CBX4 regulates long-form thymic stromal lymphopoietin-mediated airway inflammation through SUMOylation in HDM-induced asthma mice

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Abstract

Abstract Background: Thymic stromal lymphopoietin (TSLP) is present in two distinct isoforms, short-form (sfTSLP) and long-form (lfTSLP). lfTSLP promotes inflammation while sfTSLP inhibits inflammation in allergic asthma. However, little is known about the regulation of lfTSLP and sfTSLP during allergic attack in asthma airway epithelium. Methods and Results: Here, we report that SUMOylation was enhanced in HDM-induced allergic asthma airway epithelium. Inhibition of SUMOylation significantly alleviated airway Th2 inflammation and lfTSLP expression. Mechanistically, CBX4, a SUMOylation E3 ligase, enhanced lfTSLP, but not sfTSLP, mRNA translation through the RNA binding protein, MEX-3B. MEX-3B promoted lfTSLP translation through binding of its KH domains to the lfTSLP mRNA. Furthermore, CBX4 regulated MEX-3B transcription in HBE through enhancing SUMOylation levels of the transcription factor, TFII-I. Conclusion: We demonstrate an important mechanism whereby CBX4 promotes MEX-3B transcription through enhancing TFII-I SUMOylation, and MEX-3B enhances the expression of lfTSLP through binding to the lfTSLP mRNA and promoting its translation. Our findings uncover a novel target of CBX4 for therapeutic agents to lfTSLP-mediated asthma.

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