INTRODUCTION

It is now generally accepted that the workplace environment can lead to the development of different types of work-related asthma, including occupational asthma (OA) (i.e., asthma caused being at work) and work-exacerbated asthma (i.e., pre-existing or coincident asthma exacerbated by non-specific stimuli at work).\(^1\)\(^,\)\(^2\) OA may result from either immunologically-mediated sensitization to occupational agents (i.e., ‘allergic’ occupational asthma or ‘occupational asthma with a latency period’) or from exposure(s) to high concentrations of irritant compounds (i.e., ‘irritant-induced asthma’), which is best typified by ‘reactive airways dysfunction syndrome’.\(^3\)\(^,\)\(^4\) In recent years, there has been a growing recognition that work-related asthma represents a significant public health concern because of its high prevalence (~15% of adult asthma)\(^5\) and substantial health and socio-economic impacts.\(^6\) OA is potentially preventable, by effective control of respiratory sensitizers in the workplace. Accordingly, identifying causal agents and associated risk factors is a key step towards optimal prevention of the disease. This review aims at summarizing our current understanding of the factors that determine the inception of ‘allergic’ OA.

ETIOLOGICAL AGENTS

Workplace agents that are known to cause allergic OA include high-molecular-weight (HMW) (glyco-)proteins from vegetal and animal origins and low-molecular-weight (LMW) compounds. HMW proteins and a few LMW compounds (e.g., platinum salts, reactive dyes, acid anhydrides, sulfonechloramide, and some wood species) act through a documented IgE-mediated mechanism.\(^7\)\(^,\)\(^8\) The immunological mechanisms underlying the effects of most LMW agents (e.g., isocyanates, persulfate salts, aldehydes, and wood dusts) have not been fully characterized.

Sensitizing potential

Identifying characteristics associated with the induction of airway sensitization is fundamental to the implementation of

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primary preventive strategies. Research performed over recent years has highlighted the possible role of inherent protease activity, surface features, and glycosylation patterns of HMW allergens in the initiation of Th2 and IgE antibody responses.\(^7\) There is growing evidence that allergens possess common molecular features that enable them to be recognized by innate immune defenses as Th2-inducing antigens. For example, recent data suggest that allergens with lipid-binding properties, such as the major house dust mite allergen Der p2, have intrinsic adjuvant activity and can interact with the Toll-like receptor 4 signaling pathway.\(^6\) These events could be further amplified by proteolytically active allergens through the digestion of cell surface molecules involved in regulating innate and adaptive immune function, thereby favoring Th2 responses. These data support the observation that enzymes are a common cause of OA in a wide variety of occupations.\(^5\) Resistance to degradation may also be important for some occupational HMW allergens, which may be altered by physical or chemical agents during industrial or manufacturing processes. This is best illustrated by the persistence of allergenic epitopes derived from the Hevea brasiliensis tree in natural rubber latex, despite treatment with ammonia and vulcanization at high temperature.

In contrast to protein allergens, LMW agents are incomplete antigens (i.e., haptens) that must first bind to carrier macromolecules to become immunogenic. It has long been recognized that OA-causing LMW agents are typically highly reactive electrophilic compounds that are capable of combining with the hydroxyl, amino, and thiol functionalities on airway proteins.\(^6,10,11\)

LMW sensitizing agents also include transition metals salts, where the asthmagenic mechanism is thought to involve coordination bonding with human proteins.\(^12\) Quantitative structure-activity relationship (QSAR) models have been developed for the prospective identification of potentially sensitizing chemicals.\(^13\) Comparisons of the chemical substructures present in LMW organic asthmagens and non-sensitizing chemicals have identified several reactive groups that are associated with a high risk of respiratory sensitization, such as isocyanate (N=–C=O), carbonyl (C=O), and amine (NH\(_2\)), particularly when two or more groups are present within the same molecule.\(^14\) These multiple reactive groups could react simultaneously with different amino acids present on native human proteins, leading to intra-molecular cross-linking, conformational changes, and the production of neo-epitopes within the protein molecules. Such neo-epitopes could be involved in the initiation of respiratory sensitization.

### Causal agents

A large number of substances used in the workplace can lead to the development of allergic OA. Updated lists of causal agents and occupations are available on the web (e.g., http://www.asthma.csst.qc.ca and http://www.asmanet.com). A quick search of PubMed through 2009 and a personal bibliography for articles published before 1976 identified about 360 compounds or processes that have been described as causing OA, with a mean of 12 new causal agents reported annually since 1990. However, data derived from voluntary notification programs and compensation statistics of OA in various countries show that only a few agents (flour, isocyanates, latex, persulphate salts, aldehydes, animals, wood dusts, metals, enzymes) account for 50-90% of reported cases (Table 1).\(^15-23\) Nevertheless, the distribution of causal agents may vary across geographical areas, depending upon the pattern of industrial activities. For example, a high rate of OA due to metal machining fluids (11% of all cases), adhesives (7%), and chrome (7%) has been reported in the West Midlands, an area in the UK with

| Agent          | Finland\(^16\) | Canada, Quebec\(^7\) | UK\(^17\) | France\(^18\) | South Africa\(^19\) | Australia\(^15\) | Belgium\(^20\) | Belgium\(^21\) | Spain, Catalonia\(^22\) | Korea\(^23\) |
|----------------|---------------|----------------------|--------|----------|---------------|---------------|--------------|--------------|-----------------|-------------|
|                | 1989-1994     | 1995-2002            | 1990-1995 | 1996-1999 | 1997-1999 | 1996-1999 | 1997-1999 | 2000-2002 | 1993-1999 | 2002 | 1992-2006 |
| Flour, cereals | 23% (17%)     | 21% (18%)            | 9% (9%)  | 14% (13%) | 14% (20%)  | 6% (17%)    | 17% (24%)   | 15% (16%)  | 10% (15%)    | 4% (7%)    |
| Isocyanates    | 6% (2%)       | 30% (18%)            | 14% (13%) | 7% (24%)  | 3% (10%)   | 11% (23%)   | 7% (4%)     |             |                |             |
| Latex          | <1% (<1%)     | <1% (10%)            | 1% (3%)  | 7% (24%)  | 3% (10%)   | 11% (23%)   | 7% (4%)     |             |                |             |
| Persulphates   | 1% (2%)       | na (na)              | na (na)  | 6% (na)   | na (na)    | 4% (1%)     | 2% (12%)    |             |                |             |
| Aldehydes      | 2% (1%)       | na (na)              | na (na)  | 5% (4%)   | 1% (5%)    | 1% (1%)     | 1% (2%)     |             |                |             |
| Animals        | 37% (24%)     | 5% (5%)              | 5% (5%)  | 2% (1%)   | 4% (0%)    | 1% (4%)     |             |             |                |             |
| Wood dusts     | 4% (3%)       | 8% (9%)              | 4% (6%)  | 4% (na)   | 14% (3%)   | 9% (6%)     | 8% (1%)     |             |                |             |
| Metals         | 1% (1%)       | 8% (7%)              | 5% (4%)  | na (15%)  | 7% (4%)    | 4% (4%)     | na (9%)     |             |                |             |
| Enzymes        | <1% (<1%)     | na (na)              | 1% (2%)  | na (na)   | na (3%)    | 6% (4%)     | na (na)     |             |                |             |

|                | na, data not available. |
| *Medico-legal statistics; †Voluntary notification programs; ‡Unpublished data derived from the Belgian Workers’ Compensation Board. |
high manufacturing activity. In some countries, greenhouse cultivation is a growing activity that may lead to unusually high levels of exposure to airborne plant allergens that may induce occupational rhinitis and asthma in a substantial proportion of exposed workers. Additionally, greenhouse workers may become sensitized to pest insects, predatory mites used for the biological control of pests, molds, and latex gloves. In the southern part of Korea, the *Tetranychidae* mite *Panonychus citri* has been identified as a common cause of IgE-mediated respiratory allergies in citrus farmers.

There is currently little information on changes in the patterns of causal agents over time (Table 1). The number of cases of isocyanate-induced OA appears to have declined in some countries, likely due to the implementation of preventive measures. Available data also indicate that there has been a marked increase in the number of reported OA cases due to latex use during the 1990s. However, an analysis of the Belgian compensation data using the year of asthma onset, rather than the year of claim submission, showed that the incidence of latex-induced asthma decreased in the late 1990s, together with a sharp decline in the use of powdered latex gloves. Over the period from 1998 to 2002, the Finnish Register of Occupational Diseases documented a substantial increase in the rate of OA caused by sensitization to molds in white-collar workers employed in water-damaged buildings. This population accounted for up to 18% of notified cases in 1998-2002. During the same period, there was a downward trend in OA caused by cow dander, which resulted from a marked decrease in agricultural activities and changes in dairy farming practices.

**At-risk occupations**

Notification programs have generally reported the highest incidence rates of OA in bakers and pastry makers, other food processors, spray painters, hairdressers, wood workers, healthcare workers, cleaners, farmers, laboratory technicians, and welders. In fact, these occupations accounted for about two-thirds of all notified cases of OA, which may be relevant for targeting prevention and surveillance programs. In recent years, population-based studies conducted in various countries worldwide have consistently found that cleaning activities were associated with an excess risk of asthma, compared with unexposed individuals. Additionally, the Third National Health and Nutrition Examination Survey (NHANES III; 1988-1994) showed that cleaners were at an increased risk of experiencing work-related wheezing (OR: 5.4; 95% confidence interval [CI]: 2.4-12.2). Industrial and domestic cleaners use a wide variety of products containing irritant chemicals (e.g., detergents, acids, alkali, solvents, chelating compounds), as well as some potentially sensitizing substances, including biocides (e.g., chloramine-T, aldehydes, quaternary ammonium derivatives), ethanolamines, enzymes, and latex gloves. Additionally, cleaners are exposed to various workplace and domestic pollutants and allergens, such as endotoxins, house dust mites, pets, and molds. Different agents and mechanisms are presumably involved in the development of cleaning-related asthma and rhinitis. Recent studies found that a higher risk of asthma attacks and new-onset asthma was associated with exposure to bleach, ammonia, degreasing sprays, and accidental inhalation of vapors and gases from cleaning agents. These findings support an important role for acute and chronic exposure to irritants in inducing ‘irritant-induced asthma’ (e.g., ‘reactive airways dysfunction syndrome’) and ‘work-exacerbated asthma.’ Data collected by the Sentinel Event Notification System for Occupational Risks (SENSOR) in four US states from 1993 to 1997 showed that 12% of the reported cases of work-related asthma were associated with exposure to cleaning products. Among these cases, 20% were categorized as ‘work-exacerbated asthma’ and 80% as new-onset asthma, including 22% with probable ‘reactive airways dysfunction syndrome’ and the remainder with OA; however, the sensitizing agent was identified in only 14% of OA cases.

**ENVIRONMENTAL RISK FACTORS**

Environmental factors that are potentially involved in the initiation of OA include the level of exposure to sensitizing agents, the mode and route of exposure to these agents, and concomitant exposure to pollutants at the workplace.

**Level of exposure**

The assessment of dose-response relationships in OA has been greatly enhanced by the development of immunoassay techniques for the measurement of low concentrations of airborne HMW allergens in the workplace, the use of personal sampling techniques, and the implementation of prospective cohort studies. These studies have provided strong evidence supporting a dose-response relationship between the exposure level to occupational agents and the development of IgE-mediated sensitization and work-related respiratory symptoms for agents acting through an IgE-mediated mechanism (e.g., wheat flour, fungal alpha-amylase, laboratory animal proteins, detergent enzymes, snow crab allergens, platinum salts, acid anhydrides). An exposure-response gradient has been documented between the time-weighted average concentrations of isocyanates and the development of OA in a case-referent study. In a recent survey of spray painters, a log-linear relationship was found between the time-weighted average concentrations of isocyanates and the development of OA cases. The presence of specific IgE antibodies against isocyanate oligomers and the level of exposure and work-related symptoms. Specific IgE levels appeared to be merely an indicator of exposure. The determination of dose-response relationships may have a major effect on establishing permissible concentrations for prevention. However, uncertainties remain with respect to the
relative importance of peak versus average levels of exposure, the risk of sensitization at low concentrations (i.e., the ‘no-effect level’), and the shape of the dose-response curve. There is some evidence among laboratory animal workers that high-level exposures to laboratory animal allergens have a protective effect on the development of IgE-mediated sensitization and allergy symptoms. These studies observed that a high level of exposure to rat and mouse allergens was associated with increased levels of specific IgG4 antibodies, higher ratios of specific IgG4/IgE antibodies, and a reduction in work-related symptoms. A large workforce cross-sectional study of bakery workers conducted in the Netherlands also documented a bell-shaped exposure-response relationship, especially for cumulative wheat allergen exposure with IgE sensitization, allergic respiratory symptoms, and asthma; however, the healthy worker effect (HWE) may have been a possible explanation for the bell-shaped relationship. These findings are suggestive of a high-dose immunological tolerance to allergens associated with a modified Th2 cell response, which has been described for cat allergens in children. However, the attenuation of sensitization at high-dose exposure levels has not been documented for other workplace allergens, such as flour and detergent enzymes, or even in other surveys of workers exposed to laboratory animals. The mechanisms through which certain allergens induce tolerance at high exposure levels, while others drive a linear exposure–response relationship remain unknown. The functional role of IgG4 antibodies in the protection of sensitization at high allergen exposure levels has not been formally demonstrated. On the other hand, a recent survey of Korean bakery workers suggests that wheat-specific IgG4 antibodies may play a role in the development of respiratory symptoms in exposed workers who lack wheat-specific IgE antibodies.

The interpretation of exposure-response relationships may be further complicated by the discordance between reported respiratory symptoms and documented IgE-mediated sensitization to occupational allergens. For example, among Korean bakers, only a low proportion (25%) of symptomatic workers showed positive wheat-specific IgE antibodies. Additionally, individual susceptibility factors may affect the exposure–response relationships. Genetic markers could also be stronger determinants of sensitization to occupational agents at low levels of exposure to occupational agents. However, in the cohort of Dutch bakers mentioned above, associations between exposure levels and the prevalence of sensitization to wheat allergens and clinical outcomes were found only in atopic individuals. The timing of exposure may also play a role because the onset of work-related asthma symptoms is consistently higher within the early period of exposure to the occupational agents. Exposure-response gradients are more clearly documented in those workers who develop these outcomes soon after the onset of exposure. These findings indicate that the level of exposure at critical time points may be more relevant to the development of OA than cumulative doses of exposure or current levels of exposure at the time of investigation.

Mode of exposure

Differences in the mode of exposure to the same HMW agent may result in different patterns of IgE responses. In asthma epidemics caused by soybean dust released during soybean unloading into harbor silos, citizens became sensitized to Gly m 1 and Gly m 2, which are proteins with a low molecular weight (7-8 kDa) that are concentrated in the hull. In contrast, bakers are predominantly sensitized to allergens with a higher molecular weight that are present in both the soybean hull and flour. It has also been reported that workers may develop specific airway reactivity directed against one, but not the other forms of LMW chemicals (e.g., vapors of isocyanate monomers versus aerosols of isocyanates prepolymers; formaldehyde resin dust versus gaseous formaldehyde). The extent to which the physicochemical properties of LMW agents, such as volatility and solubility, may influence the patterns of airway deposition and the potential for inducing airway sensitization has not been extensively investigated. Recent experiments have shown that the biophysics of exposure may have a strong influence on the formation of human protein conjugates with diisocyanates, which might affect the immunogenicity of the resulting conjugate.

Animal experiments have consistently demonstrated that dermal exposure to LMW occupational agents can initiate IgE-mediated respiratory sensitization with a predominant Th2-like immune response, as well as the development of eosinophilic airway inflammation and airway hyperresponsiveness to these agents. The identification of type 1 keratins conjugated to hexamethylene diisocyanate after both skin and inhalation exposure offers potentially new insights into the link between skin sensitization to LMW chemicals and the induction of airway hyperresponsiveness to isocyanates in animal models. Much less is known regarding the potential impact of skin exposure on the initiation of OA in humans because the effects of dermal contact cannot readily be quantified or differentiated from those of inhalation exposure, as both occur simultaneously. Indirect evidence from a growing number of clinical and epidemiological studies in workplaces where measured airborne exposures to isocyanates were very low or non-detectable suggests that skin exposure to these reactive chemicals can contribute to an increase in the risk for sensitization and asthma.

Co-exposure to pollutants

There is growing evidence that environmental pollutants, such as ozone, nitrogen dioxide, tobacco smoke, diesel exhaust particles, and endotoxin can act as adjuvants in allergic responses to common inhalant allergens. However, there is limited information on the potential interactions between pollutants and sensitizing agents in the workplace. Smoking has been docu-
INDIVIDUAL SUSCEPTIBILITY

The observation that only a few workers typically develop OA despite similar workplace exposures strongly suggests that underlying differences in individual susceptibility exist. Host factors that have been incriminated in the development of OA include atopy, genetic factors, rhinitis, pre-existing non-specific airway hyperresponsiveness, and gender.

Atopy

Atopy, which is defined as an increased propensity to produce an IgE antibody response to low-dose environmental aeroallergens, can be established by assessing the presence of IgE antibodies against common inhalant allergens. Atopy has been consistently documented as a major risk factor for the development of IgE-mediated sensitization and OA in response to HMW agents that induce the production of specific IgE antibodies. However, the identification of atopy is not regarded as a reliable marker for excluding potentially susceptible workers from exposed jobs because it is a highly prevalent trait in the general population, and thus yields only a weak positive predictive value for sensitization to LMW agents and OA. Interestingly, studies suggest that atopy could be a stronger risk factor for laboratory animal sensitization among workers with low levels of exposure. Furthermore, pre-exposure sensitization to common allergens that are structurally related to workplace allergens, such as pets in laboratory animal workers, could be a stronger predictor of OA than atopy. In a 2-year prospective cohort study of workers beginning laboratory animal exposure, the combination of atopy and a total IgE level greater than 100 IU/mL was the best predictor for the development of laboratory animal allergies. Using these criteria may make it possible to reduce occupational sensitization by approximately 50% with less than 10% false-positive predictions. Interestingly, this cohort study found that baseline assessments of nasal inflammation parameters or cytokine production profiles did not predict the development of specific sensitization.

Genetic factors

With current advances in human genetics, research has been directed towards investigating the genetic basis of individual susceptibility to OA development. Several studies have documented significant associations between OA due to various LMW and HMW occupational allergens (e.g., isocyanates, red cedar, acid anhydrides, platinum salts, natural rubber latex, laboratory animals) and HLA class II molecules, which are involved in the presentation of processed antigens to T-lymphocytes (Table 2). Specific HLA DR, HLA-DQ, and HLA-DP alleles were found to confer either susceptibility or protection against OA; however, these findings have not always been replicated in other studies.

Possible role of genes associated with TH2-cell differentiation in the development of OA was suggested in one study that assessed the allelic variants of TH2-related cytokines, IL-4 receptor α chain (IL4RA) and IL-13, and one CD14 (C159T) gene polymorphism in isocyanate-induced OA. The IL-4RA (I50V) II genotype alone and in combination with IL-13 (R110Q) RR, and the CD14 (C159T) genotypes were significantly associated with OA caused by hexamethylene diisocyanate. Pacheco et al. evaluated whether allelic variants of TLR4, which is the predominant endotoxin-specific cell-surface receptor, could modulate allergic responses to laboratory animals. The TLR4/8551 G variant, which is less responsive to endotoxin, significantly associated with atopy and sensitization to laboratory animals.

Genes involved in protection against oxidative stress, such as...
glutathione-S-transferase (GSTP1 and GSTM1) and N-acetyltransferase (NAT), have been explored in isocyanate-induced OA.93-96 The GSTM1 null genotype was associated with an increased risk of isocyanate-induced OA,93 while the GSTP1*Val/
Val allele conferred increased protection against the development of OA. This protective effect increased with the duration of toluene diisocyanate (TDI) exposure. Slow N-acetyltransferase phenotypes were found to be at a higher risk for diisocyanate-induced asthma. A recent genome-wide association screening among Korean workers with OA caused by toluene diisocyanate found that several single-nucleotide polymorphisms of catenin alpha 3 (CTNNA3, coding for alpha T-catenin) and catenin alpha 1 (CTNNA1, encoding alpha E-catenin) were significantly associated with OA. Additionally, two genetic polymorphisms of CTNNA3 (rs10762058 and rs7088181) were significantly associated with a higher level of non-specific bronchial hyperresponsiveness. An additional polymorphism (rs1786929) was associated with higher levels of serum-specific IgG against cytokeratin 19. Alpha-catenin is a key molecule in the E-cadherin-mediated cell-cell adhesion complex. Further functional studies are needed to clarify the exact mechanisms by which CTNNA3 and CTNNA1 gene polymorphisms contribute to the development of diisocyanate-induced OA.

Overall, the currently available information indicates that genetic testing is limited for both diagnostic and preventive purposes. It is unknown why one gene may represent a risk factor in some populations, but not in others. As an example, the HLA-DQB1*0501 allele is associated with an increased susceptibility for developing specific IgE antibodies against acid anhydrides, while the same allele is protective for diisocyanate- and plicatic acid-associated OA. There is also convincing evidence that a wide variety of environmental factors can interact with genetic determinants to affect disease susceptibility. These observations highlight the importance of measuring environmental exposure in genetic studies of OA. Such environmental factors include viral infections, diet, exposure to endotoxin, tobacco smoke, and irritants, as well as the pattern and timing of exposure to sensitizers in the workplace. For example, a gene-environment interaction has been demonstrated for sensitization to platinum salts. In platinum refinery workers, the relative risk of sensitization associated with the HLA-DR3 phenotype was more apparent at lower levels of exposure. This finding indicates that the role of genetic susceptibility is likely to increase in workplace environments where exposure to sensitizers has been minimized.

Non-specific bronchial hyperresponsiveness
In recent years, prospective cohort studies of subjects entering a workplace with exposure to occupational sensitizers have provided formal evidence that baseline bronchial hyperresponsiveness and a physician-based diagnosis of asthma are associated with an increased risk of OA.

Rhinitis
Population-based and cohort studies provide compelling evidence that rhinitis (allergic and non-allergic) is a risk factor for the development of non-occupational asthma. Clinical studies have shown that the majority of workers with OA also suffer from occupational rhinitis. Of these patients, work-related rhinitis symptoms frequently precede the onset of OA, especially when HMW agents are involved. Epidemiological evidence shows that work-related rhinitis is associated with an increased risk for the subsequent development of asthma and OA, and should be considered as an early marker of OA. However, the proportion of subjects with work-related rhinitis who will go on to develop OA remains uncertain. Among apprentices in animal health technology, the predictive value of work-related nasal symptoms on the subsequent development of probable OA was only 11.4% over a 44-month follow-up period.

CONCLUSIONS
Identifying the intrinsic characteristics of OA-causing agents that determine their sensitizing potential is important for preventing the introduction of hazardous substances in the workplace. A dose-response relationship between exposure levels and the development of immunological sensitization and OA has now been convincingly established for the most frequent agents that cause OA. As a result, preventive measures aimed at reducing workplace exposure to sensitizing agents should be the most effective approach for reducing the burden of OA. However, there is some suggestion that the exposure-response relationship may bell-shaped rather than linear for some occupational agents (e.g., laboratory animals, wheat flour), suggesting a protective effect of high-level exposures. Several studies indicate that exposure to cigarette smoke can increase the risk of IgE-mediated sensitization to some HMW and LMW agents; however, the evidence supporting an association between smoking and the development of clinical OA remains very weak. The role of other environmental co-factors, such as endotoxins and chemical pollutants, should be further investigated.

Atopy has been consistently demonstrated as an important individual risk factor for the development of IgE sensitization and OA, but only for HMW agents. Identifying sub populations at higher risk within the atopic group would increase the feasi-
bility of pre-employment screening and counseling. Prospective cohort studies of individuals entering a workplace with exposure to occupational sensitizing agents have shown that the presence of rhinitis and non-specific bronchial hyperresponsiveness at baseline are associated with an increased risk of IgE sensitization and OA. Associations between genetic markers and OA have usually been modest, but there is increasing evidence that gene-environment interactions can influence these exposure-response relationships. Characterizing the complex interactions between environmental factors and individual susceptibility is a crucial step in identifying the factors that determine the development of OA, and in implementing cost-effective prevention strategies.

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