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Syk regulates pulmonary vasoconstriction

Tabeling C. (1, 2), Herbert J. (1, 2), Boiarina E. (1, 2), Hocke A.C. (1), Sewald K. (3); Lamb D.J. (4), Wollin S.L. (4), Fehrenbach H. (5), Kuebler W.M. (6), Braun A. (3), Suttorp N. (1), Weissmann N. (7), Witzenrath M. (1, 2)
(1) Department of Infectious Diseases and Pulmonary Medicine, Charité – Universitätsmedizin Berlin, Germany; (2) Division of Pulmonary Inflammation, Charité – Universitätsmedizin Berlin, Germany; (3) Department of Airway Immunology, Fraunhofer ITEM, Hannover, Germany; (4) Respiratory Diseases Research, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; (5) Division of Experimental Pneumology, Priority Area Asthma and Allergy, Research Center Borstel, Airway Research Center North, Member of the German Center for Lung Research, Borstel, Germany; (6) Institute of Physiology, Charité – Universitätsmedizin Berlin, Germany; (7) Excellence Cluster Cardio-Pulmonary System, Justus-Liebig-University, Giessen, Germany

Objectives: Pharmacological inhibition of spleen tyrosine kinase (Syk) is generally well tolerated in humans. In the airways, Syk is known to promote inflammation, smooth muscle cell proliferation and contraction. However, its expression and function in the pulmonary vasculature and its possible involvement in the pathogenesis of pulmonary arterial hypertension (PAH) remain elusive.

Methods: Vascular Syk expression was analyzed in human (PAH versus donor) and murine lung tissue via immunofluorescence and spectral confocal microscopy. The functional role of Syk was studied in human precision-cut lung slices (PCLS) and in isolated perfused and ventilated lungs of wild-type mice or mice deficient in eNOS or protein kinase C (PKC)α with or without inhibition of Syk, PKC, rho kinase, p38 MAPK and/or NO. Pulmonary vascular hyperresponsiveness was analyzed in isolated lungs following induction of pulmonary Th2 inflammation.

Results: Syk was expressed in smooth muscle cells of remodeled (PAH) and non-remodeled pulmonary arteries (donor). Syk inhibition diminished pulmonary vasoconstriction in human PCLS as well as in isolated mouse lungs independent of eNOS or PKCα. The vasopressor response to a broad range of stimuli, namely serotonin, endothelin-1, angiotensin II, thromboxane agonist U46619, sphingosine-1-phosphate and hypoxic ventilation, was shown to be blunted by Syk inhibition (either with BAY 61-3606 or with BI 1002494). In the preconstricted pulmonary vasculature, Syk inhibition rapidly reversed vasoconstriction in a NO-independent manner. Moreover, pulmonary vascular hyperresponsiveness was markedly reduced following Syk inhibition. Inhibition of p38 MAPK reduced pulmonary vasoconstriction to the same extent as Syk inhibition, and simultaneous inhibition of p38 MAPK and Syk did not show any additive effect when compared to Syk inhibition only.

Conclusions: Syk mediates pulmonary vasoconstriction in a NO-independent manner, presumably via p38 MAPK. Our data suggest that Syk inhibition may be a promising therapeutic perspective in PAH.