

Correspondence

Interferon regulatory factor 3 activation mediates viral stimulus-induced bronchial production of thymic stromal lymphopoietin

To the Editor:

I read with interest the report by Lee et al¹ showing respiratory syncytial virus (RSV)-induced production of thymic stromal lymphopoietin (TSLP) in bronchial epithelial cells (BECs). They find that RSV-infected BECs overproduce TSLP in childhood asthma and advance this as a mechanism promoting the T_H2 aspect of exacerbations of asthma in children.¹ As noted by Lee et al, the viral mimetic poly(I:C) is known to induce TSLP secretion by BECs. Indeed, by using this viral stimulus, we demonstrated significant overproduction of TSLP by BECs obtained from adult asthmatic donors and suggested that TSLP may contribute to virally induced exacerbations.² Chronic obstructive pulmonary disease (COPD) exacerbations also exhibit several T_H2 features (for references, see Calven et al³). Adding to similarities between asthma and COPD, we demonstrated overproduction of TSLP by BECs from donors with COPD in response to poly(I:C) and rhinovirus infection.³ Exacerbations of severe asthma and COPD are replete with unmet treatment needs. Hence, the pharmacology of BEC secretion of TSLP is of interest.

We discovered that simvastatin dose-dependently inhibited poly(I:C)-induced secretion of TSLP by BECs from healthy and COPD donors.⁴ Simvastatin was similarly active on BECs from asthmatic donors (unpublished data). Interestingly, the TSLP inhibitory action was not mevalonate dependent and, therefore, not representing class effects of statins.⁴ It was also unpredicted that simvastatin should act with marked selectivity, inhibiting TSLP without affecting other inflammatory cytokines such as TNF- α and CXCL8.⁴ We could explain the lack of inhibition of the latter 2 cytokines by the lack of effect of simvastatin on poly(I:C)-induced activation of nuclear factor- κ B (NF- κ B); simvastatin lacked effects on I κ B α and NF- κ B subunits, p65 and p105. Instead, simvastatin inhibited interferon regulatory factor 3 (IRF3) phosphorylation along with inhibition of TSLP production.⁴ Partly agreeing with suggestions by Kato et al,⁵ we confirmed the involvement of IRF3 signaling by demonstrating that simvastatin additionally inhibited viral stimulus-induced IFN- β production and that a selective IRF3 inhibitor, BX795, inhibited the generation of TSLP.⁴

Our mechanistic data apparently disagree with the report by Lee et al¹ who suggest that retinoic acid-induced gene I-dependent activation of NF- κ B explains viral-induced BEC secretion

of TSLP. Perhaps the difference in part reflects the fact that our data were obtained in primary BECs from different human donors⁴ whereas Lee et al¹ used an immortalized human lung cell line in their exploration of mechanisms. There are precedents regarding such differences. For example, Wang et al⁶ using a BEC cell line and Slater et al⁷ using primary BECs reported contrasting data regarding roles of retinoic acid-induced gene I in rhinovirus-induced IFN- β expression.

Although our findings strongly favor IRF3-dependent BEC production of TSLP, we do not completely rule out the possibility of the involvement of NF- κ B.⁴ Considering the discussion points above, I would not rule out an important role of IRF3 activation in the RSV-induced TSLP secretion by human primary BECs observed by Lee et al.¹

Lena Uller, PhD

From the Unit of Respiratory Immunopharmacology, Department of Experimental Medical Science, Lund University, Lund, Sweden. E-mail: lena.uller@med.lu.se.

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