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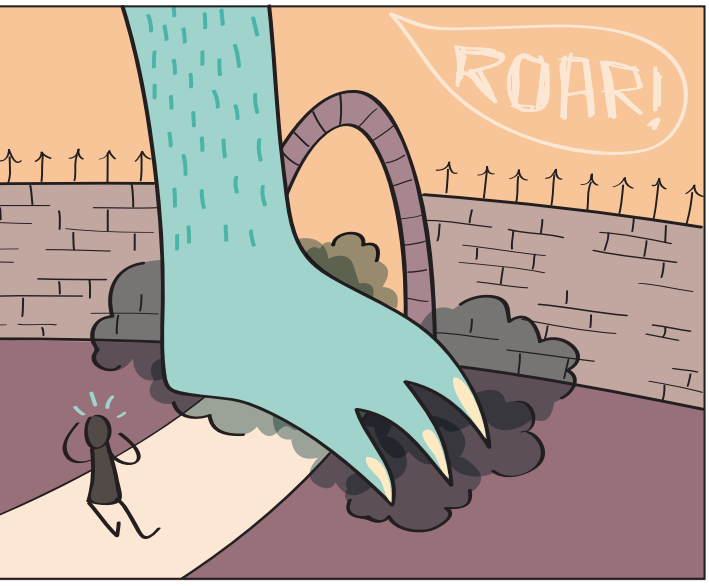
INFLAMMATORY DISORDERS

Blocking proinflammatory gene transcription

Dysregulated inflammation is a central pathological process in diverse acute and chronic disease states. Although there are multiple agents that therapeutically modulate inflammation, their use is often limited by toxicity, side effects or lack of efficacy. Writing in *Science*, Helleday and colleagues now report a novel anti-inflammatory strategy — inhibition of 8-oxoguanine DNA glycosylase 1 (OGG1) — that effectively suppresses inflammatory processes in mice.

Upon exposure to proinflammatory agents, cells produce increased levels of reactive oxygen species, which induce oxidative DNA damage. Guanine is particularly vulnerable to such damage; oxidation of guanine primarily produces 7,8-dihydro-8-oxoguanine (8-oxoG). OGG1 binds with high affinity to 8-oxoG to initiate DNA base excision repair. In addition, binding of 8-oxoG by OGG1 frequently occurs in the G-rich promoters of pro-inflammatory genes, which facilitates the loading of the nuclear factor κB (NF-κB) transcription factor, which stimulates proinflammatory gene transcription and promotion of an inflammatory response.

> “This study reveals OGG1 inhibition as a promising novel approach for the treatment of inflammation”



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With this in mind, and given that OGG1-deficient mice have previously been reported to exhibit decreased inflammatory responses but are otherwise viable and healthy, Helleday and colleagues set out to identify a small-molecule inhibitor of OGG1 as a potential novel treatment for inflammation.

First, the authors screened a library of 17,940 small molecules for inhibitors of OGG1, which together with *in silico* modelling led to the development of TH5487, a potent and selective active site inhibitor that prevented OGG1 from binding to its DNA substrate. Determination of the X-ray crystal structure of mouse OGG1 in complex with the more soluble analogue TH5675 identified the precise binding site for their newly identified class of inhibitors, revealing important amino acid residues.

Next, they assessed the activity of TH5487 *in vitro*. In human Jurkat cells, the inhibitor engaged OGG1 and inhibited DNA repair. Importantly, TH5487 did not affect cell proliferation, indicating a lack of toxicity. In addition, proinflammatory gene expression was reduced in human embryonic kidney cells lacking OGG1 and inhibited by TH5487 in mouse and human airway epithelial cells that had been stimulated with tumour necrosis factor (TNF) or lipopolysaccharide (LPS). The recruitment of OGG1 and NF-κB to regulatory regions of proinflammatory cytokines was decreased in TNF-challenged cells.

The authors then investigated the therapeutic potential of their OGG1 inhibitor. TH5487 was found to be relatively stable and well tolerated in mice. In a mouse model of inflammation in which the lungs of mice were challenged with TNF, expression of proinflammatory genes was induced. However, when mice were injected intraperitoneally with TH5487 prior to TNF exposure, the expression levels of pulmonary proinflammatory genes were decreased. Furthermore, the robust recruitment of neutrophils to the mouse airways following challenge with TNF or LPS was decreased by the prophylactic intraperitoneal administration of TH5487 in a dose-dependent manner, an effect that was seen even when TH5487 was administered up to 9 hours after the challenge.

This study reveals OGG1 inhibition as a promising novel approach for the treatment of inflammation. Although long-term inhibition of the DNA repair function of OGG1 may raise safety concerns, *Ogg1*-knockout mice are healthy and grow old exhibiting only a marginal change in mutation rates, indicating that pharmacological OGG1 inhibition may have applications in the treatment of both acute and chronic inflammatory disorders. The authors are currently developing more potent and soluble OGG1 inhibitors.

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ORIGINAL ARTICLE Visnes, T. *et al.* Small-molecule inhibitor of OGG1 suppresses proinflammatory gene expression and inflammation. *Science* **362**, 834–839 (2018)