Identification of Immunologic and Genetic Biomarkers for TMA Sensitization

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Workplace exposure to Trimellitic Anhydride (TMA), which is used in producing plastics and paints, can cause occupational health hazards. In the US, an estimated 20,000 factory-workers are exposed to TMA each year in spite of taking aggressive measures to reduce exposure. TMA is a unique chemical capable of causing both non-immunologic (irritation) and antibody-mediated immunologic responses. TMA is rapidly converted to trimellitic acid in ambient humidity causing irritation to exposed epithelial/mucosal surfaces. However, to elicit an IgE mediated response, it must bind to an endogenous protein like human serum albumin (HSA) to form a complete antigen. It is still unclear which TMA exposed workers will remain unsensitized (i.e., no specific antibody) or become sensitized (i.e., develop specific IgE) to TMA which increases their risk for developing occupational asthma. Previous investigations have suggested differential expression of genes with exposure to irritants vs sensitizing agents. There is a paucity of information regarding potential biomarkers for determining risk for TMA sensitization or gene expression signatures that can discriminate irritant from cellular immunologic responses to TMA exposure. To address whether TMA specific IgG4 is a useful biomarker for tolerance vs. sensitization, a Rat Basophil Leukemia (RBL) Cell Mediator Release Assay, will be used. RBL cells expressing human IgE receptor, will be incubated with TMA-exposed factory workers' sera with (a) no TMA-specific antibody (b) specific IgE: specific IgG4 > 1 and (c) specific IgE: specific IgG4 < 1. Cells will then be challenged with TMA-HSA conjugate to measure mediator release. We hypothesize that IgE:IgG4 <1 will inhibit or attenuate mediator release whereas IgE:IgG4 >1 ratios will promote mediator release. To assess differential molecular genetic signatures as markers for TMA sensitization vs. an irritant non-allergic response an in vitro dendritic cells (DCs) model will be used to investigate allergenicity. DCs pre-sensitized using TMA-specific serum IgE will be exposed to a TMA-HSA conjugate to assess TMA specific IgE-medicated reactions, while unsensitized DCs exposed to free TMA will be used to assess the irritant response, with appropriate experimental controls.

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