Nature Reviews Immunology | Published online 4 Apr 2018; doi:10.1038/nri.2018.23

> IL-33$_{FL}$ functions as a sensor of allergen proteases

Many airborne allergens have intrinsic proteolytic activity and sensing of this activity has been implicated in the initiation of allergic inflammation. Now, reporting in *Nature Immunology*, researchers show that rapid release and proteolytic cleavage of the alarmin cytokine interleukin-33 (IL-33) by various protease-containing allergens leads to the activation of type 2 allergic inflammation.

To study the regulation of IL-33 by allergen proteases, the authors first incubated recombinant human full length IL-33 (IL-33$_{FL}$) with extracts of the major classes of environmental allergens, including fungi, house-dust mites, cockroaches and pollens. All the aeroallergen extracts showed IL-33-processing activity and generated shortened forms of the protein. Cleavage sites were confined to the central 'sensor' domain of IL-33, and some short forms of IL-33 were similar to those generated by inflammatory proteases from neutrophils and mast cells. All processed forms of IL-33 were highly active; when recombinant versions were injected intraperitoneally into wild-type mice, they induced airway inflammation, mucus production and eosinophilia, with high levels of the type 2 cytokines IL-5 and IL-13.

The authors suggest that IL-33$_{FL}$ functions as a sensor of allergen proteases. Consistent with this, low doses of IL-33$_{FL}$ exhibited very little biological activity *in vitro*. Only when allergen extracts or allergen proteases were present did the authors observe potent production of IL-5 and IL-13 by cultured group 2 innate lymphoid cells (ILC2s). Accordingly, although mechanical damage to endothelial cell monolayers induced the release of IL-33$_{FL}$, the generation of short forms of IL-33 required the addition of allergen proteases. Allergens without protease activity, such as phospholipase A2 from bee venom and chitin, did not generate short forms of IL-33 in these cell cultures.

Further exploring the kinetics of IL-33 cleavage *in vivo*, the authors show that shortly (within 15 minutes) after intranasal exposure to allergen proteases from the fungus *Alternaria alternata*, endogenous IL-33$_{FL}$ is rapidly released into the bronchoalveolar lavage fluid and then cleaved. The generation of cleaved forms could be blocked by pre-treating the *A. alternata* extract with the protease inhibitor α1 antitrypsin. Finally, the authors generated an antibody against the central sensor domain of human IL-33. Administration of this IL-33-blocking antibody together with the allergen to *Il33*$^{-/-}$ mice reconstituted with human IL-33$_{FL}$ reduced IL-5 levels and airway inflammation.

This study identifies an important molecular mechanism for the induction of allergic inflammation based on the sensing of allergen-associated proteolytic activity by IL-33.

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ORIGINAL ARTICLE Cayrol, C. *et al.* Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat. Immunol.* **19**, 375–385 (2018)