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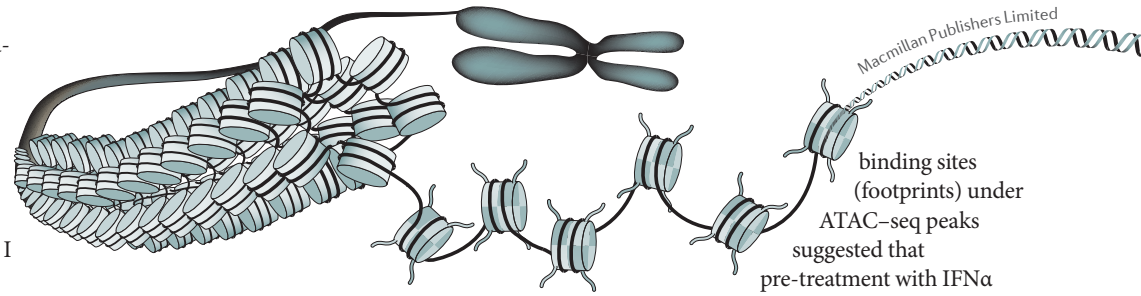
INFLAMMATION

Cytokines alter inflammatory responses via chromatin changes

TNF-induced 'cross-tolerance' has been reported to limit the inflammatory response to Toll-like receptor (TLR) ligands, but how this inhibitory mechanism is overridden to enable TNF to drive chronic inflammation is not well understood. New research published in *Nature Immunology* reveals that type I interferons effectively abolish TNF-induced tolerance by reprogramming the macrophage epigenome and thus altering the response to inflammatory stimuli.

"We discovered a new function for type I interferons in reversing tolerization of inflammatory genes by TNF," reports corresponding author Lionel Ivashkiv. "The mechanism was [the] opening of chromatin, which enabled robust transcriptional responses to very weak upstream signals," he continues. "These results suggest a way by which interferons promote chronic inflammation by potentiating and extending the inflammatory functions of TNF."

Transcriptomic analysis using RNA sequencing revealed that pre-treatment with TNF substantially altered the response of primary human macrophages to subsequent LPS-mediated stimulation of TLR4. The transcription of a number LPS-inducible genes encoding pro-inflammatory molecules and NFκB-dependent genes was inhibited by TNF treatment, indicating tolerization, whereas the expression of cytokine-induced genes was enhanced. Pre-treatment with both IFNα and TNF abolished TNF-mediated tolerance, resulting in increased LPS-induced gene expression. Notably, pre-treatment with IFNα alone did not alter LPS inducibility, suggesting a role for crosstalk between TNF and interferons.



> "type I interferons effectively abolish TNF-induced tolerance"

To investigate the role of epigenetic mechanisms in the regulation of TLR4 responses by TNF, the researchers analysed chromatin accessibility and positive histone marks associated with open chromatin using a gemone-wide approach involving chromatin immunoprecipitation followed by deep-sequencing (ChIP–seq) and assay for transposase accessible chromatin with high-throughput sequencing (ATAC–seq). They found that treatment of macrophages with the combination of IFNα and TNF increased chromatin accessibility at the promoters of genes encoding inflammatory molecules, enabling strong transcriptional responses even to weak LPS signals.

"We performed to our knowledge the first 'digital footprinting in accessible chromatin' (under ATAC-seq peaks) in the immune system, which enabled identification of transcriptional networks that regulate gene expression," reports Ivashkiv. Analysis of occupied transcription factor binding sites (footprints) under ATAC–seq peaks suggested that pre-treatment with IFNα and TNF primes chromatin by co-operatively recruiting TNF-induced NFκB and interferon-induced transcription factors to the promoters of LPS-inducible genes.

Demonstrating the consequences of chromatin priming, IL-10 could only partially suppress LPS-induced expression of *IL6* in macrophages treated with TNF and IFNα. By contrast, IL-10 potently suppressed *IL6* expression in naive, LPS-stimulated macrophages.

Future work might explore the potential of targeting chromatin regulators in the context of rheumatic disease. "Aspects of the gene and chromatin regulation we discovered were mirrored in synovial macrophages from patients with rheumatoid arthritis and monocytes from patients with systemic lupus erythematosus," Ivashkiv recounts. "This suggests that these pathways can be therapeutically targeted to rebalance the inflammatory response to prevent toxicity while preserving host defense."

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ORIGINAL ARTICLE Park, S. H. *et al.* Type I interferons and the cytokine TNF cooperatively reprogram the macrophage epigenome to promote inflammatory activation. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3818 (2017)