Innate lymphoid cells in isocyanate-induced asthma: role of microRNA-155

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ABSTRACT

Background: Occupational asthma, induced by workplace exposures to low molecular weight agents such as toluene 2,4-diisocyanate (TDI), causes a significant burden to patients and society. Little is known about innate lymphoid cells (ILCs) in TDI-induced asthma. A critical regulator of ILC function is microRNA-155, a microRNA associated with asthma.

Objective: To determine whether TDI exposure modifies the number of ILCs in the lung and whether microRNA-155 contributes to TDI-induced airway inflammation and hyperresponsiveness.

Methods: C57BL/6 wild-type and microRNA-155 knockout mice were sensitised and challenged with TDI or vehicle. Intracellular cytokine expression in ILCs and T-cells was evaluated in bronchoalveolar lavage (BAL) fluid using flow cytometry. Peribronchial eosinophilia and goblet cells were evaluated on lung tissue, and airway hyperresponsiveness was measured using the forced oscillation technique. Putative type 2 ILCs (ILC2) were identified in bronchial biopsies of subjects with TDI-induced occupational asthma using immunohistochemistry. Human bronchial epithelial cells were exposed to TDI or vehicle.

Results: TDI-exposed mice had higher numbers of airway goblet cells, BAL eosinophils, $CD4^+$ T-cells and ILCs, with a predominant type 2 response, and tended to have airway hyperresponsiveness. In TDI-exposed microRNA-155 knockout mice, inflammation and airway hyperresponsiveness were attenuated. TDI exposure induced IL-33 expression in human bronchial epithelial cells and in murine lungs, which was microRNA-155 dependent in mice. $GATA3^+CD3^-$ cells, presumably ILC2, were present in bronchial biopsies.

Conclusion: TDI exposure is associated with increased numbers of ILCs. The proinflammatory microRNA-155 is crucial in a murine model of TDI asthma, suggesting its involvement in the pathogenesis of occupational asthma due to low molecular weight agents.