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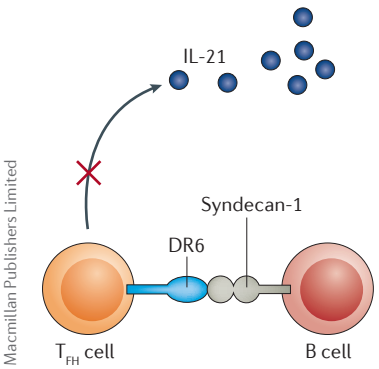
SYSTEMIC LUPUS ERYTHEMATOSUS

New pathway blocks disease in lupus-prone mice

> The research team … identified syndecan-1 as a ligand for [death-receptor 6]

Interaction between death-receptor 6 (DR6; also known as TNF receptor superfamily member 21) on T follicular helper (T_{FH}) cells and syndecan-1 on B cells presents a novel mechanism for regulating the progression of disease in lupus-prone mice. "We have identified syndecan-1 as a novel functional ligand for DR6 and successfully generated a functional antibody against DR6," states Daisuke Fujikura, corresponding author of the new study. "The anti-DR6 antibody has provided us with molecular information about the role of DR6 in disease progression in a murine model of systemic lupus erythematosus (SLE)," he continues.



Induction of *TNFRSF21* is linked to disease progression in patients with SLE and, unlike other members of the TNF receptor superfamily, DR6 is known to suppress the production of B-cell-activating cytokines by T cells. Fujikura and colleagues first created a highly specific functional antibody against DR6; they then used this antibody to establish that DR6 is expressed on T_{FH} cells and that this population is expanded in lupus-prone mice. The research team then identified syndecan-1 as a ligand for DR6 by screening a complementary DNA library made from cells that bound to a DR6–Fc fusion protein, and pinpointed the location of syndecan-1 to autoreactive germinal centre B cells in lupus-prone mice.

Noticing that strains of lupus-prone mice with high levels of syndecan-1 in their germinal centre B cells had a reduced expansion of T_{FH} cells, Fujikura and colleagues investigated a role for syndecan-1 in the regulation of T_{FH} cells in these mice. *In vitro* stimulation of activated $DR6^+$ T_{FH} cells with recombinant syndecan-1 caused the suppression of IL-21 production by these cells. These results were confirmed *in vivo* using anti-DR6 antibody, which mimics the action of syndecan-1.

The same antibody administered therapeutically to lupus-prone mice reduced levels of circulating anti-double stranded DNA antibodies, reduced kidney damage and increased survival compared with a control antibody. Mice treated with the anti-DR6 antibody also had fewer $DR6^+$ T_{FH} cells, germinal centre B cells and plasma cells than mice treated with the control antibody. "This study provides us with a therapeutic concept for targeting DR6 in SLE," says Fujikura. "The generation of a humanized anti-DR6 functional antibody is of great importance to take this work forward," he concludes.

Joanna Collison

ORIGINAL ARTICLE Fujikura, D. *et al.* Death receptor 6 contributes to autoimmunity in lupus-prone mice. *Nat. Commun.* **8**, 13957 (2017)
FURTHER READING Tsokos, G. C. *et al.* New insights into the immunopathogenesis of systemic lupus erythematosus. *Nat. Rev. Rheumatol.* **12**, 716–730 (2016)