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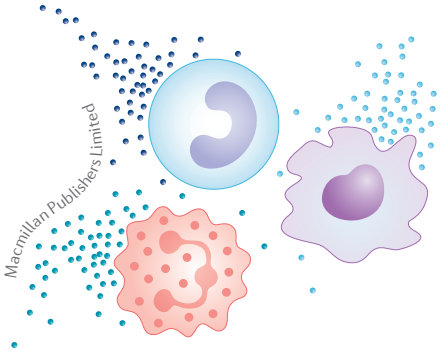
SYSTEMIC LUPUS ERYTHEMATOSUS

Defective CD11b raises IFN levels in SLE

> Patients carrying *ITGAM* risk alleles had higher serum levels of type I IFN than those who did not...

Genetic variants of *ITGAM* that produce integrin αM (also known as CD11b) with reduced activity are associated with increased levels of type I interferon (IFN) in patients with systemic lupus erythematosus (SLE), according to new research. "Mutations in the coding region of *ITGAM*, which codes for CD11b, strongly associate with an increased risk of SLE," states Vineet Gupta, one of the corresponding authors on the study. "We wanted to identify the molecular mechanism behind how mutant CD11b increases disease risk in SLE and whether it could be therapeutically targeted," he continues.



Gupta and colleagues measured the levels of type I IFN in 171 patients with SLE who were tested for single nucleotide polymorphisms in the coding region of *ITGAM*. Patients carrying *ITGAM* risk alleles had higher serum levels of type I IFN than those who did not carry *ITGAM* risk alleles, although levels of disease activity were not significantly different between the two groups.

The researchers used a genome-wide mRNA screening approach to identify components of Toll-like receptor (TLR) signalling pathways involved in CD11b-mediated type I IFN production. "Our mechanistic studies *in vitro* suggest that CD11b negatively regulates the TLR-dependent AKT–FOXO3–IRF3/7 pathway to control type I IFN production and that this pathway is dysregulated in patients carrying *ITGAM* risk alleles," says Gupta.

To investigate whether defective CD11b activity can be rescued therapeutically, the research team utilized a small-molecule agonist of CD11b called LA1 that they had discovered previously. LA1 treatment activated integrins and reduced the production of type I IFN in wild-type mice but not in mice lacking CD11b. *In vitro*, LA1 activated mutant CD11b and suppressed TLR signalling with equal efficacy to wild-type CD11b. *In vivo*, treatment with LA1 ameliorated disease in the MRL/lpr mouse model of lupus, with reduced renal, skin and cardiovascular manifestations in mice treated with LA1 compared with vehicle-treated mice.

"Altogether, these data suggest that LA1 can activate both wild-type and mutant CD11b and that such CD11b activation is able to modulate or control TLR signalling in cells," explains Gupta. "We now have a novel small molecule that can perhaps be moved forward as a therapeutic lead for SLE as well as lupus nephritis clinical trials," he concludes.

Joanna Collison

ORIGINAL ARTICLE Faridi, M. H. *et al.* CD11b activation suppresses TLR-dependent inflammation and autoimmunity in systemic lupus erythematosus. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI88442 (2017)