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RHEUMATOID ARTHRITIS

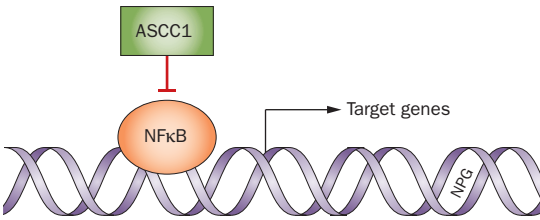
Novel NFκB inhibitor associated with RA severity

New research identifies ASCC1 (activating signal cointegrator 1 complex subunit 1) as a potent inhibitor of NFκB activation and, furthermore, suggests that an inactive variant of ASCC1 contributes to disease outcome in patients with rheumatoid arthritis (RA). The investigators had previously studied other NFκB regulators and how variants of the genes encoding them affect their regulatory capacity. "As NFκB controls the inflammatory response, we argued that by altering the activity of this transcription factor, these genetic variants could modify the course of the disease," explains Jose Fernández-Luna, corresponding author of the current study.

Next-generation sequencing was used to analyse 158 regulators of the NFκB pathway in genomic DNA from lymphocytes of 66 patients with RA and 30 healthy individuals. From among several truncating variants of NFκB-regulatory genes found in both groups, *ASCC1* was selected for further studies on the basis of allelic frequencies, predicted effect on protein function and novelty.

In human cell lines, transfection with full-length *ASCC1* potently inhibited NFκB transcriptional activity and inhibited expression of NFκB target genes, including *TNF, TNFSF10* and *IL8*, in a dose-dependent manner. By contrast, says Fernández-Luna, "a truncating variant of *ASCC1* that deleted all functional domains was found to generate an inactive protein unable to inhibit NFκB activation." The truncated p.S78* variant did not inhibit uninduced or TNF-induced NFκB transcriptional activity in comparison with control (transfection with empty vector). Moreover, truncated ASCC1 did not regulate the expression of NFκB target genes or secretion of TNF in response to inflammatory stimuli.

In DNA samples from 433 patients with RA and 214 controls, the allele frequency of the p.S78* variant was similar in both groups (1.8% and 2.3%, respectively). Consistent with the *in vitro* studies, heterozygous carriers of the p.S78* variant ($n = 8$) had more severe disease than non-carriers, as indicated by the need for



a greater number of DMARDs ($P = 0.03$). Rates of remission tended to be lower and use of glucocorticoids and biologic therapy higher in carriers, although not statistically significant. The researchers intend to replicate the study in a larger cohort, as well as investigate other genetic variants of NFκB regulators, which, they argue, could provide markers of disease progression and prognosis in RA.

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Original article Torices, S. *et al.* A truncated variant of ASCC1, a novel inhibitor of NF-κB, is associated with disease severity in patients with rheumatoid arthritis. *J. Immunol.* doi:10.4049/jimmunol.1501532