S100A8/A9: A Mediator of Neutrophilic Airway Inflammation, Airway Hyperresponsiveness and Biomarker of Severe Asthma

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Abstract

Background: Most severe asthmatics exhibit steroid refractory disease that limits effectiveness of therapy and typically associated with chronic neutrophilia, and release of a unique repertoire of “steroid refractory” mediators. Thus, a better understanding of severe disease, including triggers of these steroid refractory mediators is critical to address unmet clinical needs. Our aim was to identify whether S100A9 knock-out mice (the subunit that stabilizes the functional S100 protein heterodimer) elicits attenuated hallmarks of asthma including, airway inflammation (neutrophilia and eosinophilia), airway hyperresponsiveness and airway remodeling in a murine model of allergic asthma.

Methods: Eight week old Balb/c mice were subjected to intranasal (i.n) challenges with house dust mite (HDM) (Dermatophagoides pteronyssinus) extract (0.7 mg/mL in saline) - acute (5 consecutive daily i.n challenge for 2 weeks) and chronic (3 daily mid-week HDM i.n challenge for additional 5 weeks). Animals were assessed for S100A8/A9 at: ~8hrs and 48hrs post acute protocol (peak neutrophilia and eosinophilia respectively); and 48 hrs post chronic protocol (established airway remodeling). We also assessed baseline respiratory mechanics in S100A9 knockout (KO) mice via flexiVent. Using Human endobronchial biopsies (severe asthma) and patient-matched bronchoalveolar lavage fluid (BALF), we also performed immunohistochemistry and Enzyme Linked Immunoabsorbent Assay (ELISA) to assay S100A8/A9 and Receptor for Advanced Glycation Endproducts (RAGE) expression.

Results: Expression of S100A8/A9 and its primary receptor, RAGE, are increased in asthmatic biopsies compared to healthy biopsies. S100A8/A9 release in BALF fluid was elevated by 6 fold in human asthmatic [605 ng/ml (24-2420)] compared to healthy subject BALF [107 ng/ml (38-400)]. In mice, acute HDM challenge induces and sustains S100A8/A9 release in BALF, and this tracks with neutrophil cell numbers in BALF. S100A8/A9 and RAGE from lung tissue is increased in acute and chronic HDM challenged mice compared to naïve controls. Using the acute HDM protocol, HDM S100A9 KO mice elicit reduced airway resistance (AR), tissue resistance (TR) and tissue elastance (TE) to methacholine challenge (6-50 mg/ml) compared to HDM wild-type mice. Similarly basal AR and TE are both reduced in the HDM S100A9 KO mice compared to HDM wild-type mice. Furthermore, total BALF cells including eosinophils and neutrophils appear reduced in S100A9 KO mice for both naïve and HDM groups.

Conclusion: In severe asthma and murine models of allergic asthma there is an elevated release and expression of S100A9/A9 and RAGE. Improved lung mechanics and attenuated lung inflammation in S100A9 KO mice suggest that sustained levels of S100A8/A9 may contribute to disease pathogenesis.