



B-CELL DEVELOPMENT

Plasma-cell differentiation requires Blimp1

Although the transcriptional repressor B-lymphocyte-induced maturation protein 1 (Blimp1) has been previously shown to induce B-cell differentiation into immunoglobulin-producing plasma cells, until now, it has not been identified as non-redundant and essential for this process.

Mice lacking the gene encoding Blimp1, *Prdm1*, die *in utero*, so to study the dependence of B-cell differentiation and function on Blimp1, Shapiro-Shelef *et al.* generated mice in which *Prdm1* was specifically eliminated in mature B cells, *Prdm1^{fllox/fllox}CD19^{cre/+}* mice. B-cell development was normal in these animals but serum immunoglobulin was markedly reduced, even in unimmunized mice.

After immunization with either a thymus-independent (TI) or thymus-dependent (TD) antigen, the immunoglobulin response generated in *Prdm1^{fllox/fllox}CD19^{cre/+}* mice was substantially diminished when compared with control animals, as was immunoglobulin secretion after re-challenge with TD antigen. This decrease in immunoglobulin production correlated with a marked reduction in the number of antigen-specific immunoglobulin-secreting cells and consistent with this, few plasma cells or pre-plasma memory B cells could be detected in *Prdm1^{fllox/fllox}CD19^{cre/+}* mice after either primary or secondary

exposure to TD antigen. So, Blimp1 is required for the development of both plasma cells and pre-plasma memory B cells during both a primary and memory response.

To investigate the mechanisms by which Blimp1 regulates immunoglobulin secretion and plasma-cell differentiation, Shapiro-Shelef *et al.* analysed Blimp1-deficient B cells that were exposed to lipopolysaccharide (LPS) *ex vivo*. In the absence of Blimp1, switching from the membrane-associated form of the immunoglobulin heavy chain (M) to the secreted form (S) was markedly impaired, as was the induction of S messenger RNA. In addition, the transcription factor X-box binding protein 1 (XBP1) was not induced by LPS stimulation of *Prdm1^{-/-}* B cells, identifying it as a downstream target of Blimp1. However, retrovirus-mediated over-expression of XBP1 by Blimp1-deficient B cells was insufficient to rescue plasma-cell development, indicating that Blimp1 must target many factors to induce plasma-cell differentiation.

These studies using a conditional gene-deletion strategy define Blimp1 as essential for the differentiation of plasma cells and immunoglobulin secretion, and indicate that this transcription factor also has a key role in pre-plasma memory B-cell development.

Karen Honey

References and links

ORIGINAL RESEARCH PAPER Shapiro-Shelef, M. *et al.* Blimp-1 is required for the formation of immunoglobulin secreting plasma cells and pre-plasma memory cells. *Immunity* **19**, 607–620 (2003)

WEB SITE

Kathryn Calame's lab: <http://cpmnet.columbia.edu/dept/gsas/biochem/faculty/calame.html>

IN BRIEF

CYTOKINES

IL-23 produced by CNS-resident cells controls T-cell encephalitogenicity during the effector phase of experimental autoimmune encephalomyelitis.

Becher, B., Durell, B. G. & Noelle, R. J. *J. Clin. Invest.* **112**, 1186–1191 (2003)

Interleukin-23 (IL-23) consists of a unique p19 subunit and the p40 subunit of IL-12, and is crucial for the development of experimental autoimmune encephalomyelitis in mice. Becher *et al.* use p40-deficient mice to generate irradiation bone-marrow chimaeras and show that in the absence of p40 expression by irradiation-resistant cells, previously activated antigen-reactive cells infiltrate the central nervous system (CNS), but do not induce encephalitogenicity. In addition, disease induced by immunization is markedly diminished when p40 is absent from irradiation-resistant cells and this is associated with a bias towards the production of T helper 2-type cytokines by infiltrating cells. The authors, therefore, suggest that p40 expression by CNS-resident cells contributes to T-cell polarization and thereby modulates disease pathogenesis.

TRANSPLANTATION

Prevention of organ allograft rejection by a specific Janus kinase 3 inhibitor.

Changelian, P. S. *et al. Science* **302**, 875–878 (2003)

The development of effective immunosuppressive agents that are targeted specifically to immune cells and do not produce serious side effects remains a pressing need for the prevention and treatment of transplant rejection. This study reports pre-clinical trials of a new immunosuppressive agent (CP-690,550) that prolonged survival in both a mouse model of heart transplantation and a cynomolgus monkey model of kidney transplantation, but that did not result in the dose-limiting side effects that are associated with present therapies. CP-690,550 inhibits Janus kinase 3 (JAK3), which is crucial for signalling through cytokine receptors that use the common γ -chain and, therefore, for development and homeostasis of immune cells. It is the first JAK3 inhibitor to have shown efficacy in non-human primates.

IMMUNOTHERAPY

A critical role for OX40 in T cell-mediated immunopathology during lung viral infection.

Humphreys, I. R. *et al. J. Exp. Med.* **198**, 1237–1242 (2003)

Respiratory infections are an important example of how an over-active T-cell response can be more of a hindrance than a help, with T-cell responses resulting in airway occlusion and pathology. Previous T-cell-targeted therapies have affected both bystander and antigen-specific T cells, which might result in dangerous immunosuppression. These authors used an OX40-immunoglobulin fusion protein to target recently activated T cells specifically. OX40 signalling prevents the death of activated T cells, but it is not expressed by naive T cells. Interference with this T-cell survival signal in a mouse influenza model reduced immunopathology without preventing virus clearance.