Glutathione Reaction Products With The Chemical Allergen, Methylene-Diphenyl Diisocyanate (mdi), Stimulate Eosinophilic Airway Inflammation And Alternative Macrophage Activation

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RATIONALE: Isocyanates have been a leading chemical cause of occupational asthma since their utility for generating polyurethane was first recognized over 60 years ago, yet the mechanisms of isocyanate asthma pathogenesis remain unclear. We tested the hypothesis that glutathione (GSH) reaction products with the chemical allergen, methylene-diphenyl diisocyanate (MDI), mediate asthma-like inflammatory responses upon respiratory tract isocyanate exposure.

METHODS: Reaction products between GSH and MDI (GSH-MDI) were generated in vitro and characterized by liquid chromatography-mass spectrometry (LC-MS). Balb/C mice were exposed to GSH-MDI via the respiratory tract, and airway inflammatory responses were characterized based on analysis of airway lavage fluid, and lung tissue samples. Additional analysis of airway fluid was performed using isobaric tags for relative and absolute quantitation (iTRAQ) of protein levels.

RESULTS: In naive mice, GSH-MDI induced innate immune responses, characterized by significantly increased airway levels of chitinase YM-1, and IL-12/IL-23ß (but not α) subunit. However, in mice immunologically sensitized to MDI via prior skin exposure, identical GSH-MDI doses induced substantially greater inflammatory responses, including significantly increased airway eosinophil numbers (see Figure below) and mucus production, along with IL-12/IL-23ß, chitinases and other indicators of alternative macrophage activation. The "self"-protein, albumin, in airway fluid was uniquely modified by GSH-MDI reaction products, at the same site (Lys^{414}) previously identified as a favored site for MDI conjugation to human albumin in vitro.

CONCLUSION: The data suggest a thiol-mediated transcarbamoylating mechanism links MDI exposure and pathogenic inflammatory responses.

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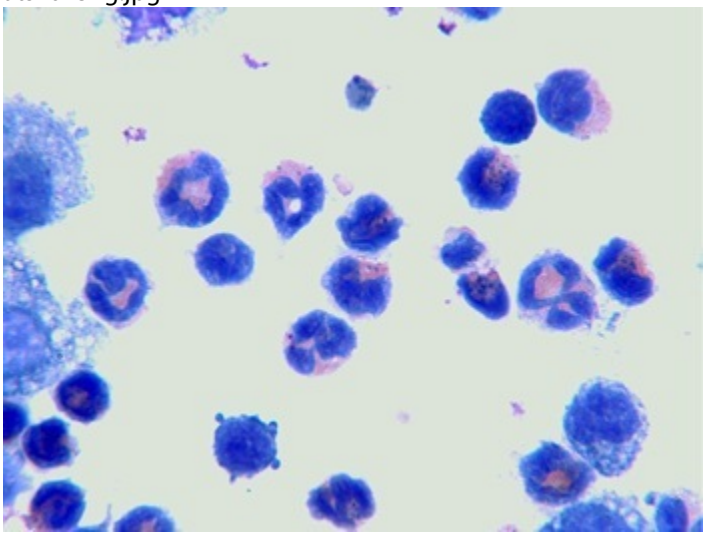

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