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AUTOINFLAMMATORY DISEASES

# TNF drives cryopyrinopathies in mice

> the inflammatory phenotype of *Nlrp3*$^{A350V}$ mice was rescued by treatment with the TNF inhibitor etanercept

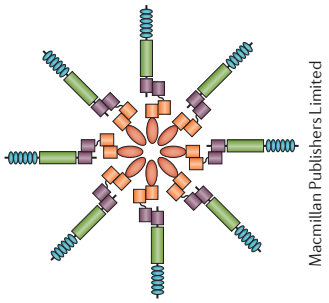
The results of studies in mice with *Nlrp3* mutations point to an important and unexpected regulatory role for TNF in inflammasome-mediated disease. The findings could have therapeutic implications for patients with cryopyrin-associated periodic syndromes (CAPS), autoinflammatory diseases arising from mutations in *NLRP3* that result in an overactive inflammasome and IL-1β release.

Most patients with CAPS are treated effectively with IL-1-targeted therapies, but in some cases the response to available treatments is incomplete, indicating that disease mechanisms other than IL-1 could be involved. Previous studies of *Il1b*$^{-/-}$*Il18*$^{-/-}$ mice support this idea, as these mice had substantial inflammation despite having disrupted IL-1 and IL-18 signalling. In the current study, McGeough *et al.* investigated disease-related inflammatory pathways using *Nlrp3*-knock-in mouse lines on various knockout backgrounds.

The researchers found that *Nlrp3*$^{L351P}$*Il1b*$^{-/-}$*Il18*$^{-/-}$ mice exhibited systemic inflammation from 6 months of age. This inflammation was dependent on caspase 1 and/or caspase 11, as it was not apparent in *Nlrp3*$^{L351P}$*Casp1/11*$^{-/-}$ mice. Moreover, injection of *Nlrp3*$^{L351P}$*Il1b*$^{-/-}$*Il18*$^{-/-}$ mice with low-dose lipopolysaccharide (LPS) led to markedly increased serum levels of TNF, which did not occur after LPS injection in *Nlrp3*$^{L351P}$*Casp1/11*$^{-/-}$ mice or in *Il1b*$^{-/-}$*Il18*$^{-/-}$ control mice.

Further investigations of TNF in a less severe mouse model of CAPS revealed that the inflammatory phenotype of *Nlrp3*$^{A350V}$ mice was rescued by treatment with the TNF inhibitor etanercept or by breeding onto a *Tnf*$^{-/-}$ background. Notably, *Nlrp3*$^{A350V}$*Tnf*$^{+/-}$ mice had an intermediate phenotype with respect to skin rash, inflammatory infiltrate and survival, suggesting a gene dosage-dependent effect of TNF expression.

Further studies are needed to clarify the mechanisms by which TNF drives NLRP3 inflammasomopathies, as well as the potential therapeutic role of TNF blockade. "The results of this paper suggest that combination therapy targeting TNF in addition to IL-1β could be useful in some patients with incomplete responses to IL-1 targeted therapy alone," explains corresponding author Hal Hoffman. "However, the potential benefits would need to be weighed against the risk of increased infections as demonstrated in a previous combination therapy study in rheumatoid arthritis."





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**ORIGINAL ARTICLE** McGeough, M. D. *et al.* TNF regulates transcription of NLRP3 inflammasome components and inflammatory molecules in cryopyrinopathies. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI90699 (2017)