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Pollen polarize dendritic cells

How do pollen particles provoke allergic reactions? On page 627, Traidl-Hoffmann et al. put some of the blame on bioactive lipids that are released from pollen and cause dendritic cells (DCs) to initiate a T helper 2 (Th2)-biased, allergy-promoting immune response. This response may explain in part why increased car fumes are associated with greater prevalence of allergies.

This group had discovered previously that pollen grains rapidly liberate eicosanoid-like substances, which are similar to prostaglandins and leukotrienes, when in an aqueous environment. These lipids bound to neutrophils and eosinophils (both involved in allergies and other immune reactions) and induced their activation, leading the group to propose that the release of these lipid mediators is an important event in allergic sensitization. What these data did not explain, however, was how the adaptive immune system becomes biased toward an allergy-inducing Th2 response.

Traidl-Hoffmann et al. now show that soluble extracts from birch pollen and other common allergens inhibit the production of interleukin (IL)-12—the key cytokine involved in inhibiting Th2 responses—from activated DCs. These DCs could in turn bias naive T cells into becoming typical allergy-promoting Th2 cells.

Biochemical analysis of these extracts allowed the authors to identify the culprit of the IL-12 inhibitory activity: a group of prostaglandin-like compounds called E1 phytoprostanes (PPE1). These results fit nicely with the known Th2-polarizing effect of human prostaglandin E2 (PGE2) on DCs. The signaling pathways are not identical, however, as PGE2, but not PPE1, also inhibits tumor necrosis factor (TNF) and IL-10.

The function of these lipids in the plant is not completely clear, but they may be triggered in response to stress, as pollen

exposed to air pollutants produce more of these compounds than do pollen from unpolluted areas. This may help explain why allergies are more prevalent in areas with high levels of car exhaust emissions. The authors are now looking for the receptor this compound uses to bind DCs. They also plan to assess whether DCs from allergy-prone individuals are more sensitive to the effects of PPE1 than those from nonallergic individuals. JEM

Signaling survival

Thymocytes must pass a series of checkpoints on the road to becoming mature T cells. On page 603, Mandal et al. show that cells use Bcl2A1, a member of the Bcl2 family of survival proteins, to pass one critical checkpoint. The cell cannot make substitutes for this protein in a pinch, revealing that Bcl2A1 may be uniquely specialized for promoting survival without suppressing proliferation.

To become mature T cells, thymocytes must express a functional T cell receptor (TCR). A requisite early step in fulfilling this goal is the expression of the pre-TCR—the β chain of the mature TCR coupled with a pre-α chain—which sends essential survival and proliferation signals to the developing cell. Activation of NF-κB was shown recently to be required at this checkpoint, known as β-selection, but beyond that the components of this survival signal have remained elusive.

In an attempt to define these components, Mandal and colleagues searched for NF-κB–responsive proteins that may have a hand in β-selection. Their search led them to Bcl2A1, a protein involved in protecting B cells from apoptosis.

When the authors looked for Bcl2A1 in developing thymocytes, they found that it was the sole member of the Bcl2 family whose expression was coordinated with β-selection. Introduction of Bcl2A1 into thymocyte progenitors lacking a pre-TCR, which cannot undergo β-selection, allowed the cells to survive and differentiate in vivo.

What remains mysterious is why the cell doesn’t turn on one of the other Bcl2 proteins, which are known to have redundant functions, to make up for the loss of Bcl2A1 in deficient cells. The authors think this may be because Bcl2 and Bcl-xL, although good at promoting survival, inhibit proliferation—an indispensable feature of pre-TCR signaling. JEM
Phagocytosis without inflammation

The rare brain disorder Nasu-Hakola disease is a fatal neurodegenerative syndrome that has been linked to mutations in immune signaling proteins, but the mechanism had not been explored. In a study on page 647, Takahashi et al. connect this disease to defects in phagocytic cells that are required for removal of apoptotic cells and suppression of inflammation in the brain.

The link to disease involves the TREM2 (triggering receptor expressed on myeloid cells-2) receptor and its associated adaptor protein DAP12, both known to be mutated in patients with Nasu-Hakola disease. TREMs are orphan receptors that associate with DAP12 to transmit signals in a variety of myeloid cells. The signals are primarily stimulatory; TREM1 signaling activates macrophages and neutrophils and can amplify Toll-like receptor signals, and TREM2 activates immature dendritic cells. TREM2 is also expressed on microglial cells (phagocytic cells in the brain that remove apoptotic cells and debris from the brain), but its function on these cells had not been examined until now.

Impaired phagocytosis in the absence of TREM2 or functional DAP12 confirmed their role in phagocytosis. This experiment, however, also revealed a more striking finding. The loss of TREM2 provoked the microglial cells into producing inflammatory cytokines such as TNF and IL-1β, suggesting that TREM2 signals actively interfere with these pathways under normal circumstances. When TREM2 is missing, the lack of interference may explain the defective phagocytosis and aberrant activation of microglial cells that accompanies the buildup of cellular debris in the brain.