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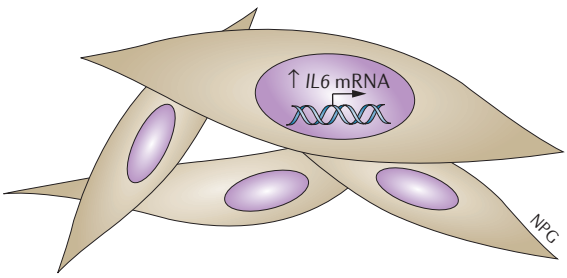
CYTOKINES IN DISEASE

Genetic variation affects IL-6 response in synovial fibroblasts

> The findings highlight the complexity of the genetic contribution to IL-6 expression

New research reveals that a single nucleotide polymorphism (SNP) in the *IL6* promoter is associated with patterns of IL-6 expression in synovial fibroblasts, but not in other IL-6-producing cell types. Michael Brenner, one of the corresponding authors of the paper reporting the findings, highlights that the study "draws attention to the role of fibroblasts as inflammatory cytokine producers — in this case IL-6 — and to the fact that genetic differences in cytokine production may relate to cytokine loci in a cell-type or tissue-type specific manner."

Synovial fibroblasts are a major source of IL-6, but the investigators found in previous studies that the IL-6 response to inflammatory stimuli in these cells seemed to vary in a donor-dependent manner. To investigate this heterogeneity, Brenner and colleagues systematically measured IL-6 production in response to TNF stimulation in primary fibroblasts from patients with rheumatoid arthritis (RA) or osteoarthritis (OA). "We found that fibroblasts separated into distinct high, moderate and low IL-6 expression patterns," reports co-corresponding author Erika Noss. "Furthermore," she continues, "IL-6 expression was associated with genetic variation in the *IL6* proximal promoter; specifically, high expression was associated with the minor allele of SNP rs1800795."



The patterns of IL-6 expression did not differ on the basis of the underlying disease, and were not unique to TNF stimulation but were also induced by IL-1β or lipopolysaccharide. Moreover, the protein response correlated with total *IL6* mRNA expression levels rather than mRNA stability, indicating transcriptional regulation of IL-6 expression.

Notably, the rs1800795 minor allele genotype was also associated with increased IL-6 expression in human dermal fibroblasts, but not in $CD14^+$ monocytes (another cell type that contributes to synovial IL-6 expression). Consistent with this finding, the minor allele rs1800795 genotype was associated with increased *IL6* promoter activity in synovial and dermal fibroblasts, but not in HeLa cells, in luciferase expression assays.

These results highlight the complexity of the genetic contribution to IL-6 expression, which has relevance for our understanding of the pathogenesis of not only RA but also other autoimmune diseases in which this cytokine has a role. "Much of the work studying how genetic variation influences autoimmune disease development focuses on cells of the immune system," says Noss. "Our work highlights that the effects of genetic variation can be very cell-type specific, and that stromal cells such as fibroblasts also need to be considered when deciphering how genetics influence autoimmunity."

Sarah Onuora

ORIGINAL ARTICLE Noss, E. H. *et al.* Genetic polymorphism directs IL-6 expression in fibroblasts but not selected other cell types. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1520861112