HHS Public Access

Author manuscript

Immunol Allergy Clin North Am. Author manuscript; available in PMC 2015 December 18.

Published in final edited form as:

Immunol Allergy Clin North Am. 2011 November ; 31(4): 699–vi. doi:10.1016/j.iac.2011.07.008.

Pathogenesis and Disease Mechanisms of Occupational Asthma

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Keywords

occupational asthma; airway hyperresponsiveness; workplace allergens; immune mechanisms; airway remodeling; oxidative stress; genetic susceptibility

Classification of occupational asthma (OA)

A generally accepted definition proposed in an authoritative text, Asthma in the Workplace[1], has defined 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 pre-existing asthma symptoms, which is called work-aggravated asthma. OA can be further subclassified into two different types:

1. OA appearing after an asymptomatic latent period (during which immune sensitization is thought to develop), including (a) IgE-associated OA typically triggered by high molecular weight (HMW) protein antigens, and (b) IgE-independent OA typically triggered by low molecular weight (LMW) chemicals (isocyanates, red cedar dust). This type is sometimes called immunological OA.
2. OA that appears after a single, or multiple, workplace exposure(s) to non-specific irritants at a high concentration. The term "reactive airways dysfunction syndrome"

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The authors have nothing to disclose

or RADS has been coined to describe this type of OA. This type is sometimes called non-immunological OA. Since RADS is covered in detail in Chapter 7, it will not be covered in this chapter.

Clinical manifestations of OA

Symptoms and degree of severity

The clinical manifestations of occupational asthma are similar to those found in non-occupational asthma, and patients present with varying degrees of disease severity. Mild cases 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 subjects may develop bronchitis, nocturnal awakening, or concomitant symptoms of rhinoconjunctivitis[2].

Airway hyperresponsiveness

Nearly all asthmatics with active symptoms exhibit airway hyperresponsiveness (AHR), an exaggerated response to bronchoconstrictor stimuli, which can be assessed by pharmacologic testing (e.g., methacholine inhalation challenge) or non pharmacologic means (e.g., 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, since it may precede development of asthma [4, 5]. Although pre-existing airway hyperresponsiveness 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 airway hyperresponsiveness corresponding with reduced or disappearance of symptoms following 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 FEV1 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 – 2 hours is characterized by smooth muscle contraction and/or edema, and is not usually associated with inflammatory cells or increased airway hyperresponsiveness. 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 airway hyperresponsiveness.

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 mucus 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 proven to be causative agents of OA

Compendia of more than 250 specific causative agents can be found in other publications or on special websites [9–12], and 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 (e.g., 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 (e.g. proteolytic activity) that promotes their allergenicity [13, 14]. Other HMW allergens, (e.g., house dust mites), possess pattern recognition receptors capable of stimulating innate immune responses via toll receptors which may enhance their sensitizing potential [15]. While 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 suggest that certain characteristics, particularly the presence of two or more reactive nitrogen or oxygen containing functional groups, 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 their migration to regional lymph nodes where antigen is presented to $CD4^+$ T helper 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, helper T cells differentiate into subpopulations of effector cells that produce different cytokines. The two most polarized subsets are Th1 and Th2 cells. Interferon gamma is the principle effector cytokine produced by Th1 cells, which promotes isotype switching of B cells to immunoglobulin isotypes associated with phagocyte-

dependent host reactions. Th2 cells produce three cytokines, IL-4, IL-5, and IL-13, shown to critically influence asthma pathogenesis in mouse models [19] and all of these are increased in asthmatic patients [20]. IL-4 is essential for differentiation and expansion of Th2 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 effect 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 a number of other T helper subsets, including Th9, Th17, Th25, as well as Th1, Th3, Tregs and iNKT 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. It is noteworthy that despite the fact that specific IgE is detectable in only a minority of cases of diisocyanate-induced asthma (DA), the histopathologic findings are indistinguishable from those observed in subjects with allergic asthma[31–33]. Bronchial biopsies of workers after inhalation challenge with diisocyanates, however, failed to demonstrate expression of m-RNA for IgE epsilon chains and IL-4; 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 to chemical causes of OA (e.g., 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 non-asthmatic subjects[37]. However, in vitro lymphocyte proliferative responses to diisocyanate antigens have not been rigorously validated as predictors of DA.

Innate Responses

Non adaptive immune responses could play a role in chemically induced OA. Isocyanates may have intrinsic effects resulting in production of pro-inflammatory cytokines. For example, peripheral mononuclear cells challenged in vitro with diisocyanate-albumin conjugate antigens show enhanced release of histamine releasing factors and beta-chemokines, particularly 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 et al demonstrated that human PBMCs stimulated in vitro with HDI-albumin or control albumin antigens showed marked changes in gene/protein expression that appeared to be specific for the isocyanate moiety. Significant changes were noted in lysosomal genes, as well as increased expression of chemokines including MIF and MCP-1 which attract mononuclear cells, chitinases (pattern-recognition receptors) and oxidized low-density lipoprotein (CD68)[39]. 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 non adaptive immune responses which 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 occupational asthma, 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 would not trigger responses in non-sensitized workers) elicit airway inflammation and asthma [48].

Despite being long overlooked as a potential exposure route contributing to occupational asthma, 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 induce strong TH-2 skewed responses, while others induce Th-1 skewed responses [62–64]. Exposure dose further influences the outcome of skin exposure, which may be non-linear and/or paradoxically limited at higher doses [45, 47].

Increasing recognition of the potential for occupational skin exposure to contribute to occupational asthma 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.

Non-Immunologic mechanisms

While the immune system clearly plays an important role in occupational asthma, 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 due to 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 above), supporting the overall concept of "barrier defect"-driven inflammation at epithelial cell surfaces [72].

Epithelial Injury-Repair

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, it is most susceptible to their damaging effects. As mentioned above, some compounds that cause occupational asthma are enzymes (e.g. detergents/baking allergens) capable of directly disrupting cell-cell or cell-matrix interactions, while 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 a number of autocrine growth factors as well as signals from the adjacent mesenchyme [76, 77]. Epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor–beta, and their corresponding receptors, have emerged as critical mediators in this process [78–80]. Increased expression of these and other growth factors (IGF, PDGF, NGF, VEGF) 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 (EMTU)

Opposing layers of epithelial and mesenchymal cells constitute trophic units in which the resident cells counter regulate eachother's differentiation via secreted factors [85–87]. The area between these two cell layers contains extracellular matrix and a network of nerve fibers [85]. Dysregulation of the EMTU, in response to specific inhaled exposures, has been documented in non-human 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

occupational asthma include, hyalinization/thickening of the laminar reticularis, increased numbers of myofibroblasts, and hypertrophy/metaplasia of smooth muscle and mucus 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 occupational asthma 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 occupational asthma are cytotoxic at relatively low doses, including the low molecular weight 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 inter-relationship between these effects may exist. The “danger” signals elicited by certain occupational exposures (or co-exposures) may play an important role in the development of specific immune responses [106–109].

Oxidative Stress

A number of 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 broncho-alveolar lavage samples from affected individuals have been shown to contain increased levels of 8-isoprostane, and other well established maker 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 sulfhydrils) may be increased, concomitant with decreased levels of specific anti-oxidants (superoxide dismutase, catalase activity, glutathione, and glutathione peroxidase activity, etc) [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 pro-inflammatory mediators, and effects on smooth muscle and mucus secretion [117–119].

The molecular mechanisms by which oxidative stress effect 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 >200 genes with anti-oxidant response elements in their promoters [120]. When oxidative stress exceeds the protective capacity of Nrf2-induced genes, additional intracellular cascades (MAPK, NF-kB) may be triggered, leading eventually to the expression of pro-inflammatory 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 uM), greater than 10-fold above systemic blood levels, and are intimately connected to redox-sensitive (pro-inflammatory) 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 as its levels are known to modulate TH-1 vs. TH-2 priming by dendritic cells, and subsequent asthmatic response in animal models [137, 138]. Human genetic studies that associate glutathione-dependent enzymes 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 the neuropeptides, substance P (SP), neurokinins (NK), calcitonin gene-related and vasoactive intestinal peptides (GCRP and VIP), 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, NEP, which breaks down pro-inflammatory 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, cholrine), and endogenous compounds (reactive oxygen/nitrogen species, arachodonic acid derivatives) has now been molecular cloned [148, 149]. In animal studies, TRPA1 expression co-localizes 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, like non-occupational 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; those associated with Th2 immunity; and anti-oxidant enzyme genes.

Genes Associated with immunoregulation and innate immunity

Candidate gene studies have been reported investigating associations between HLA Class II alleles or haplotypes and isocyanate induced OA. Bignon et al 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 appeared to be protective as these were increased among healthy exposed controls and decreased in DA [153]. These findings were confirmed in a second study [154]. A single amino acid substitutions at residue 57 of aspartic acid in DQB1 * 0503 was significantly increased in DA workers 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 latter Korean study, HLA DRB1*1501-DQB1*0602-DPB1*0501 haplotype was significantly increased in 84 workers with TDI asthma compared with two 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 (AA) antigen [159].

Among 335 laboratory animal workers were genotyped for TLR4/8551 and TLR4/8851 single nucleotide polymorphism (SNP) variants and workers with the TLR4 8851 G variant has reduced responsiveness to inhalation of endotoxin and were at higher risk for atopy and sensitization to laboratory animal allergens [160].

Th2 gene markers

Th2 cytokine gene polymorphisms of IL4 receptor alpha (IL4RA) and IL13 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. MDI, TDI) and specific genotype combinations (i.e., 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 comparator 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].

Anti-oxidant enzyme genes

Gene SNPs associated with the Mu (M), Theta (T), and Pi (P) 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 two-fold increased risk of diisocyanate-induced asthma[140]. The GSTP1 Val/Val homozygous genotype was lower in DA suggesting a protective modifying effect (OR, 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 alpha-T-catenin (CTNNA3) gene were identified to be significantly associated with DA. Alpha-T-catenin is a molecule involved in E-cadherin mediated cellular adhesion. The significance of this finding is unknown.

Summary

Occupational asthma 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 non-occupational 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 high molecular weight antigens accounts accounts for 90 percent of cases of OA. Low molecular weight 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 non-immunological 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, and genes associated with innate immunity, Th2 immunity, and anti-oxidant enzyme genes.

Acknowledgments

This work was supported by Grant No. R01 OH008795 from the National Institute for Occupational Safety and Health/Centers for Disease Control

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