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Lung alert

IL6 and dendritic cells in allergic asthma

Interleukin (IL)6 production by antigen-presenting dendritic cells (DCs) is integral to the differentiation of T helper cells into T helper type Th1, Th2 and Th17 subsets. However, molecular mechanisms that regulate IL6 production in DCs are yet to be elucidated. Stimulation of bone marrow-derived dendritic cells with the allergen house dust mite (HDM)—which causes asthma in humans—or the mucosal adjuvant cholera toxin promoted cell surface expression of c-Kit and its ligand, stem cell factor (SCF), resulting in sustained signalling downstream of c-Kit, prompting IL6 secretion. DCs from c-Kit mutant mice secreted smaller amounts of IL6 following HDM or cholera toxin stimulation, resulting in an inability to induce a robust Th2 or Th17 response and reduced allergic airway inflammation. In addition, expression of Jagged-2, a Notch ligand which has been associated with Th2 differentiation, is reduced in DCs lacking functional c-Kit, implying that c-Kit upregulates expression of Jagged-2 in addition to IL6. Cell signalling downstream of c-Kit is likely to involve phosphorylation of Akt via activation of phosphatidylinositol-3 kinase (PI3k), as DCs expressing a catalytically inactive form of PI3K secrete less IL6 on cholera toxin stimulation.

It is concluded that cell surface expression of c-Kit by DCs in conjunction with SCF causes extended activation of the PI3K-Akt pathway, promoting a higher IL6 expression profile in DCs which, in turn, promotes T cell differentiation towards Th2 and Th17 lineage. This may have implications for the understanding and treatment of allergic airway inflammation in asthma as downregulation of c-Kit may reduce such inflammation. Inhibition of c-Kit may also promote the efficacy of vaccines in cancer therapy by augmenting a Th1 response.

Krishnamoorthy N, Oriss TB, Paglia M, et al. Activation of c-Kit in dendritic cells regulates T helper cell differentiation and allergic asthma. Nat Med 2008;14:565–73.

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