T-CELL RESPONSES

DCs get KITted out

Dendritic cells (DCs) coordinate T-cell responses by establishing a cytokine milieu that favours the differentiation of T helper (T_H) cells into T_H1-, T_H2- or T_H17-cell subsets. Although much is known about the cytokines that drive divergent T-cell differentiation, less is known about how antigens or allergens influence DCs to initiate a particular pathway. Now, a study published in *Nature Medicine* provides a new mechanism to explain how the allergen house-dust mite (HDM) and the mucosal adjuvant cholera toxin act on DCs to promote T_H2-cell differentiation, through a pathway involving the tyrosine kinase receptor KIT and interleukin-6 (IL-6).

IL-6 is a crucial regulator of T-cell differentiation, promoting T_H2- and T_H17-cell responses and inhibiting T_H1-cell responses — a T-cell bias that is characteristic of allergic diseases. Krishnamoorthy *et al.* show that, consistent with their association with allergic immune responses, both HDM and cholera toxin promote the release of large amounts of IL-6 and low levels of the T_H1-cell-inducing cytokine IL-12 by bone-marrow-derived DCs (BMDCs). Moreover, intranasal immunization of mice with HDM primed the T cells from the lung-draining lymph nodes towards a T_H2-type response; this effect was decreased in IL-6-deficient mice, which indicates a key role for allergen-induced IL-6 in regulating the ensuing T-cell response.

To define the mechanism underlying IL-6 upregulation by HDM and cholera toxin, the authors carried out microarray analysis to identify genes induced in DCs by cholera toxin. Together with that encoding IL-6, the gene encoding KIT was significantly upregulated in BMDCs after cholera toxin treatment. A comparison of KIT^+ and KIT^- BMDCs sorted from cholera-toxin-treated cultures revealed that those expressing KIT promoted T_H2- and T_H17-cell responses, whereas KIT^- BMDCs favoured T_H1-cell differentiation.

Further studies confirmed that signalling through KIT in DCs is important for inducing IL-6 production, as BMDCs or lung DCs from mice expressing an inactive form of KIT ($Kit^{W/W\text{-}v}$ mice) secreted lower amounts of IL-6 following *in vitro* stimulation with cholera toxin or HDM than did wild-type BMDCs. Moreover, following intratracheal transfer into wild-type recipients and antigen challenge, $Kit^{W/W\text{-}v}$ DCs were unable to induce strong T_H2- and T_H17-cell responses and elicited less allergic airway inflammation than did wild-type BMDCs.

The authors next investigated how KIT might be stimulated to induce IL-6 production. Their analysis revealed that, similar to KIT, expression of the ligand for KIT, stem-cell factor (SCF), on the surface of BMDCs was increased in the presence of cholera toxin or HDM. SCF expression proved to be important for KIT-mediated IL-6 production, as BMDCs from mice lacking membrane-bound SCF had decreased IL-6 production after allergen stimulation. High-level expression of both KIT and SCF on allergen-stimulated DCs was shown to support persistent signalling through KIT, leading to prolonged activation of the downstream enzyme phosphoinositide 3-kinase (PI3K) and ultimately to IL-6 production. Accordingly, BMDCs from mice that lack the p110δ subunit of PI3K, which tend to be resistant to allergic airway disease, secreted less IL-6 in response to cholera toxin.

Together, these results support a model of allergen-mediated regulation of DCs, involving a KIT–PI3K–IL-6 signalling pathway that promotes T_H2- and T_H17-cell responses.

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ORIGINAL RESEARCH PAPER
Krishnamoorthy, N. *et al.* Activation of c-Kit in dendritic cells regulates T helper cell differentiation and allergic asthma. *Nature Med.* **14**, 565–573 (2008)
FURTHER READING Sheppard, D. Dust mites' dirty dealings with dendritic cells. *Nature Med.* **14**, 487–488 (2008)