IRF5 AND B CELLS IN LUPUS DEVELOPMENT

The transcription factor interferon regulatory factor 5 (IRF5) has previously been implicated in systemic lupus erythematosus (SLE) development, but its precise role in this process is unknown. David Savitsky and colleagues in Japan have now shown that IRF5 contributes to murine lupus via its influence on B lymphocytes.

B lymphocytes have been linked to the development of lupus; loss of B cell tolerance increases the incidence of lupus in mice and humans, and anti-B-cell therapies are effective treatments for the disease. *IRF5*—a gene with a role in Toll-like receptor-mediated innate immune responses—is implicated in genetic susceptibility to SLE in humans and has recently been shown to be necessary for murine lupus. Specifically, IRF5 causes aberrant production of type 1 interferon, but no specific mechanism for its involvement in SLE has been identified.

Savitsky *et al*. injected *Irf5*$^{-/-}$ and wild-type (*Irf5*$^{+/+}$) mice with pristane oil, which typically induces the development of features characteristic of human SLE. They found markedly reduced IgG glomerular deposits and antinuclear autoantibodies, and a lack of IgG2a autoantibody secretion, in the *Irf5*$^{-/-}$ mice.

Subsequent *in vivo* and *in vitro* analyses showed that IRF5 is responsible for the secretion of these pathogenic IgG2a antibodies through its direct control of class-switch recombination of the γ2a locus.

Savitsky *et al.*'s work demonstrates that *IRF5* is necessary for lupus-like manifestations in mice, and indicates a mechanism for this gene's influence via its effect in B cells. The identification of this molecular mechanism could lead to further understanding of the role of IRF5 in SLE. The authors hope that further work will "clarify to what extent IRF5 (is) involved in the activation and/or induction of class-switch recombination of autoreactive human B cells."

Eleanor Beal

Original article Savitsky, D. *et al*. Contribution of IRF5 in B cells to the development of murine SLE-like disease through its transcriptional control of the IgG2a locus. *Proc. Natl Acad. Sci. USA* **107**, 10154–10159 (2010)