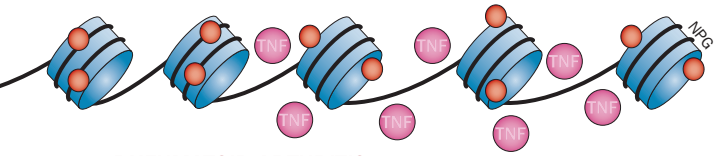
Nature Reviews Rheumatology **10**, 636 (2014); published online 23 September 2014; doi:10.1038/nrrheum.2014.165



RHEUMATOID ARTHRITIS

TNF targets histones to loosen chromatin in RA FLS

That TNF is central in the pathogenesis of rheumatoid arthritis (RA) is well accepted, but how prolonged exposure to this proinflammatory cytokine effects cells within the synovium is the subject of ongoing study. A paper published in *Arthritis & Rheumatology* investigating the effect of chronic TNF exposure on RA fibroblast-like synoviocytes (FLS) shows that TNF, by influencing histone levels and acetylation, opens up the chromatin around proinflammatory chemokine genes and increases the proinflammatory responses of these cells.

Sohn *et al.* isolated FLS from patients with RA, who were undergoing synovectomy or total knee replacement, and cultured these cells for 3 days with TNF before stimulating them with interferons. "Using this system we tested the hypothesis that chronic TNF primes FLS for enhanced inflammatory responses to subsequent stimuli," explains George Kalliolias, the lead author of the study.

Prolonged exposure to TNF resulted in increased production of proinflammatory chemokines (CXCL9, CXCL10 and CXCL11) by FLS after interferon stimulation compared with cells not stimulated with interferons, and extended the duration of this production. Even after TNF was removed, the increased chemokine production continued for several days. "The most striking finding of our study is that upon prolonged exposure to TNF, FLS acquire an 'inflammatory memory' that reverses slowly within a few days," says Kalliolias.

Next, the authors performed ChIP assays to investigate the mechanisms behind this enhanced proinflammatory behaviour of FLS. "We found that chronic exposure of FLS to TNF depletes histones and hyperacetylates remaining histones at the locus of chromosome 4 where the *CXCL10*, *CXCL9* and *CXCL11* genes are located next to each other," explains Kalliolias.

"This is additional progress on understanding how nongenetic factors influence RA risk," states Gary Firestein, who was not involved in this study but whose previous research showed that cytokines alter DNA methylation in RA FLS. "Do cytokines actually imprint cells permanently or simply alter their behaviour when *in situ* and the cytokines are present?" asks Firestein. "Given the long term changes in FLS function, it is likely that cytokines contribute, but that other factors are probably also involved."

Kalliolias concludes, "Our research suggests that targeting the signalling pathways that open chromatin in pathogenic genes of FLS might represent an attractive strategy to break the vicious cycle of chronic synovitis in RA."

Jenny Buckland

Original article Sohn, C. *et al.* Prolonged TNFα primes fibroblast-like synoviocytes in a gene-specific manner by altering chromatin. *Arthritis Rheum.* doi:10.1002/art.38871

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