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Exploring the role of SYK in respiratory *in vivo* models

Michael Caniga[1], Janice D Woodhouse[1], Alan Wilhelm[1], Malgorzata A Gil[1], Yanlin Jia[1], Hongshi Yu[1], Stella Vincent[1], Richard Miller[1], Gissela Lieber[2], Xiomara Fernandez[2], Richard Chapman[2], Robbie McLeod[1], Lily Y Moy[1], Nancy Kelly[1], Emily Hickey[2], Michael A Crackower[1], Thomas Miller[1], William M Abraham[3], Milenko Cicmil[1*]

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Background

Spleen Tyrosine Kinase (SYK) is a key activator of signaling pathways downstream of multiple surface receptors implicated in asthma. SYK function has been extensively studied in Last cells downstream of the high-affinity IgE receptor (FcεR1). Most studies evaluating SYK function in preclinical models have relied on poorly selective compounds, anti-sense oligonucleotides, or SYK knockout mice. Here we describe the characterization of SYK mechanism in multiple in vivo model settings.

Materials and methods

The effect of SYK inhibitor MRK-A on allergic airway responses was evaluated in IgE-mediated tracheal extravasation in rat, Brown Norway Ova rat models of allergic inflammation and the sheep inhaled ascaris allergen challenge model.

Results

MRK-A dose-dependently blocked IgE-mediated tracheal extravasation in rat. In a Brown Norway rat ovalbumin-sensitized airway challenge model oral dosing of MRK-A led to a dose-dependent inhibition of airway inflammation. Intravenous dosing of MRK-A was able to significantly inhibit both early and late allergen- induced changes in airway resistance in an ascaris-sensitive sheep allergen challenge model as well as airway hyper responsiveness.

Conclusions

Here we demonstrated that SYK mechanism plays a significant role in several in vivo allergen challenge models. This ranges from simple PK/PD mast cells driven models such as the IgE-mediated tracheal extravasation to the more complex and clinically relevant sheep inhaled allergen challenge model.

Authors' details
[1]Merck Research Laboratories, Boston, MA 02115, USA. [2]Merck Research Laboratories, Kenilworth, NJ 07033, USA. [3]Mount Sinai Medical Center, Miami Beach, FL 33140, USA.

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[1]Merck Research Laboratories, Boston, MA 02115, USA
Full list of author information is available at the end of the article