

ALLERGY & ASTHMA

Neuroendocrine cells amplify asthma

A new role for a rare type of airway epithelial cell — known as pulmonary neuroendocrine cells (PNECs) — in amplifying allergic asthma has been described in a recent study published in *Science*. The study shows that PNECs are strategically positioned at airway branch points where they transmit signals to nearby goblet cells and type 2 innate lymphoid cells (ILC2s) to promote allergic responses to airborne particles.

PNECs contain vesicles that are filled with neuropeptides, amines and neurotransmitters and released on cell activation. Previous reports have suggested an involvement of PNECs in various lung diseases, but little was known about their function. Sui et al. hypothesized that PNECs act as sensors in the lungs. To investigate this, they generated mice that specifically lack PNECs by inactivating the essential PNEC gene *Ascl1* in the airway epithelium. The lungs developed normally in these PNEC-deficient animals, including the development of neurons that normally innervate PNEC clusters.

To assess their ability to respond to environmental cues, young mice were sensitized by injection of ovalbumin (OVA) and then challenged by OVA inhalation, according to an established model for allergic asthma. PNEC-deficient mice showed severely

reduced goblet cell hyperplasia, eosinophil infiltration and induction of type 2 immune responses in the lungs compared with control mice. A similar abrogation of allergic responses was seen in adult mice that were made PNEC deficient using a diphtheria toxin-mediated deletion system.

Detailed analysis of the lung responses of PNEC-deficient mice after OVA challenge revealed that levels of the epithelial cell-derived type 2 cytokines, such as IL-25 and IL-33, were similar to controls. However, there was a marked decrease in levels of the PNEC-derived neuropeptides calcitonin gene-related peptide (CGRP), chromogranin A and neuropeptide Y. Similarly, levels of the PNEC-produced neurotransmitter γ -aminobutyric acid (GABA), which

“administration of CGRP and GABA was sufficient to restore allergic responses in PNEC-deficient mice”

is known to stimulate goblet cell hyperplasia, were reduced.

Imaging approaches using fluorescent markers revealed close proximity of PNECs and ILC2s at airway branch points, suggesting ILC2s could be targets of PNEC signalling. Accordingly, ILC2s were shown to express the receptors for CGRP and GABA, and ILC2s could be stimulated in vitro to release IL-5 on exposure to CGRP and IL-33. Exposure to GABA had little effect on ILC2s. Instead, GABA was shown to target goblet cells, as mice with a defect in GABA production by PNECs did not develop goblet cell hyperplasia following OVA challenge, yet induced type 2 immune responses similar to controls.

Confirming the key roles for PNEC-derived CGRP and GABA, the authors showed that intratracheal administration of CGRP and GABA was sufficient to restore allergic responses in PNEC-deficient mice following OVA challenge. Finally, antibody staining of lung sections showed an expansion of PNECs and a greater proportion of CGRP⁺ PNECs in patients with asthma than in controls, suggesting that the findings in mice may be relevant to humans.

So, PNECs and ILC2s establish a neuroimmunological module to respond to environmental stimuli and represent new targets for treating allergic lung diseases.

Lucy Bird

ORIGINAL ARTICLE Sui, P. et al. Pulmonary neuroendocrine cells amplify allergic asthma responses. *Science* **360**, eaan8546 (2018)



Credit: Monty Rakusen/Getty