Nature Reviews Rheumatology | Published online 8 Dec 2016; doi:10.1038/nrrheum.2016.203

RHEUMATOID ARTHRITIS

Reduced TRAF1 exacerbates inflammation

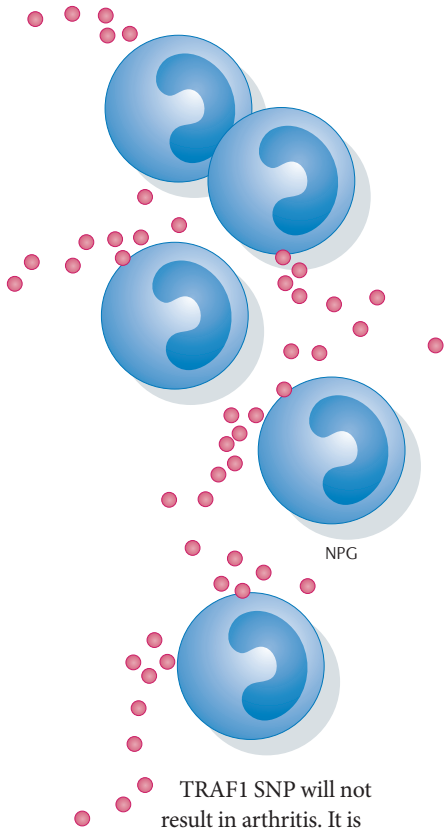
> Traf1 $^{-/-}$ mice are more susceptible to LPS-induced shock than their Traf1 $^{+/+}$ littermates

A new paper published in *Nature Immunology* proposes a mechanism by which certain single-nucleotide polymorphisms (SNPs) within the gene encoding TNF receptor-associated factor 1 (TRAF1) increase the risk of rheumatoid arthritis (RA). "TRAF1 is a negative regulator of Toll-like receptor (TLR) signalling, functioning through sequestering the linear ubiquitin chain assembly complex (LUBAC) complex — a role which was not previously suspected," reveals the corresponding author Tania Watts. Disease-associated SNPs within *TRAF1* reduce its expression and increase proinflammatory cytokine production in certain contexts.

The researchers isolated T cells and monocytes from healthy individuals and stimulated these cells in culture. Samples from healthy individuals were used, rather than patients with RA, in order to avoid the confounding effects of chronic inflammation or treatment on nuclear factor-κB (NF-κB) levels. "We expected that TRAF1 positively regulated NF-κB and indeed we found that T cells from individuals with the disease-associated SNP expressed less TRAF1 protein and made smaller amounts of cytokines than those with the disease-resistant SNP following CD3 plus CD28 stimulation, but this did not explain the disease association," explains Watts. However, monocytes from patients with RA-associated SNPs also expressed less TRAF1 protein upon stimulation with lipopolysaccharide (LPS) but produced increased amounts of proinflammatory cytokines, including TNF and IL-6.

Further experiments revealed that TRAF1 binds components of the LUBAC complex (an important player in TLR signalling), interfering with linear ubiquitination of NF-κB essential modulator (NEMO) and resulting in decreased NF-κB activation independent of TNF signalling. These findings demonstrate a negative role for TRAF1 in regulating TLR signalling, and explain how reduced TRAF1 expression in monocytes renders these cells hyper-responsive, thus exacerbating inflammation. Consistent with these findings, *Traf1*$^{-/-}$ mice were more susceptible to LPS-induced septic shock than their *Traf1*$^{+/+}$ littermates.

The SNPs highlighted in this study are in strong linkage disequilibrium with other SNPs and Watts explains that further research is required to pinpoint which SNP is responsible for the change in TRAF1 protein expression observed. "It is worth pointing out that having an RA-associated TRAF1 SNP will not result in arthritis. It is but one small contributor to this complex disease," she remarks.



NPG

Jessica McHugh

ORIGINAL ARTICLE(S) Abdul-Sater, A. A. *et al.* The signaling adaptor TRAF1 negatively regulates Toll-like receptor signaling and this underlies its role in rheumatic disease. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3618 (2016)