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Mechanistic and Therapeutic Approaches to Occupational Exposure-Associated Allergic and Non-Allergic Asthmatic Disease

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Abstract

Purpose of Review Occupational lung disease, including asthma, is a significant cause of disability worldwide. The dose, exposure frequency, and nature of the causal agent influence the inflammatory pathomechanisms that inform asthma disease phenotype and progression. While surveillance, systems engineering, and exposure mitigation strategies are essential preventative considerations, no targeted medical therapies are currently available to ameliorate lung injury post-exposure and prevent chronic airway disease development.

Recent Findings This article reviews contemporary understanding of allergic and non-allergic occupational asthma mechanisms. In addition, we discuss the available therapeutic options, patient-specific susceptibility and prevention measures, and recent scientific advances in post-exposure treatment conception.

Summary The course of occupational lung disease that follows exposure is informed by individual predisposition, immunobiologic response, agent identity, overall environmental risk, and preventative workplace practices. When protective strategies fail, knowledge of underlying disease mechanisms is necessary to inform targeted therapy development to lessen occupational asthma disease severity and occurrence.

Keywords Allergy · Asthma · Occupational lung disease · Airway hyperresponsiveness · Immunotherapy · Inflammation

Introduction

Occupational respiratory diseases represent a broad spectrum of preventable disorders that are either caused or made worse by inhalant exposure to aerosolized particles at the workplace. Every situation along the exposure continuum, from long-term, low-level exposure to one-time, high-dose exposure, can cause lung injury, inflammation, and subsequent pathology [1]. A prominent example of the latter is the pulmonary disease that developed in first responders exposed to aerosolized dust from the catastrophic World Trade Center collapse of September 11, 2001 [2–4]. Various mechanisms can mediate post-occupational exposure-induced respiratory disease, generally dichotomized as allergic and non-allergic. In general, limitations in diagnostic criteria, physician awareness, and management strategies have also led to widespread underreporting of occupational lung disease in clinical practice [5]. Whereas efforts to reduce exposure, promote respiratory protective equipment, and improve surveillance are needed, there are currently no therapies for managing post-occupational exposure-induced lung injury/inflammation. Available therapies such as bronchodilators, corticosteroids, and other supportive treatments are relatively non-specific and address symptomology instead of the underlying immunopathologic etiology. Since efficacious options for exposed workers are relatively nonexistent, targeted therapeutic interventions capable of slowing or preventing progressive airway obstruction and symptom chronicity post-exposure are paramount. This review aims to describe the role of key cellular players in the lung immunologic response critical for chronic lung disease manifestation post-occupational exposure, with an asthmatic focus, to ultimately inform post-exposure interventions and therapeutic approaches capable of preventing progression to a chronic disease state.

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Allergic Respiratory Disease

Occupational exposure to agents capable of producing allergic disease affects an estimated 11 million workers in the USA, with 25% of all adult-onset asthma cases being occupationally derived [6, 7]. Upwards of 400 inhalable agents have been identified as occupational allergens, with that number increasing each year [8]. These "respiratory sensitizers" include natural and synthetic products typically classified as high and low molecular weight (HMW/LMW) compounds. Common occupational respiratory disease-causing LMW agents (< 5–10 kDa) include chemicals (e.g., diisocyanates, quaternary ammonium compounds, acid anhydrides, disinfectants), metals (e.g., gold, chromium, cobalt), and medicinal drugs that promote immunologic responses predominately by forming hapten–carrier complexes and/or possessing adjuvant functionality [9]. HMW agents (> 5–10 kDa), including proteins and glycopeptides derived from cereal flour, laboratory animals, livestock, molds, and natural rubber latex, induce immunoglobulin (Ig)E-mediated allergic responses [10, 11]. Resultant immune-mediated mechanisms cause the characteristic symptoms of allergic respiratory disease, including rhinitis, sneezing, congestion, shortness of breath, and wheezing. These mechanisms mediating occupational exposure-induced allergic disease will be presented with a focused discussion of research assessing individual risk of occupational allergic disease, interventional strategies to lower disease risk, and ultimately mechanism-informed management strategies to reduce symptoms and control allergy.

Allergy: Mechanism

Occupational allergic respiratory disease is an IgE-dependent hypersensitivity reaction resulting from occupational antigen (allergen) sensitization (Fig. 1). An immediate-type hypersensitivity (Type 1), the allergic response is initiated

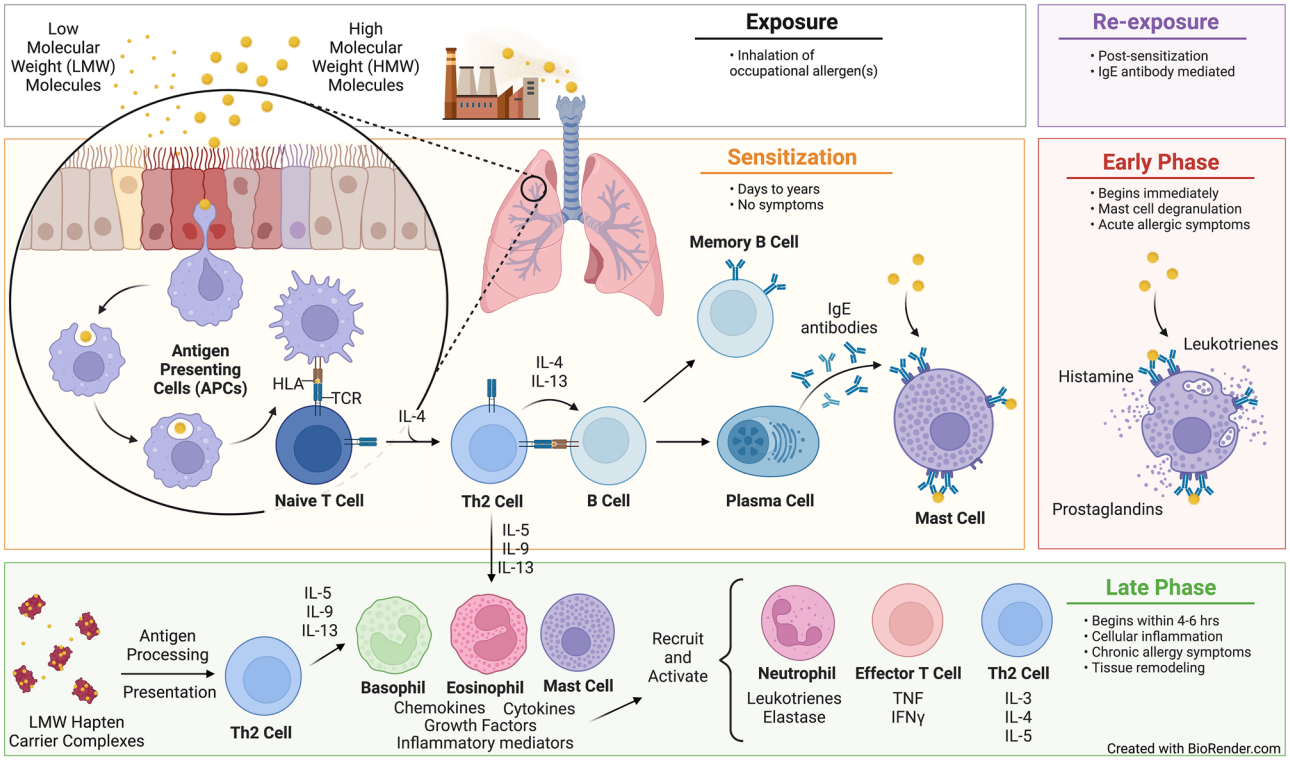

Fig. 1 Mechanistic overview of IgE and non-IgE-mediated occupational asthmatic disease. High molecular weight (HMW) molecules activate a classical IgE-mediated allergic mechanism beginning with antigen-presenting cell (APC) recognition, processing, and presentation to naïve T lymphocytes. Co-stimulation and T cell receptor recognition of MHC class II presented allergen initiates Th2 cell polarization and cytokine-mediated B cell class switch and plasma cell maturation. Subsequently, allergen-sensitized memory B cells and mast cells await re-exposure. Re-exposure to sensitized allergen initiates mast cell degranulation and release of cellular mediators, notably histamine, leukotrienes, and prostaglandins, which induce acute airway symptoms. Low molecular weight (LMW) molecules often must associate with proteins in hapten–carrier complexes to be recognized by the immune system. Rarely do these LMW–carrier complexes elicit an IgE-mediated response. Instead, activated T lymphocytes induce a cell-mediated pathomechanism of respiratory disease similar to the late phase of a classical IgE-mediated allergic response. T helper cell-sourced cytokines recruit and stimulate basophils, eosinophils, and mast cells which degranulate and mobilize neutrophils, effector T cell populations, and additional Th2 cells which provoke chronic allergic symptoms and facilitate tissue remodeling processes. The nature of the LMW allergen influences the resultant cell effector populations responsible for mediating disease development

by allergen processing by antigen-presenting cells (APCs), predominately dendritic cells (DCs) in the skin or mucosal surfaces [12]. APC-mediated antigen presentation to T helper type 2 (Th2) cells initiates cytokine (interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31) secretion in genetically predisposed individuals [13]. IL-4 encourages naïve CD4 T cell differentiation into Th2 cells and, in conjunction with IL-13, drives IgE and IgG_1 class switching. IL-13 induces goblet cell hyperplasia, airway hyperreactivity, and extracellular matrix generation. IL-4 and IL-13 additionally stimulate alternative macrophage activation, epithelial barrier leakiness, and T cell and eosinophil recruitment to allergic tissues [14, 15]. IL-5 is a potent pro-inflammatory cytokine that critically regulates eosinophil survival, maturation, and effector functions [16]. IL-9 augments the allergic response initiated by these cytokines by enhancing eosinophil and mast cell recruitment, epithelial mucus production, and promotes IL-4-induced IgE production [17]. IL-31 is a key mediator of pruritic symptomology and contributes to airway hypersensitivity [18].

Additionally, epithelial-derived thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are important regulators of type 2 immunity following allergic insult. Recent studies have demonstrated potential regulatory roles for both TSLP and IL-33 specifically in occupation-induced allergic lung inflammation and occupational asthma [19, 20]. These cytokines (TSLP, IL-25, and IL-33) activate type 2 innate lymphoid cells (ILC2s), a cell subset identified as an essential driver of type 2 inflammation and allergic disease, in addition to regulating Th2, mast cell, basophil, and dendritic cell responses [21]. While both ILC2s and Th2s produce type 2 cytokines and mediate allergic responses, ILC2s are more involved in the early allergy phase. Notably, ILC2s do not require antigen presentation for activation and are critical for early induction of eosinophilia with IL-33 specifically inducing ILC2s to produce 80% of the IL-5 and IL-13 present in the lung post-allergic exposure [22]. ILC2s are essential for cultivating Th2 memory responses in conjunction with tissue-resident DCs; however, they exhibit independent memory capabilities as evidenced by primed responses to TSLP or IL-33 with subsequent antigen stimulation [23].

The principal effector cells of the allergic response are mast cells, basophils, and eosinophils. Allergen-specific IgE secreted by plasma cells bind and crosslink high-affinity IgE receptors (Fcε) on the surface of these cells [24]. These sensitized effector cells are activated upon re-exposure, causing immediate degranulation of their pre-formed mediators, including histamine, proteases, and proteoglycans, and delayed release of de novo synthesized biogenic mediators such as histamine, arachidonic acid metabolites, and cytokines [25]. Repeat exposure to the sensitized allergen will initiate this process, producing the described pro-inflammatory mediators and resultant symptoms characteristic of an allergic response.

Asthma: Mechanism

Asthma is an aggregate of several distinct subtypes characterized by different pathophysiological mechanisms or endotypes [26]. While both immunologically and non-immunologically (irritant-induced occupational asthma) mediated asthma have been recognized, immunologically mediated asthmatic disease will be discussed. Irritant-induced occupational asthma has been recently reviewed elsewhere [27].

IgE-Mediated Asthma

Occupational IgE-mediated asthma is initiated by respiratory sensitization to chronic, low-level HMW or occasionally complexed LMW antigen (Fig. 1) [28]. Specific IgE-mediated sensitization to antigen present in the workplace accounts for 90% of occupational asthma cases [29]. The early phase of IgE-mediated occupational asthma pathogenesis closely resembles the classical allergic disease mechanism where sensitized plasma cells release occupational trigger-specific IgE antibodies that bind to high-affinity receptors on mast cells and basophils [30]. Histamine, prostaglandins, and leukotrienes released from these effector cells post-secondary exposure contract the smooth muscle and cause airway tightening [31]. The late phase occurs several hours later when eosinophils, basophils, neutrophils, and helper/memory T cells localize to the lungs. Mast cells are critical mediators of this late-phase cell recruitment which in turn causes cell-mediated inflammation and bronchoconstriction (Fig. 1) [32].

A characteristic feature of both occupational and non-occupational asthma is airway hyperresponsiveness, where the degree of bronchoconstriction is out of proportion to the inciting stimulus. In addition to mast cell-sourced mediators, increased vagal tone and intracellular-free calcium augment airway smooth muscle contractility [33]. Th2 cell production of IL-3 and IL-5 supports eosinophil and basophil survival, while IL-13 induces tissue remodeling, fibrosis, and hyperplasia, all with consequences on airway obstruction [30]. Specifically, epithelial cells transition to mesenchymal cells, thereby increasing smooth muscle content and airway contractile responsiveness [34]. Myofibroblasts facilitate extracellular matrix accumulation beneath the basal lamina, further narrowing the airway [35•]. Goblet cell hyperplasia leads to increased mucin secretion and accumulation of mucus in the bronchiolar trees, which may become impacted and lead to airway closure [36]. The resultant effect of these processes increases airway obstruction and airway sensitivity to insult. These processes can cause irreversible tissue remodeling that worsens airway hyperresponsiveness, inflammation, and

increases the work of breathing without adequate treatment [37]. These mechanisms underlying the progressive, obstructive airway disease characteristic of asthma have been reported in both occupational and non-occupational asthma alike [29].

Non-IgE-Mediated Asthma

Non-IgE-mediated asthma proceeds through a cellular mechanism where activated T lymphocytes directly mediate airway inflammation. Interestingly, occupational asthma patients with non-IgE-mediated disease may produce exposure-specific IgE; however, the IgE molecules cannot cause passive sensitization and do not contribute to disease pathogenesis [38]. Instead, inhalation of LMW agents generally induces a delayed immune reaction more characteristic of the late phase of a classical IgE-mediated asthma exacerbation (Fig. 1) [39]. While the exact nature of the non-IgE immunologic mechanisms of occupational asthma remains unclear, evidence implicating a cell-mediated hypersensitivity in LMW agent-induced asthma exists with various LMW compound exposures. In the case of diisocyanate-induced asthma, increased peripheral blood mononuclear cell (PBMC) expression of monocyte chemoattractant protein-1 (MCP1) (also known as chemokine (CC-motif) ligand 2 (CCL2)), a chemokine that recruits inflammatory cells and enhances expression of inflammatory factors, was observed [40]. Diisocyanate-induced asthma patients also exhibited increased CD8-positive T lymphocytes and eosinophils in the peripheral blood [41]. One study of diisocyanate-induced asthma demonstrated that most T cells on bronchial biopsy exhibited the CD8 phenotype and produced IFN-gamma and IL-5, with few T cells producing the Th2 cytokine IL-4 [42]. The peripheral blood lymphocytes of patients with Western red cedar, nickel, or cobalt-induced asthma exhibit proliferation in response to incubation with the sensitized antigen [43, 44]. T lymphocytes of patients with platinum salt-induced occupational asthma even exhibited cellular expansion of specific T cell receptor-bearing blood T cell subpopulations (Vβ21.3, Vβ11, and Vα2a) in response to platinum salt insult [45]. Further research identifying non-IgE-mediated mechanisms of occupational exposure-induced asthma, especially those caused by LMW agents, should be prioritized, given the specificity of responses to diverse exposures and paucity of existing knowledge.

Workplace exposures of greater complexity have also been linked to non-asthmatic airway hyperresponsiveness and occupational respiratory disease due to non-IgE exclusive mechanisms. Specifically, inhaled occupational dusts present in textile, dairy, animal feed and grain, sewage treatment plant, and agricultural work settings have been linked to occupational lung diseases such as asthma, chronic bronchitis, pulmonary fibrosis, and chronic obstructive pulmonary disease (COPD) [46–50]. Historically relevant occupational lung diseases characteristic of specific work environments include coal miners' pneumoconiosis, sandblasting and quartz countertop production-induced silicosis, and mesothelioma resulting from amphibole asbestos exposure [51]. Notably, agricultural dust exposure-induced respiratory disease has been increasingly investigated in recent years, given nearly 18% of farmers and ranchers in the central USA have been diagnosed with a chronic respiratory condition [52]. Agriculturally derived dusts are complex, microbially enriched bioaerosols with high Toll-like receptor (TLR2/4/9) agonist activity [50]. One such immunogenic agonist highly prevalent in agricultural dust is lipopolysaccharide (LPS) or endotoxin, a bacterial membrane component of gram-negative bacteria [53]. Interestingly, early life exposure to TLR agonist-/endotoxin-enriched environments exercises a protective effect against the development of IgE-mediated disease; however, workplace organic dust exposure elevates occupational/workplace exacerbated asthma, neutrophil-predominant respiratory inflammation, chronic bronchitis, and COPD risk [54]. Organic dust extract (ODE) collected from agricultural work settings has been shown to elicit characteristic markers of inflammation in animal models of repetitive and acute agriculture-derived inhalant exposure, characterized by increased bronchoalveolar lavage fluid (BALF) cell numbers, neutrophil recruitment to the lung, and ODE-induced TNF-α, IL-6, and murine neutrophil chemoattractant (CXCL1 and CXCL2) [55]. While the TLR/IL-1R/IL-18R adaptor protein myeloid differentiation factor 88 (MyD88) has been implicated in the classic airway inflammatory response to agriculture-derived ODE in a mouse model of repetitive exposure, ODE-induced mucous cell metaplasia, lymphocyte influx, and IgE responsiveness are not dependent on MyD88 signaling and require further mechanistic investigation [55–57]. After repetitive exposure, a long-lasting adaptation response was also observed upon rechallenge with ODE. Elevated levels of IL-10 and amphiregulin, both characteristically anti-inflammatory, were central mediators of this adaptive process [55]. Exploiting the MyD88 signaling pathway, the tolerogenic mechanisms demonstrated through repetitive ODE exposure and subsequent rechallenge, and/or non-MyD88 dependent processes could represent future preventative and/or therapeutic targets to hasten recovery and prevent chronic disease development.

Risk Assessment and Mitigation

First and foremost, risk assessment and informed management strategies to prevent the induction of sensitization in exposure naïve individuals need to be prioritized. While a growing number of causative agents have been identified, a persistent challenge in assessing respiratory sensitization,

especially by LMW respiratory allergens, has been the absence of standardized methods for their identification and characterization. Indeed, no validated methods for assessing the respiratory sensitizing potential of LMW agents exist despite more than three decades of research [9]. Primary prevention strategies where the causative agent is elusive must therefore apply control methods to prevent worker exposure to any potentially biohazardous agents and ensure adequate use of personal protective equipment [58]. Secondary prevention methods related to workplace exposure monitoring and characterization, as is feasible, can inform approaches to modify identified allergens to mitigate risk or substitute known allergens with a less harmful agent [59, 60].

Medical monitoring of allergen-specific biomarkers of sensitization may prevent the development of occupational allergic disease through removal from causative agent before symptom onset. The presence of blood biomarkers such as allergen-specific IgE indicates allergic sensitization; however, this approach is limited given the causal allergen must be elucidated and initiate an IgE-mediated pathophysiologic response [61]. If the causal agent is known, allergen-specific IgG:IgE ratios may predict disease development and symptom severity. IgE sensitization almost always occurs with a robust IgG_1 response to the same allergen [62, 63]. Among sensitized individuals, low house dust mite-specific IgG:IgE antibody ratio coincided with more severe disease [64]. Additionally, children with asymptomatic atopic disease had lower IgG:IgE antibody ratios for dust mite and grass allergens than asymptotic atopic children in two birth cohorts from Australia and the UK [64]. While the potential protective effect of IgG_1 has only been hypothesized, IgG_4 competes with IgE for allergen bindings and therefore possesses a protective mechanism [65]. Although the IgG:IgE antibody ratio has yet to be translated to clinical practice, it may help differentiate between benign and pathologic sensitization and inform approaches to diagnose and reduce occupational allergy burden [66]. An increase in fractional exhaled nitric oxide (FeNO) levels following positive specific inhalation challenge (SIC) with either HMW or LMW agents is apparent in patients with occupational asthma [67]. Therefore, elevated FeNO levels after SIC testing may reveal underlying pathology, given an increase of FeNO ($\geq$ 13 ppb) 24 h after SIC is highly predictive of occupational asthma [68]. Standardized diagnostic and predictive methods in work settings where occupational allergic disease is possible will enable earlier causal agent identification and intervention.

Preclinical biomarker identification without knowledge of the causal allergen is increasingly necessary, given that occupational agent characterization is only sometimes possible. The presence of elevated eosinophil counts in blood or sputum is notably representative of allergic inflammation, given these cells are central effectors of the allergic response [67, 69]. The baseline sputum inflammatory profile of occupational asthma patients can also demonstrate neutrophilia [70]. Neither sensitization assessment method requires the identification of casual allergens, so it may be useful in worker cohort monitoring to determine the presence of an occupational allergen. Notably, uniquely expressed microRNAs (miRNAs) are emerging as noninvasive biomarkers to diagnose allergic disease. In one study, 30 differentially expressed miRNAs were identified in the blood of healthy, allergic, and asthmatic subjects, where miR-125b, miR-16, miR-299-5p, miR-126, miR-206, and miR-133b were most predictive of allergic disease status [71]. In addition to their potential as biomarkers, miRNAs have been found to play a crucial role in the pathogenesis of asthma and allergic disease. Further understanding of their pathologic contributions will inform targeted therapeutic interventions and improve understanding of the molecular mechanisms that differentiate the heterogeneous group of allergic diseases [72]. Furthermore, a study utilizing samples from nasal epithelial cells and Th2-enriched CD4 + T cells in blood revealed 8 and 14 differentially expressed genes with the combination of *POSTN* in nasal mucosa and *PENK* and *CDC25A* in blood exhibiting good predictive value as biomarkers for allergic rhinitis pathogenesis [73•]. Another study sought to characterize biomarkers of nonallergic asthma (non-gE-mediated) from patient peripheral blood samples. The genes (*PI3*, *CHI3L1*, and *IL8*) that best discriminated between nonallergic asthma patients and healthy control subjects are closely related to neutrophils corroborating the role of noneosinophilic mechanisms in nonallergic respiratory disorders [74]. Allergy sensitization and occupational respiratory disease assessments naïve to casual exposure are especially necessary in workplace settings where LMW respiratory allergens are present, given the complexity intrinsic to the immunologic agent and dearth of identification methods. Whereas these biomarkers have been predominately described in non-occupational respiratory disease, translatability studies should be prioritized to elucidate and/or corroborate biomarkers of occupational respiratory disease susceptibility, severity, and eventually therapy responsiveness.

While environmental risk mitigation is crucial in ameliorating occupational allergy risk, genetic predisposition to agent sensitization is critical to predicting disease development and informing early interventions to curb condition chronicity. Genetic heritability estimates for allergic disease can be as high as 91% for allergic rhinitis, 95% for asthma, 84% for serum immunoglobulin E, and 41% for blood eosinophil counts [75]. Genes of the human leukocyte antigen (HLA) system have shown associations with various types of occupational asthma. Specific HLA haplotype alleles have been implicated in occupational asthma susceptibility resulting from exposure to diisocyanates (e.g., HLA-DRB1, HLA-DPB1, HLA-DQA1) and Western red cedar (HLA DQB1, HLA-DQB1) using genome

wide association studies (GWAS) [76]. Specific HLA phenotypes associated with elevated occupational asthma risk have also been identified in patients exposed to platinum salts (HLA-DR3), laboratory animals (HLA-DR7), and anhydrides (HLA-DR3) [77, 78]. Conversely, HLA alleles can exhibit protective effects against occupational asthma; for example, DRB1 and DQB1 HLA class II alleles were identified as potentially protective against Western red cedar asthma [79]. HLA genes have been identified as risk factors in other allergic respiratory diseases, such as allergic rhinitis (HLA-DQB1, HLA-B, and HLA-G) and allergic bronchopulmonary aspergillosis (HLA-DRB1). GWASs have also elucidated atopic airway disease-associated risk loci predominately related to airway epithelial or immune function. In the context of diisocyanate-induced asthma, a major cause of occupational asthma, GWAS elucidated at least 4 potential regulatory single-nucleotide polymorphisms (SNPs) (*FAM71A* (rs147978008), *ATF3* (rs1157537), *TAC R1* (rs2287231), and *CDH17* (rs2446824 and rs2513789)), where the ability of each oligonucleotide to modify transcriptional events may influence clinical phenotype of occupational asthma [80]. An intensive database and literature review of 31 GWAS, not specific to occupational disease, demonstrated 267 significantly associated loci with 170 protein-coding GWAS-level risk genes of symptomatic atopic disease corroborating Th2 endotype skewing in most allergic rhinitis cases [81•]. Previous GWAS findings assessing loci associated with allergy or allergic sensitization identified the importance of *C11orf30*, a gene implicated in interferon-stimulated gene regulation, *LRRC32*, a gene involved in regulatory T cell (Treg)-specific TGF-β signaling [82]. The significance of Th2-relevant immune mechanisms (*BCL6*, *GATA3*, *IL1RL1*, *IL33*, *STAT6*, *TSLP*) and innate immune responses (*TLR1/6/10*) has become increasingly apparent in the pathogenesis of allergy through the identification of common risk variants from GWAS [83].

Altered airway microbiome composition, as informed by both environmental factors and genetic bias, has recently been found to inform allergic disease susceptibility, given its ability to modulate immune responses [84]. Increases in Proteobacteria in the human lung microbiome, Th17 pathway suppression via *Enterococcus faecalis*, and IgE-basophil axis dysregulation due to impaired commensal population development have all been implicated in respiratory allergy [85–87]. Interestingly, compositional associations exist between the lung and gut microbiome that influence allergic disease development, implicating extra-organ commensal populations in mediating lung allergic responses [88]. Identifying and restoring altered microbiome functionality may prove beneficial in reducing occupational allergic lung disease and inform worker susceptibility assessments and the subsequent need for preventive action [87]. However, considerable investigation is still necessary to dissect the lung microbiota's complex role in facilitating allergic disease.

Therapeutic Approaches

While post-exposure interventions to mitigate occupational allergy development risk are currently predicated on agent identification and risk reduction, interventions to address allergic symptoms are being widely studied and applied in clinic. Management for allergic respiratory disease resulting from occupational exposure falls into three categories: avoidance, pharmacotherapy, and immunotherapy. The first and most effective measure in occupational allergy management is avoidance of occupational sensitizing agents (primary prevention) and exacerbating agent(s) post-sensitization. Definitive removal from exposure is an interventional necessity for workers who have already developed occupational allergy [89]. While pharmacologic treatment is the mainstay of management in these patients, interventions are palliative rather than curative. Intranasal glucocorticoids (e.g., mometasone, fluticasone, triamcinolone) and minimally sedating oral antihistamines (e.g., cetirizine, fexofenadine) are typically first-line management options for symptoms related to respiratory allergy such as sneezing, rhinorrhea, nasal congestion, and allergic conjunctivitis. Although not explicitly studied for occupational allergy, adjunctive therapies, including ipratropium nasal spray, leukotriene-modifying drugs (e.g., montelukast, zafirlukast), and saline nasal irrigation, have been symptomatically prescribed [90]. A recent small study found that the use of a hypertonic (vs. normotonic) saline nasal lavage post-work shift resulted in increased anti-inflammatory IL-10 levels in dairy workers from high-volume dairy operations [91]. This study, and the discussed mechanisms of occupational-induced respiratory disease, suggest a role for IL-10 therapy post-occupational exposure. Indeed, short-term, lung-delivered recombinant IL-10 (rIL-10) to WT mice has been shown to hasten recovery after an acute, high-dose inhalant LPS exposure [92••]. Prior studies have also demonstrated more injurious/inflammatory airway outcomes in IL-10-deficient mice treated with repetitive agriculture dust extract (LPS-enriched); however, rIL-10 treatment reversed these effects [93]. Pretreatment with a human IL-10 expressing adenoviral vector has also been shown to mitigate airway injury in IL-10-deficient mice exposed to chronic, high-concentration LPS [94]. Lung-targeted IL-10 is therefore an emerging post-exposure therapy that could prevent the progression of occupational-induced airway inflammation toward a chronic disease phenotype.

As previously discussed, occupational asthma has different pathomechanisms depending on the inciting trigger. However, initial pharmacotherapy for occupational asthma

does not differ from other types of asthma, assuming an IgE and Th2 pathway-dependent disease process. Given this, the severity of asthma directly informs management strategy [95]. Briefly, short-acting beta-agonists (SABAs), such as albuterol and levalbuterol, are used as "rescue" medications to relieve asthma symptoms quickly. Poor control of asthma symptoms with SABAs necessitates additional interventions such as inhaled long-acting beta-agonists (LABA) or oral glucocorticoid therapy to achieve asthma control. Specific allergen immunotherapy (AIT) is disease-modifying in the cases of asthma and allergic rhinitis, with long-term remission of symptoms lasting up to 10 years after discontinuation. Specifically, AIT is an immune tolerance-inducing treatment capable of effectively reducing allergic rhinitis and asthma symptoms [96, 97]. This effect proceeds through the induction of IL-10 and TGF-β producing antigen-specific Tregs. These cytokines suppress mast cells, basophils, eosinophils, and inflammatory dendritic cells in addition to Th2 and other effector T cells [98]. IL-10 and TGF-β additionally promote immunoglobulin class switch, promoting IgG_4 and IgA production. IgG/IgG4 specifically exercise a "blocking" effect which inhibits IgE-dependent activation through mast cell and basophil high-affinity IgE receptors (FcεRI) and B cell low-affinity IgE (FcεRII) receptors [99]. The ratio between IgE and IgG_4 is therefore responsive to immunological change and thus emerging as a promising marker for AIT efficiency [100]. Immature transitional regulatory B cells (itBregs) also produce IL-10 in response to AIT, potentially through a CD40L + group 3 innate lymphoid cell (ILC3)-assisted mechanism [98, 101]. AIT also prevents seasonal increases in ILC2 cells and induces tolerogenic dendritic cells, further modulating the Th2 immune response [102]. The development of allergen tolerance resulting from AIT therefore engages cytokine mechanisms (IL-10, TGF-β) that regulate the suppression of effector mechanisms (via histamine receptor 2, programmed death 1 (PD-1), and cytotoxic T lymphocyte antigen 4 (CTLA-4)) resulting in a decreased IgE:IgG_4 ratio, reduced mast cells and eosinophils, and suppressed mediator release [103]. Whereas mechanisms underlying AIT have been described largely in non-occupational allergy, it is likely that these AIT mechanisms of action in occupational allergy are conserved assuming an IgE-mediated response; however, further research is necessary to link AIT efficacy and mechanism to occupational exposure-induced allergy.

Despite the widespread use of AIT for asthma and allergy treatment, it is scarcely used and inadequately studied for occupational triggers. Immunotherapy for occupational allergy has yet to be translated entirely into clinical practice. Therapeutic extracts of occupational allergens for subcutaneous/sublingual immunotherapy have yet to be produced or, in some cases, may possess untoward toxicity [104]. To date, immunotherapy has been most studied in occupational allergic disease specific to cereal grain, latex, and laboratory animal exposure. A double-blind placebo study demonstrated that asthmatic bakers and pastry workers who received wheat flour extract AIT for up to 20 months exhibited reduced bronchial hyperresponsiveness and skin sensitivity to wheat flour [105]. A retrospective cohort study showed that wheat flour-sensitized patients who received subcutaneous immunotherapy (SCIT) for at least 4 years achieved desensitization, reduced symptoms, and decreased medication usage despite continued occupational exposure 5–10 years after the initial treatment began [106]. However, the application of AIT in baker's asthma has been limited by poor quality and lacking standardization of allergen extracts, complicated by the uncertainty intrinsic to identifying the significant allergens in wheat flour-induced baker's asthma [107]. In the case of latex allergy, clinical trials of AIT corroborated beneficial effects; however, pervasive side effects were noted in the small studies reviewed [108, 109]. Two of three randomized trials and five out of six randomized placebo-controlled studies of AIT in latex allergy demonstrated clinical symptom improvement but adverse side effect occurrence [110]. Asthma due to laboratory animal exposure is relatively common among laboratory workers managing rat, mouse, or rabbit colonies. In a study where AIT was administered to 11 patients with 12 different extracts (five mice, six rats, and one rabbit), 9 of the 11 patients improved, with all patients demonstrating a significant IgG dose-related increase [111]. A case report showing the efficacy of rat epithelium for AIT in a biologist with allergic asthma symptoms revealed complete symptom relief after 18 months of treatment [112]. While available data is scarce, AIT has a potential, demonstrable impact on occupational allergic disease management when the workplace cannot be avoided, symptoms persist despite removal from exposure setting, and/or cross-reactivity occurs with other allergic antigens.

Immunotherapy in the form of biologic agents has shown clinical efficacy alone and in conjunction with AIT in non-work-related allergy respiratory disease therapy, prompting translation to occupational allergic disease management. The monoclonal anti-IgE antibody, omalizumab, has demonstrated efficacy in improving control of occupational asthma despite allergen size (LMW or HMW) where complete elimination of inciting compound was not possible [113]. A more recent case report corroborated the efficacy of omalizumab addition in treating moderate to severe persistent occupational IgE-mediated asthma [114]. Omalizumab also demonstrated adequate disease control and improved quality of life in bakers allergic to flour [115]. Combination treatment with omalizumab and AIT in patients with allergic rhinitis and comorbid asthma demonstrated a significant 40% reduction in patient symptoms when compared with AIT alone, demonstrating the potential for combination therapy in occupational allergic disease [116]. Omalizumab pretreatment 2 weeks

before the start of pollen season even demonstrated better symptom control and reduced symptom-relieving medication usage in patients with seasonal allergic rhinitis [117••]. Therefore, omalizumab pretreatment of individuals entering occupations with potential allergic exposure and/or prior atopy may prophylactically decrease occupational allergic disease severity and frequency. Given the reported success of omalizumab translation to occupational exposure-induced allergic disease, studies are needed to further describe the long-term effect of biologic and combination therapy with AIT targeting IgE, IL-5/IL-5R, and IL-4Rα, given their reported efficacy in non-occupational allergy [96].

Conclusion

Occupational lung diseases including asthma are a primary cause of occupation-associated illness and disability in the USA [118]. While occupation-induced and/or exacerbated respiratory disorders are avoidable, technological developments and industrialization continue to outpace the implementation of workplace preventative measures, disease-causing agent identification, and occupational exposure-induced lung disease surveillance. Given the changing industry landscape and workforce composition, implementing effective safety regulations and employee medical monitoring has become an increasing challenge. Therefore, research furthering mechanistic understanding of occupational airway disease etiology is necessary to inform post-exposure treatment options, given new occupational agents with unknown respiratory risk are constantly introduced. Investigations uncovering the immune-mediated relationship between occupational exposure and lung pathology are essential to prevent chronic disease development and improve well-being among exposed workers.

Compliance with Ethical Standards

Conflict of Interest The National Institute for Occupational Safety and Health grant U54OH010162 (JAP, ADS) and R01OH012045 (JAP), Department of Defense #PR200793 (JAP). Central States Center of Agricultural Safety and Health (CS-CASH). JAP has received research reagent from AstraZeneca (no monies) and is a site investigator for clinical studies for Takeda, GlaxoSmithKline, and AstraZeneca (no monies).

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any authors.

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