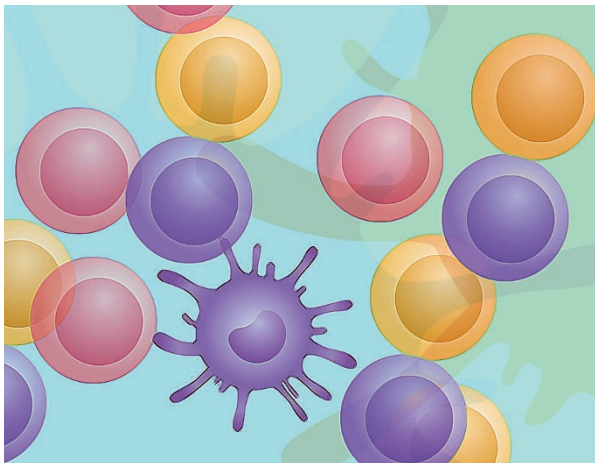
Nature Reviews Rheumatology | Published online 20 Jul 2017; doi:10.1038/nrrheum.2017.121

SYSTEMIC LUPUS ERYTHEMATOSUS

A repertoire for disaster

> "Treatment of female CKO mice with a CTSS inhibitor… suppressed the development of the lupus-like phenotype"

Loss of PR domain zinc finger protein 1 (PRDM1, also known as BLIMP1) in dendritic cells (DCs) results in an altered T follicular helper (T_{FH}) cell repertoire, thereby potentially contributing to the development of systemic lupus erythematosus (SLE), according to new findings published in *Nature Immunology*. "Our data help explain how the SLE-associated *PRDM1* risk allele contributes to the risk of developing SLE," states corresponding author Betty Diamond.



Macmillan Publishers Limited

Previous studies report that monocyte-derived DCs from individuals who carry the SLE-associated *PRDM1* risk allele express lower levels of PRDM1 than those from individuals who carry a non-risk allele. To investigate the pathologic function of PRDM1, the researchers generated mice in which the dendritic cells lacked PRDM1 (CKO mice). The female CKO mice developed a lupus-like phenotype and their DCs resembled those derived from individuals carrying the *PRDM1* risk allele, expressing high levels of MHC class II and being hyper-responsive to stimulation via their Toll-like receptors. Female CKO mice also had expanded populations of T_{FH} cells.

Diamond and colleagues sought to investigate whether this expansion was accompanied by an altered T cell receptor (TCR) repertoire. "This aspect is rarely addressed but has therapeutic implications," explains Diamond. They initially measured the expression of genes encoding proteins involved in antigen presentation. Of note, DCs lacking PRDM1 had increased expression levels of the gene encoding cathepsin S (CTSS) relative to the DCs of wild-type controls, which correlated with an increase in the functional activity of CTSS. PRDM1 directly bound to the *Ctss* promoter *in vivo* and negatively regulated *Ctss* transcription *in vitro*. Furthermore, siRNA inhibition of *Prdm1* in DCs from wild-type mice increased *Ctss* expression whereas restoration of PRDM1 expression in PRDM1-deficient DCs suppressed *Ctss* expression.

Importantly, T_{FH} cells from female CKO mice exhibited a more diverse TCR repertoire than T_{FH} cells from wild-type mice. Treatment of female CKO mice with a CTSS inhibitor reduced the number of T_{FH} cells and the diversity of their TCR repertoires, and suppressed the development of the lupus-like phenotype. "These findings must be confirmed in human patients but lead to a new question: is it the number or specificity of T_{FH} [cells] that is important in SLE development?" remarks Diamond.

Jessica McHugh

ORIGINAL ARTICLE Kim, S. J. *et al.* Increased cathepsin S in Prdm1$^{-/-}$ dendritic cells alters the T_{FH} cell repertoire and contributes to lupus. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3793 (2017)