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Title: Syk mediates airway hyper-responsiveness and airway remodeling in a chronic mouse model of house dust mite induced allergic airways disease

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Body: BACKGROUND: Asthma is characterized by airways hyper-responsiveness (AHR), chronic inflammation, remodeling and reversible obstruction. We have shown treatment with Syk (spleen tyrosine kinase) inhibitor to abrogate AHR to methacholine (MCh) in a mouse model of established ovalbumin-induced airways inflammation. The role of Syk in airway remodeling is not known. OBJECTIVE: To investigate the role of Syk in the pathogenesis of AHR and remodeling in a mouse model of allergic airways inflammation. METHODS: We used acute and chronic mouse models of house dust mite-induced (HDM; Dermatophagoides farina and D. pteronyssinus, respectively) airways inflammation. The role of Syk was investigated by pharmacological inhibition and in $Syk^{flox/flox}$//$rosa26CreER^{T2}$ conditional knockout mice. Respiratory mechanics and MCh-responsiveness were assessed using the flexiVent® system, and airway remodeling determined by semi-quantitative histological analysis. RESULTS: AHR in response to HDM was abrogated in the Syk knockout when compared with Syk-expressing mice. Similarly, AHR was reduced to control levels in response to a single dose of the Syk inhibitor, NVP-QAB-205, given intratracheally after establishment of allergic airways inflammation. Airways inflammation was not affected by either Syk knockout or NVP-QAB-205. Histological analysis indicated fibrosis, epithelial thickening, mucus cell hyperplasia and smooth muscle cell hypertrophy to be attenuated in the Syk knockout model when compared with Syk-expressing controls. CONCLUSIONS: These studies suggest that Syk mediates AHR and airway remodeling in a chronic model of allergen-induced airways inflammation.