

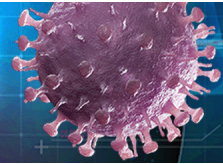


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Response to Comment on "Cutting Edge: Inhibition of NF- κ B-Mediated TSLP Expression by Retinoid X Receptor"

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Steven F. Ziegler

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Comment on “Cutting Edge: Inhibition of NF- κ B-Mediated TSLP Expression by Retinoid X Receptor”

The article published by Lee et al. in the October 15, 2008 issue of *The Journal of Immunology* (1) presents a series of experiments demonstrating the importance of the retinoid X receptor (RXR) on the inhibition of TSLP gene expression. Lee et al. (1) postulate that “RXR agonists may be useful as a therapeutic modality in treating allergy.”

The main problem is that Lee et al. (1) did not use a selective RXR ligand that can prove their hypothesis. The used derivative was the potential endogenous RXR ligand 9-*cis*-retinoic acid (9CRA), which also obtains strong retinoic acid receptor (RAR) activating potential (2) as well as strong activation potential for various other nuclear receptor heterodimers (reviewed in Ref. 3). Additionally, our group could not confirm the found effects of the “RXR agonist” by Lee et al. (1) in epithelial cells in vitro. In contrast, we used selective synthetic RXR or RAR agonists in mice for NF- κ B and TSLP gene expression analysis in the skin, obtaining an opposite outcome (J. Gericke, A. Gamlieli, J. Mihaly, K. Weiss, and R. Rühl, manuscript in preparation). We postulate that the described effects of 9CRA possibly act via RAR-mediated pathways or via other still unknown mechanisms.

The described results in Lee et al. (1) indicating that RXR ligands inhibit NF- κ B signaling and TSLP expression as well as the hypothesis that RXR ligands might be useful in treating allergy might not be correct and have not been proven in this study.

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Response to Comment on “Cutting Edge: Inhibition of NF- κ B-Mediated TSLP Expression by Retinoid X Receptor”

I am writing in response to a letter from Gericke et al. commenting on our paper recently published in *The Journal of Immunology*. In that paper we showed that 9-*cis*-retinoic acid was capable of inhibiting the NF- κ B-mediated induction of TSLP gene expression. The main point of the paper was that this inhibition, which had been first postulated by Lli et al. (1), was actually an indirect effect on the activation of NF- κ B, and not a direct effect on the TSLP promoter. Gericke et al. in their letter refer to data in a manuscript in preparation, which we have not seen, and therefore cannot comment on, that the data are suspect because we did not use RXR- or RAR-selective agonists. They also state that they could replicate our observations, although no details were provided as to the experiments they performed. While we agree that our studies would have benefited from selective agonists (we have recently shown that all-*trans* retinoic acid can also inhibit NF- κ B-mediated TSLP gene expression), this point does not detract in any respect from the general conclusion of the paper: that the effect of these agonists on TSLP gene expression is indirect through inhibition of NF κ B activation.

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