ALLERGY

SOCS3: a new target for anti-allergy drugs

Suppressor of cytokine signalling (SOCS) proteins, due to their action as negative regulators of cytokine signalling, are implicated in the pathogenesis of numerous inflammatory diseases. Cytokines secreted by T helper 2 (T_H2) cells are central to the development of allergic disease — what role do SOCS proteins have in this setting? Here, Seki *et al.* show that SOCS3, which is mainly expressed by T_H2 cells, regulates the onset and maintenance of T_H2-cell-mediated allergic responses.

First, Seki *et al.* studied the expression patterns of SOCS3 in patients with atopic asthma or dermatitis compared with healthy people. Expression of SOCS3 by peripheral T cells correlated with the severity of disease — the more severe the disease pathology, the higher the level of SOCS3 expression by T cells from those individuals. Serum immunoglobulin E levels, which have been implicated in the pathogenesis of allergic disease, were also increased in individuals with high SOCS3 expression. The authors concluded that the increased levels of SOCS3 reflected an accumulation of T_H2 cells in patients with allergic inflammatory disease and were associated with increased disease pathology.

To investigate the functional relevance of SOCS3 overexpression, the authors generated transgenic mice in which T cells constitutively expressed Socs3. The differentiation of $CD4^+$ Tcells into interleukin-4-producing T_H2 cells was enhanced in these mice. Using an ovalbumin-induced asthma model, the authors showed that airway hyper-responsiveness was markedly higher in the *Socs3*-transgenic mice, as were the levels of IgE, T_H2 cytokines and eosinophils in the bronchoalveolar lavage fluids, compared with control mice. These results indicate that elevated expression of SOCS3 by T cells results in enhanced T_H2-cell responses, which contributes to the onset and development of asthmatic disease.

Finally, Seki *et al.* studied *Socs3*$^{+/-}$ mice and transgenic mice expressing a dominant-negative Socs3 protein in their T cells to see what effect interfering with the expression of Socs3 would have on T_H2-cell development. As expected, reduced Socs3 activity resulted in suppressed T_H2-cell development in these models.

So, as the authors state, "SOCS3 expression in T cells could be an important diagnostic marker of T_H2-type diseases, as well as a candidate for therapeutic targeting of these diseases".

Jenny Buckland

References and links

ORIGINAL RESEARCH PAPER Seki, Y. *et al.* SOCS-3 regulates onset and maintenance of T_H2-mediated allergic responses. *Nature Med.* 29 June 2003 (DOI: 10.1038/nm896)

FURTHER READING Alexander, W. S. Suppressors of cytokine signalling (SOCS) in the immune system. *Nature Rev. Immunol.* **6**, 410–416 (2002)

TRANSPLANTATION

Past encounters

An individual's acquired immune history has been shown to influence the course of immune responses to future encounters with pathogens. T-cell memory elicited by infection with a specific virus can enhance the clearance of unrelated pathogens. However, this heterologous immunity might have other, more unfavourable consequences. Now, Adams *et al.* report in the *Journal of Clinical Investigation* that virus- induced memory T cells that are cross-reactive with donor alloantigens are a potent barrier to the induction of tolerance in transplant recipients. They propose that this is one potential explanation why strategies that effectively promote long-term allograft acceptance in specific pathogen-free rodents have been unsuccessful in non-human primate models and in human patients.

First, the authors showed that infection with virus results in the induction of virus-specific memory T cells that can also recognize foreign MHC molecules. They next tested whether the presence of this memory population could prevent tolerance induction using a protocol that has been shown to induce robust, life-long tolerance to fully MHC-mismatched skin grafts in naive mice. Indeed, mice that had previously been exposed to multiple viral infections were refractory to tolerance induction and rejected their allografts.

By adoptive-transfer experiments, they went on to show that the ability to resist tolerance induction was dependent on the dose of donor-specific memory T cells that were transferred to graft recipients. Contrary to expectation, $CD8^+$ central memory T cells, as opposed to effector memory T cells, were the main mediators of rejection, indicating that these cells might have a lower threshold for activation. Finally, resistance to tolerance could be overcome when deoxyspergualin (DSG) — an inhibitor of nuclear factor-κB (NF-κB) translocation, which is a key event in T-cell activation — was included in the tolerance protocol.

In the light of these results, future strategies to induce tolerance in 'immune-experienced' patients should take into account the existence of allogeneic memory T cells.

Lucy Bird

References and links

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