Occupational asthma update

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Various kinds of workplace agents causing occupational asthma (OA) in which high-molecular-weight (HMW) and low-molecular-weight (LMW) allergens were included. HMW allergens such as wheat flour, enzymes and some LMW compounds such as isocyanates, reactive dye, antibiotics act through a documented IgE-mediated mechanism. For most LMW agents, the immunologic mechanism has not yet been fully characterized.

1. Immunologic mechanisms

Most HMW allergens such as wheat flour, digestive enzymes, herbal agents and spider mites could induce IgE mediate responses to induce work related symptoms in exposed workers. Allergy skin prick test and/or measurement of serum specific IgE antibody will be useful for predicting the phenotype OA and identifying asymptomatic sensitizers among the exposed workers. ADRB2 and IL-10 may be genetic markers for enhance IgE sensitization to HMW agents. Some LMW agents could induce IgE mediated responses. Three diisocyanates including TDI, MDI and HDI are a common cause of OA(2) and TDI is the most common cause of OA in developing countries. A leading hypothesis in the pathogenesis of TDI-OA is that the chemical acts as a hapten and undergoes nucleophilic addition reactions (conjugates) in vivo with airway proteins. Serum specific IgE and IgG antibodies to TDI-human serum albumin (HSA) conjugate were found to be significantly higher in TDI-OA patients than control groups. However, the prevalence of this serum specific IgE antibody varied between 0 and 50% of TDI-OA patients, which were derived from preparatory conditions of the conjugate and type of TDI-HSA conjugate used. Regarding MDI, when serum-specific IgE antibodies were found in sera of confirmed MDI-OA patients compared to control groups, although sensitivity was low. These findings suggested that IgE mediated mechanism is one of the major pathogenic mechanism of isocyanate induced OA in which detection rate of serum specific IgE antibody will be improved if we develop more biological isocyanate –tissue protein conjugate. Several kinds of reactive dyes including Black GR and Orange 3R could induce IgE mediated OA in exposed workers. Inhalation of cephalosporin powders could induce IgE mediated occupational allergies in exposed subjects working in pharmaceutical industry or in health care workers. Monitoring of

serum specific IgE antibody to corresponding cephalosporin-HSA conjugate or reactive dyes will be useful for detecting the sensitized subjects and potential OA patients.

The role of serum specific IgG still remains controversial. Most studies including spider mite, wheat flour, and reactive dyes demonstrated that the presence of wheat-specific IgG1 and IgG4 antibodies was found to be significantly higher in exposed workers in association with exposure intensity. The possibility of IgG4 mediated OA seems extremely low. Therefore, serum specific IgG to occupational allergens may represent current or previous exposure, not directly related with the pathogenic mechanism.

Possible autoimmune mechanisms were suggested in pathogenic mechanisms of TDI-OA as the recent studies reported two serum autoantibodies, IgG to cytokeratin (CK) 19 and transglutaminase (tTG). The prevalence of serum IgG to CK19 and tTG in TDI-OA was significantly higher than in control groups.

2. Non-immunologic mechanism

The previous in vitro studies demonstrated that TDI exposure could induce IL 8 and chemokine productions from the bronchial epithelial cells interacted with activation of pro-inflammatory cyotokines, indicating that isocyante exposure could initiate and prime immune response in asthmatic airway and propagate various inflammatory cells. Furthermore, the immunohistochemical study of airway mucosa of TDI-OA patients demonstrated the increased infiltration of neutrophils as well as lymphocytes and eosinophil. Increased levels of MPO and IL 8 were found in the airway secretion of TDI-OA patients after the TDI challenges indicating that activated neutrophils can involve in the pathogenic mechanism of TDI-OA. Furthermore, increased production of matrix metalloproteinase-9 (MMP-9), and VEGF was noted in the airway secretion and/or sera of TDI –OA after the TDI challenges, indicating that these cytokines may involved in the airway inflammation as well as airway remodeling.

3.Molecular genetic mechanisms

A study performed in a Korean population demonstrated that HLA DPB1*0501 haplotype may be a genetic marker for the development of TDI-OA. A genome-wide association study reported the alpha-T catenin (CTNNA3) as a candidate gene that was associated with the degree of airway inflammation. There have been several studies showing that anti-oxidant genes such as NAT and GST were associated with TDI-OA phenotype, however, they were not replicated in Asian population. The ADRB2 polymorphisms may affect IgE-specific sensitization to TDI. The TLR4 and IL4R genes were related with development of respiratory symptoms in baker's asthma.

4. Perspectives

To date, occupational challenge test is the gold standard for diagnosis of OA, but it is an

invasive and time consuming procedure under the supervision of specialists. Permanent impairment of lung function was noted in the long-term follow-up of OA. It is essential to develop applicable biomarkers to predict the phenotype of OA and to identify the susceptible subjects.