level was significantly increased in 84 workers with TDI asthma compared with 2 asymptomatic comparator groups.[157]

HLA associations have been identified with other chemical causes of OA. A higher frequency of HLA DQB1*0603 and DQB1*0302 alleles and a reduced frequency of the DQB1*0501 allele has been reported in western red cedar sawmill workers with DA when compared with healthy workers.[158] Among chemical workers exposed to acid anhydride chemical sensitizers, HLA class II allele DQB1(*)0501 within DQ5 HLA was associated with specific IgE to at least one acid anhydride antigen.[159]

A total of 335 research workers were genotyped for TLR4/8551 and TLR4/8851 single nucleotide polymorphism (SNP) variants, and it was found that workers with the TLR4 8851 G variant have reduced responsiveness to inhalation of endotoxin and were at higher risk for atopy and sensitization to laboratory animal allergens.[160]

T_H2 Gene Markers

T_H2 cytokine gene polymorphisms of IL-4 receptor alpha (IL4RA) and IL-13 have been associated with allergic asthma and/or allergic sensitization.[161] A candidate gene study was performed in 103 isocyanate-exposed workers with DA confirmed by a positive SIC test, 115 symptomatic workers with negative SIC tests, and 150 asymptomatic spray painters exposed to HDI. DNA was extracted, and workers were genotyped for IL4RA (I50V), IL4RA (Q551R), IL4RA (E375A), IL13 (R110Q), and CD14 (C159T) SNPs. The interactions between diisocyanate exposure (HDI vs methylene diphenyl diisocyanate, TDI) and specific genotype combinations (ie, IL4RA II + IL13 RR, IL4RA II + CD14 CT, and IL4RA II + IL13 RR + CD14 CT) were significantly associated

with DA compared with SIC-negative workers. When comparing HDI-exposed workers with DA (n = 50) and a different comparison group of asymptomatic HDI-exposed workers (n = 150), the association between DA and the IL4RA II + CD14 CT and IL4RA II + IL13 RR + CD14 CT genotype combinations trended toward statistical significance ($P<.10$) after adjustment for relevant confounding variables.[161–163]

Antioxidant Enzyme Genes

Gene SNPs associated with the mu, theta, and pi classes of the glutathione-S-transferase (GST) isoenzyme superfamily have been studied as predictors of DA. There is good rationale to explore GST genotype variants in that GST has been shown to modify biotransformation of isocyanates and excretion of metabolic products.[164] Reduced glutathione directly inhibits in vitro binding of diisocyanates with albumin.[165] Deletion of the GSTM1 gene (null genotype) has been associated with a 2-fold increased risk of DA.[140] The GSTP1 Val/Val homozygous genotype was lower in DA, suggesting a protective modifying effect (odds ratio, 0.23; $P = .074$).[139]

Genome-wide association studies have not been performed extensively in OA. Recently, groups of Korean workers including 84 with TDI asthma and 263 unexposed controls underwent genotyping with GeneChip arrays consisting of 500,000 SNPs.[166] Several SNPs of the α-T-catenin (CTNNA3) gene were identified to be significantly associated with DA. CTNNA3 is a molecule involved in E-cadherin–mediated cellular adhesion. The significance of this finding is unknown.

SUMMARY

OA is one of the most common forms of work-related lung disease in all industrialized nations. The clinical management of patients with OA depends on an understanding of the multifactorial pathogenetic mechanisms that can contribute to this disease. Once established, the clinical manifestations of OA are similar to those found in nonoccupational adult asthma, but the unique relationship of OA to a specific workplace antigen offers the possibility of successful therapy by early diagnosis and cessation of exposure to the causative agent. Specific IgE-mediated sensitization to HMW antigens accounts for 90% of cases of OA. LMW chemical sensitizers have generally not been found to cause OA by an IgE-mediated mechanism. Numerous factors have been found to contribute to the pathogenesis of chemically induced OA, including innate immune mechanisms and nonimmunologic mechanisms of epithelial injury, airway remodeling, oxidative stress, neurogenic inflammation, and genetic risk factors. Genes found to be associated with increased susceptibility to OA include HLA class II genes, genes associated with innate immunity and T_H2 immunity, and antioxidant enzyme genes.

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