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Review

Overview of immunotoxicology and current applications to respiratory diseases

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Abstract

Immunotoxicology has been defined as the study of adverse effects on the immune system resulting directly from environmental, occupational, or therapeutic exposure to chemicals (including drugs), biological materials and, in certain instances, physiological factors, collectively referred to as agents. It encompasses immunosuppression, allergy, autoimmunity and inflammation. Published by Elsevier Science B.V.

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As the lung is the portal of entry for many agents, as well as a target organ, considerable attention has been directed to the development of predictive tests for assessing pulmonary immunotoxicity and understanding their mode of action. Regarding pulmonary immuntoxicology, the majority of agents of interest is associated with environmental or occupational exposure and is responsible for causing chronic inflammatory disease, granulomatous lung disease, asthma, exacerbation of asthma, respiratory hypersensitivity and increased respiratory infections (Table 1). As the ability of an agent to exacerbate asthma may be due to its inflammatory properties, all toxicants that cause pulmonary inflammation may, by definition, be suspect causative agents. The current database suggests that agents, which produce inflammatory responses or respiratory hypersensitivity, are more common than those that are responsible for producing granulomatous reactions or local immunosuppression.

The origins of immunotoxicology lie in human risk assessment and, as such, emphasis in this area has been placed on the development of sensitive and predictive tests for identifying immunotoxic agents, monitoring epidemiological studies and laboratory-based mechanistic research that may be used to improve human risk assessment. For the most part, immunotoxicity testing has focused on detecting agents that cause allergic contact dermatitis or systemic immunosuppression rather than pulmonary effects (Luster et al., 1988). While not validated, tests to monitor pulmonary immunosuppression, have been conducted and often involve quantifying inflammatory and immune markers, as well as host resistance measurements following challenge with infectious

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Table 1
Examples of agents that cause immune-mediated respiratory reactions in humans

Hypersensitivity	Inflammation	Immunosuppression	Granulomas
Low molecular weight	Ozone	Benzo(*a*)pyrene	Beryllium
Nickel	Sulfur dioxide	Phosgene	
Platinum	Silica	Nitrogen dioxide	
Isocyanates	Organic dusts		
Anhydrides	Heavy metals		
High molecular weight	Asbestos		
Detergent enzymes			
House dust mite			
Pollens			

agents in experimental animals (NRC, 1995). Historically, these tests monitor the lower airway, which has raised some concern, as the upper airway is the site for most pulmonary infections. However, cells responsible for both nonspecific and specific (humoral and cell-mediated immunity derived from interstitial lymphocytes and bronchus-associated lymphoid tissue) immune mechanisms are found in the lower airway and are more readily obtainable for study than in the upper airway. Nonspecific mechanisms include the mucociliary escalator of the large airways that removes the bulk of inhaled foreign materials, alveolar macrophages that help protect against particulate materials reaching the lung alveoli, and interstitial macrophages that participate in antigen processing. The lung also possesses a significant number of NK cells, possibly an evolutionary development to combat lung neoplasia from inhaled carcinogens. Functional tests for these cell types are similar to those used for examining systemic immunosuppression but require more elaborate cell isolation procedures.

While testing the potential of xenobiotics to induce allergic contact dermatitis is relatively routine, assessment of respiratory sensitizers is considered expensive and complex and is performed only on a limited basis (Karol, 1992). Historically, the guinea pig has been the model of choice and both specific immunologic responses (reagenic antibody) and pulmonary sensitivity (reactivity) to inhaled or intratracheally administered allergens have been measured. Although the guinea pig has some significant immunological differences compared to humans (e.g., IgG_1 vs. IgE reaginic antibodies), it has been proven to be a predictable model for humans given the limited comparative data available. Variations of the guinea pig model have been used to test for low- and high-molecular weight sensitizers, although they all include an aerosol sensitization and challenge phase. Many of these tests also include measurements of both immediate and delayed onset responses, although this will not distinguish between nonspecific pulmonary hyper-reactivity and specific immune responses. The latter can be established by determining the requirement for T-lymphocytes, particularly CD4 cells, or monitoring for the presence of reagenic antibodies in sera. Of concern in guinea pig lung models has been the need to employ chemical-carrier conjugates to elicit a response in the challenge phase. Efforts are underway to identify respiratory allergens in mice by determining changes in serum IgE levels or cytokine profiles in draining lymph nodes following dermal application of the test material. Following topical exposure in mice, chemical respiratory allergens can stimulate Th2 cells to secrete interleukin (IL)-4 resulting in IgE. Alternatively, IL-13 may be induced, which also elicits a pulmonary hypersensitivity response. These approaches, if validated, would provide marked advantages compared to existing guinea pig assays, particularly in that it replaces the need for inhalation exposure.

A common pulmonary response to environmental or occupational toxicants is inflammation. Although usually self-limiting, depending upon the agent and dose, inflammation may persist and lead to a fibrotic response. Cellular and biochemical profiles of bronchoalveolar lavage (BAL) constituents following inhalation exposure in experimental animals and humans have been an increasingly used tool for screening inflammatory lung injury (Koren et al., 1994).

Although the presence of elevated levels of histamine and other arachidonate metabolites have been used as markers of allergic response in the lung, analysis of the BAL is informative mainly for establishing inflammatory, nonspecific immune responses. Sensitive markers of toxicity include changes in the level of enzymatic activities in BAL, such as lactate dehydrogenase (LDH) or β-glucuronidase. LDH is a cytoplasmic enzyme that is not found extracellularly except in the presence of lysed or damaged cells. β-Glucuronidase or hydrolytic enzymes are useful markers for the toxicity of inhaled particles because these enzymes are released from activated macrophages following phagocytosis. The secretion of bioactive products from pulmonary epithelial cells and alveolar macrophages is a key event in lung diseases following inhalation of toxic environmental agents and numerous studies have implicated the progression of lung disease with postactivational release of growth factors and inflammatory cytokines, such as IL-1, tumor necrosis factor α, IL-6, and IL-8. In addition to the release of cytokines, alveolar macrophages secrete a variety of short-lived products that may contribute to altering resistance to pulmonary infections and inflammation. Among these are reactive oxygen species such as superoxide anions and hydrogen peroxide, as well as nitric oxide.

In summary, systematic and validated approaches to identify potential pulmonary immunotoxic agents are still in their infancy. Our increased understanding of the biological mechanisms responsible for these pathologies will need to be used to improve existing test methods. Work is underway to elucidate the molecular basis for many hereditary diseases. Thus, it would follow that pulmonary immunotoxicological evaluation would also incorporate molecular markers to supplement and eventually replace the more conventional tests that are currently conducted. As this process evolves, it will be essential that we maintain a practical understanding of these molecular changes as they pertain to our knowledge of risk assessment.

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