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Title: Syk mediates airway contractility independently of leukocyte function

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Body: BACKGROUND: Syk plays a role in inflammatory diseases such as asthma and rheumatoid arthritis. We reported a role for epithelial expression of Syk in the airways hyperresponsiveness in a mouse model of asthma. These observations led us to posit a role of epithelial Syk in airway contractility. OBJECTIVE: To investigate the role of Syk in airway contractility in response to methacholine (MCh). METHODS: We used $Syk^{flox/flox}$//rosa26$CreER^{T2}$ conditional Syk knockout mice to evaluate respiratory mechanics and MCh-responsiveness in vivo using the ventilator-based flexiVent® system, and used live microscopy to assess airway contractility by measuring airway lumen diameter in lung slices ex vivo. RESULTS: In vivo studies showed that Syk-deficient mice were less responsive to MCh compared with Syk-intact mice. Central airways resistance (R_N) was significantly different between the Syk-intact and Syk-deficient mice ($R_{N\ (max)}$: 2.06±0.29 vs 1.29±0.10, respectively, $p < 0.05$, n=6 and 8/group). The total and differential cell counts in the bronchoalveolar lavage fluid were similar between the two groups. In ex vivo lung slices, which are devoid of circulating leukocytes, MCh (100 mg/ml) induced a 20% reduction in the luminal area in the Syk-expressing mice to 80.5±0.6% of baseline. In contrast, MCh-induced contraction of the airways was virtually abrogated in ex vivo lung slices obtained from Syk-deficient mice (luminal area 92.2±0.6 % of baseline in Syk-deficient mice, n=4/group, $p <0.05$). CONCLUSIONS: These observations suggest that Syk mediates AHR independent of its role and function in leukocytes, and supports a potential paracrine role for airway epithelial Syk in modulating airway smooth muscle activity.