IN BRIEF

INFLAMMATION

Resolution of lung inflammation by CD44

Teder, P. *et al. Science* **296**, 155–158 (2002)

Lung injury caused by pulmonary fibrosis results in matrix deposition and inflammation. Resolution of the inflammatory response is required for the lung tissue to be repaired successfully. Teder *et al.* examined the role of the cell-surface adhesion molecule and hyaluronan receptor CD44 in resolving lung inflammation. *Cd44*$^{-/-}$ mice suffer from unremitting inflammation after lung injury, which is characterized by the impaired clearance of apoptotic neutrophils, the accumulation of hyaluronan fragments and the impaired activation of transforming growth factor-β1. Reconstituting these mice with CD44^{+} alveolar cells partially reversed the phenotype, which shows that CD44 has a role in the resolution of lung inflammation.

IMMUNE REGULATION

T-bet regulates IgG class switching and pathogenic autoantibody production.

Peng, S. L., Szabo, S. J. & Glimcher, L. H. *Proc. Natl Acad. Sci. USA* **99**, 5545–5550 (2002)

T-box transcription factor T-bet has a pivotal role in the development of T-helper type 1 cells. But, what about B-cell responses? When *Tbet*$^{-/-}$ mice were crossed onto the autoimmune-prone *Fas*$^{lpr/lpr}$ background, autoimmune T-cell responses remained high. However, *Tbet*$^{-/-}$*Fas*$^{lpr/lpr}$ mice did not develop antibody-mediated kidney disease or DNA-specific antibodies. *Tbet*$^{-/-}$ B cells were shown to have an impaired ability to switch to the production of IgG2a in response to interferon-γ. Preliminary studies indicate that T-bet regulates the production of germline γ2a mRNA transcripts, which are a prerequisite for isotype switching to IgG2a.

IMMUNOTHERAPY

Single-chain trimers of MHC class I molecules form stable structures that potently stimulate antigen-specific T cells and B cells.

Yu, Y. Y. *et al. J. Immunol.* **168**, 3145–3149 (2002)

The assembly of MHC-class-I–peptide complexes involves several chaperones and multiple steps, many of which are targeted by viruses to avoid immune recognition. This study reports the development of single-chain trimers (SCTs) of MHC class I molecules that eliminate the need for chaperones and might prevent these viral immune-evasion mechaisms. These peptide–spacer–β_2-microglobulin–spacer–heavy-chain constructs assembled efficiently and stably at the cell surface and are recognized by cytotoxic T lymphocytes (CTLs). Unlike normal class I molecules, the expressed SCT molecules exclude competing peptides. Furthermore, SCTs are potent stimulators of peptide-specific CTLs and B cells, when delivered as a DNA vaccine, which makes them attractive as vaccine candidates.

T-CELL SIGNALLING

Mechanic required

As anyone whose car has ever broken down knows, working out the mechanical defect that is responsible can be rather tricky. Similarly, elucidating the basis for the phenotypes that result from gene-targeting experiments can also prove to be difficult. Mice that are deficient for T-cell protein tyrosine phosphatase (Tcptp) have severe defects in the haematopoietic compartment — including splenomegaly, lymphadenopathy, and defects in lymphocyte proliferation and haematopoiesis — but the pathways that are disrupted in these mice have not been identified. Simoncic and colleagues now report in *Current Biology* that the Janus-family tyrosine kinases Jak1 and Jak3 are physiological substrates for Tcptp, and that defects in cytokine signalling are to blame for the defective immune homeostasis that is seen in *Tcptp*$^{-/-}$ mice.

The authors used an *in vivo* substrate-trapping approach to identify substrates of Tcptp. They constructed wildtype and substrate-trapping mutants of Tcptp (which bind, but cannot dephosphorylate, substrates); these were transfected into cells and, after cytokine stimulation, immunoprecipitation and anti-phosphotyrosine immunoblotting were performed. Using this approach, they showed that tyrosine phosphorylated Jak1 and Jak3 are substrates for Tcptp downstream of interleukin-2 (IL-2), and that Jak1 is a substrate for Tcptp downstream of interferon-γ (IFN-γ). They also showed that the interaction between Tcptp and Jak1/Jak3 is mediated by the catalytic domain of Tcptp.

Cytokine signalling results in the activation of Jaks and subsequent tyrosine phosphorylation of signal transducer and activator of transcription (Stat) proteins, which then dimerize and translocate to the nucleus to activate target genes. Simoncic and coworkers investigated the effect of overexpression and loss of function of Tcptp on Stat phosphorylation. When IL-2-treated T cells were transfected with wildtype Tcptp, Stat5 phosphorylation was impaired, whereas in *Tcptp*$^{-/-}$ T cells, Stat5 was hyperphosphorylated. To investigate the role of Tcptp in additional downstream events, the authors assessed the effect of IFN-γ treatment on *Tcptp*$^{-/-}$ T cells and macrophages. IFN-γ treatment resulted in an increased level of Stat1 phosphorylation in *Tcptp*$^{-/-}$ T cells, and an increased level of Jak1 tyrosine phosphorylation and increased expression of inducible nitric oxide synthase (iNOS; a primary target of IFN-γ signalling) in *Tcptp*$^{-/-}$ macrophages, compared with wildtype cells.

These results indicate that Tcptp has a negative regulatory role in cytokine signalling through the dephosphorylation of Jak1 and Jak3, a role that correlates with the phenotype of *Tcptp*$^{-/-}$ animals.

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References and links

ORIGINAL RESEARCH PAPER Simoncic, P. D. *et al.* The T-cell protein tyrosine phosphatase is a negative regulator of Janus family kinases 1 and 3. *Current Biol.* **12**, 446–453 (2002)

FURTHER READING You-Ten, K. E. *et al.* Impaired bone marrow microenvironment and immune function in T-cell protein-tyrosine-phosphatase-deficient mice. *J. Exp. Med.* **186**, 683–693 (1997)