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INFLAMMATION

TET2: the terminator

> TET2 … selectively mediates the repression of *Il6* transcription through HDACs

A failure to resolve inflammation in a timely manner can have serious consequences for health. As such there are numerous molecular 'brakes' that can be applied to inflammatory responses. In a recent *Nature* paper, a new role is described for the methylcytosine dioxygenase TET2 in specifically repressing transcription of the pro-inflammatory cytokine interleukin-6 (IL-6) and ensuring timely termination of inflammation.

Deficiency of TET2 in mouse or human myeloid cells did not affect the rapid induction of IL-6 expression that occurs within 4 hours of stimulation with lipopolysaccharide (LPS). However, TET2-deficient cells failed to downregulate IL-6 expression at the late phase of the LPS response (after 8 hours). TET2 was also found to repress the transcription of other LPS-induced genes (including *Rsad2*, *Cmpk2* and *Ifit2*) that have the same dynamic transcription patterns as *Il6*, but it had no effect on transcription of tumour necrosis factor (*Tnf*).

The biological significance of TET2-mediated repression of inflammation was assessed in mice with a myeloid cell-specific deletion of *Tet2* given a systemic challenge with LPS. These mice produced much more IL-6, especially at the late phase, and showed more severe lung damage and diffuse inflammation than wild-type mice. *Tet2*-deficient mice were also more susceptible to dextran sulfate sodium-induced colitis, showing exacerbated colon inflammation and tissue damage compared with control mice.

During the late phase of LPS stimulation, higher levels of TET2 bound to the *Il6* promoter. Moreover, co-immunoprecipitation and mass spectrometry studies identified several transcription factors that associated with TET2 in myeloid cells. Of these binding partners, NF-κB inhibitor-ζ (IκBζ), which is known to target the *Il6* promoter during the LPS response, was shown to mediate specific targeting of TET2 to the *Il6* promoter. In addition, TET2 was found to associate with histone deacetylase 1 (HDAC1) and HDAC2. In the presence of inhibitors of HDACs, high levels of *Il6*, but not *Tnf*, transcription were maintained during the late phase of the LPS response, suggesting that loss of histone acetylation is important for repressing *Il6* transcription.

So, this study shows that TET2, independent of its established roles in DNA methylation and hydroxymethylation, selectively mediates the repression of *Il6* transcription through HDACs that erase histone acetylation during inflammation resolution in myeloid cells. Importantly, it implies that repression at the chromatin level, and not termination of Toll-like receptor signalling, is a key mechanism for regulating inflammatory cytokine expression.

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ORIGINAL RESEARCH PAPER Zhang, Q. *et al.* Tet2 is required to resolve inflammation by recruiting Hdac2 to specifically repress IL-6. *Nature* http://dx.doi.org/10.1038/nature15252 (2015)