INFLAMMATION

TNF snuffs out steroids

Therapies targeting tumour necrosis factor (TNF) are commonly used to treat patients with inflammatory bowel disease (IBD), but the exact mechanisms by which this pleiotropic cytokine drives IBD pathogenesis remain unclear. Huang *et al.* now show that TNF can promote chronic colitis by suppressing glucocorticoid synthesis in the intestine.

Glucocorticoids are anti-inflammatory steroid hormones that decrease the severity of IBD. To examine how glucocorticoid synthesis is regulated during chronic intestinal inflammation, the authors exposed mice to repeated cycles of treatment with dextran sulphate sodium (DSS) to induce chronic colitis. They found that the expression of *Cyp11a1* and *Cyp11b1*, which encode enzymes that are required for glucocorticoid synthesis, was increased in the inflamed colon during the acute phase of colitis but returned to baseline levels as the disease became chronic. Accordingly, colonic levels of corticosterone — the main glucocorticoid found in rodents — were increased during the acute phase of colitis but returned to baseline levels during chronic disease.

To explore how glucocorticoid synthesis is inhibited during chronic colitis, the authors treated a mouse intestinal epithelial cell (IEC) line that was engineered to overexpress NR5A2 (the transcription factor that drives *Cyp11a1* and *Cyp11b1* expression) with different cytokines. They found that the expression of *Cyp11a1* and *Cyp11b1* in this cell line was suppressed by TNF, but not by other pro-inflammatory cytokines, such as interleukin-1 β (IL-1 β) or IL-6, or by anti-inflammatory cytokines,

such as IL-10. They further showed that treatment of NR5A2-expressing IECs with TNF for 3 hours led to the transient induction of *Cyp11a1* and *Cyp11b1* expression, but that treatment with TNF for a longer time course or at higher doses suppressed the expression of these enzymes.

Closer analysis of the signalling pathways involved showed that TNF suppresses glucocorticoid expression by activating the transcription factors JUN and nuclear factor- κ B (NF- κ B). Both JUN and NF- κ B were found to directly interact with NR5A2 to repress *Cyp11a1* reporter activity, and inhibitors of NF- κ B or JUN N-terminal kinase (JNK) prevented the TNF-mediated suppression of *Cyp11a1* promoter activity. Finally, the authors showed that treating mice with chronic DSS-induced colitis with XPro1595 (a dominant-negative inhibitor of TNF that blocks soluble but not membrane-bound TNF) decreased JUN and NF- κ B activity in the colon and increased the abundance of *Cyp11a1* and *Cyp11b1* transcripts. Importantly, the increased expression of *Cyp11a1* and *Cyp11b1* was associated with decreased disease severity in colitic mice.

Notably, decreased expression of *CYP11A1* and *CYP11B1* has previously been detected in inflamed colonic tissue from patients with IBD. Therefore, one way in which anti-TNF therapies may benefit patients with IBD is by restoring intestinal glucocorticoid synthesis.

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ORIGINAL RESEARCH PAPER Huang, S.-C. *et al.* Tumor necrosis factor suppresses NR5A2 activity and intestinal glucocorticoid synthesis to sustain chronic colitis. *Sci. Signal.* **7**, ra20 (2014)

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