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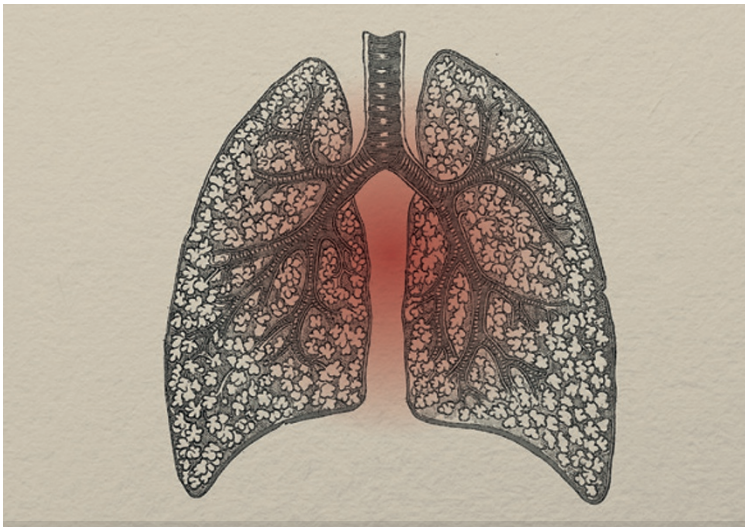
S. Bradbrook/NPG



MUCOSAL IMMUNOLOGY

Neuroendocrine cells regulate lung inflammation

A study in *Science* has described a novel neuroendocrine pathway that regulates the development of lung inflammation. Branchfield *et al.* show that pulmonary neuroendocrine cells (PNECs) — a rare, innervated epithelial cell population — function as airway sensors and shape immune responses and tissue remodelling through the release of neuropeptides.

PNECs are the only innervated cell type found in the airway epithelium. They release bioactive neuropeptides in response to fluctuations in oxygen levels and, in the mouse lung, have been shown to reside in clusters known as neuroepithelial bodies. Notably, alterations in PNEC number have been associated with several debilitating airway diseases, including asthma, cystic fibrosis, chronic obstructive pulmonary disease and congenital diaphragmatic hernia (CDH).

Branchfield *et al.* set out to determine the mechanisms underlying CDH, a disease characterized by increased airway inflammation, pulmonary hypertension and marked lung dysfunction. Using a genetic mouse model of CDH, they uncovered a failure of PNEC clustering in these animals, which resulted in increased production of neuropeptides by PNECs, increased immune cell infiltration and remodelling of the lungs. Human CDH has been associated with mutations in Roundabout receptor (ROBO) genes, so the authors examined the effect of specifically inactivating *Robo1* and *Robo2* (hereafter referred to as *Robo*) in the endoderm-derived epithelium (which includes the lung). *Robo*-mutant mice showed a reduction in the gas-exchange surface area of the lungs (alveolar simplification) by day 15 after birth and this was preceded by the upregulation of genes encoding chemokines and cytokines and an increase in the numbers of neutrophils, eosinophils, macrophages and T cells in the airways. Further analyses showed that the *Robo*-expressing cells in the lung epithelium were PNECs, and mice with a PNEC-restricted inactivation of *Robo* also showed decreased PNEC clustering, alveolar simplification and increased macrophage numbers in the lungs. Therefore, expression of *Robo* by PNECs is necessary for their clustering, for limiting immune cell infiltration and for preventing alveolar simplification.

To examine how PNECs regulate these responses, the authors assessed their neuropeptide production. Compared with controls, *Robo*-mutant mice showed upregulation of several neuropeptides, in particular calcitonin gene-related peptide (CGRP). Notably, although unclustering of PNECs was observed by embryonic day 15.5 in *Robo* mutants, upregulation of neuropeptides was only seen after birth. The authors crossed the *Robo* mutants with *Cgrp*-mutant mice and found that these animals showed a significant reduction in macrophage numbers in the lung and less evidence of alveolar simplification. Chemical depletion of macrophages from *Robo*-mutant mice also prevented alveolar simplification. These findings confirm that immune cell infiltration and alveolar simplification occur as a downstream consequence of PNEC dysfunction.

This study indicates that PNECs have an important role in regulating immune responses and tissue remodelling in the lungs. Although PNEC dysfunction was seen in embryonic *Robo*-mutant mice, neuropeptide upregulation, immune cell infiltration and alveolar simplification did not occur until after birth — suggesting that these physiological effects are dependent on the exposure of the lungs to air. As such, the authors suggest that PNECs can act as 'rheostats' at the airway epithelium, translating environmental cues into immune responses.

Yvonne Bordon

> “PNECs can act as ‘rheostats’ at the airway epithelium, translating environmental cues into immune responses”

ORIGINAL ARTICLE Branchfield, K. *et al.* Pulmonary neuroendocrine cells function as airway sensors to control lung immune response. *Science* http://dx.doi.org/10.1126/science.aad7969 (2016)