ASTHMA AND ALLERGY

Pollen found guilty

For the large proportion of the population that suffers the misery of hayfever every year, the usual explanation has been that it is our immune system that should shoulder the blame for an overactive response to foreign, but harmless, pollen antigens. However, new work published in *The Journal of Clinical Investigation* shows that pollen can no longer be considered the innocent party and itself has an active role in inducing the airway inflammation that is responsible for symptoms.

Pollen antigens induce an adaptive immune response that leads to the recruitment of granulocytes, such as eosinophils and mast cells, to the airways. Granulocytes, in turn, contribute to the inflammatory response through the production of reactive oxygen species (ROS) by NADPH oxidase. Boldogh and colleagues now show that pollen also contains a plant NADPH oxidase that can cause oxidative stress in the absence of an adaptive immune response.

Fractionated extracts of ragweed pollen (RWE) were tested for their ability to reduce nitroblue tetrazolium (NBT) to generate ROS. The activity of the fractions that reduced NBT ($pRWE^{OX+}$) required NADPH substrate and was blocked by superoxide dismutase, which shows that ROS generation in the NBT assay is due to superoxides produced by a pollen NADPH oxidase.

RWE increased intracellular ROS levels in cultured epithelial cells and in the airway epithelium in a mouse model of airway challenge. Mice were given a single intrapulmonary challenge, and RWE and $pRWE^{OX+}$, but not fractions that lacked NADPH-oxidase activity ($pRWE^{OX-}$), led to increased levels of ROS and oxidative-stress markers in bronchoalveolar-lavage fluid. This occurred in mice that were deficient in mast cells, or in B cells and T cells, indicating that the ROS are generated by intrinsic pollen NADPH oxidases rather than by immune cells.

In wild-type mice, challenge with RWE resulted in recruitment of eosinophils and other inflammatory cells to the lungs, possibly through the production of CXC-chemokine ligand 8 (CXCL8), but challenge with heat-treated RWE ($pRWE^{H}$; which lacks NADPH-oxidase activity) recruited significantly fewer cells than did challenge with RWE. Addition of a surrogate ROS generator to $pRWE^{H}$ reconstituted allergic airway inflammation, but the ROS generator alone could not induce inflammation.

The authors therefore suggest a two-signal model for the induction of allergic airway inflammation, in which signal 1 is the innate response generated by pollen NADPH oxidases (that is, oxidative stress) and signal 2 is the adaptive immune response to pollen antigens. Signal 1 is not sufficient to induce allergic inflammation in the absence of signal 2, but signal 1 has an important role in augmenting signal 2.

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References and links

ORIGINAL RESEARCH PAPER Boldogh, I. *et al.* ROS generated by pollen NADPH oxidase provide a signal that augments antigen-induced allergic airway inflammation. *J. Clin. Invest.* **115**, 2169–2179 (2005)

IN BRIEF

SIGNALLING

Membrane recruitment of NOD2 in intestinal epithelial cells is essential for nuclear factor-κB activation in muramyl dipeptide recognition.

Barnich, N. *et al*. *J. Cell Biol.* **170**, 21–26 (2005)

Mutations in nucleotide-binding oligomerization domain protein 2 (NOD2) are associated with Crohn's disease. When expressed by intestinal epithelial cell lines, ligation of the Crohn's-disease-associated 3020insC NOD2 mutant does not activate nuclear factor-κB (NF-κB). In this study, wild-type NOD2 was detected in the cytoplasm, in vesicles and associated with the membrane of intestinal epithelial cell lines, whereas the 3020insC NOD2 mutant was present only in the cytosol and in vesicles. A panel of NOD2 deletion mutants was used to show that the last six amino acids of NOD2 are necessary, but not sufficient, to target NOD2 to the membrane. Furthermore, for these mutants, membrane targeting correlated with the ability of the protein to activate NF-κB.

HAEMATOPOIESIS

NF-Ya activates multiple hematopoietic stem cell (HSC) regulatory genes and promotes HSC self-renewal.

Zhu, J. *et al*. *Proc. Natl Acad. Sci. USA* **102**, 11728–11733 (2005)

Nuclear transcription factor Y (NF-Y) is a trimer, the activity of which is regulated by the level of expression of the NF-Ya subunit. Zhu *et al.* set out to investigate the role of NF-Y in haematopoietic stem cell (HSC) self-renewal and differentiation. NF-Ya was most highly expressed by the most primitive HSCs, and overexpression of NF-Ya in these cells induced the expression of many genes encoding proteins that influence HSC self-renewal and differentiation. When transferred to lethally irradiated mice, larger numbers of primitive HSCs accumulated in recipients of HSCs that were engineered to express NF-Ya than in recipients of control HSCs. Similar expansion of primitive HSC numbers was seen *in vitro*. Therefore, the authors suggest that NF-Ya is a potent regulator of HSC self-renewal.

TOLERANCE

A critical role for the programmed death ligand 1 in fetomaternal tolerance.

Guleria, I. *et al*. *J. Exp. Med.* **202**, 231–237 (2005)

What prevents the maternal immune system from rejecting a fetus, which expresses paternally inherited alloantigens, is poorly understood. Using a mouse model of allogeneic pregnancy, this study shows that the inhibitory T-cell co-stimulatory molecule programmed death ligand 1 (PDL1) has a crucial role in conferring fetomaternal tolerance. Pregnant mice treated with antibody specific for PDL1, but not those treated with control antibody, had increased rates of fetal rejection and reduced litter sizes. This rejection was T-cell mediated, because mice lacking T and B cells, but not B-cell-deficient mice, had normal pregnancies when treated with PDL1-specific antibody. The numbers of interferon-γ-producing cells were increased systemically and in the placenta of PDL1-specific-antibody-treated mice, indicating that blockade of this inhibitory molecule promotes fetal rejection by clonal expansion of alloreactive T helper 1 cells.