

## NEUROINFLAMMATION

# Targeting neuroinflammation through inhibition of NLRP3

Two studies published recently in *Nature Medicine* describe new approaches for reducing inflammation mediated by the protein NLRP3 (NACHT, LRR and PYD domains-containing protein 3). The results indicate that NLRP3 could be a target for treating several disorders, including Alzheimer disease (AD), epilepsy and multiple sclerosis (MS).

NLRP3 becomes active in response to various environmental and pathogen-related factors, thus starting a chain of inflammatory events that includes upregulation of the proinflammatory cytokine IL-1 $\beta$ . Increased activation of the NLRP3 inflammasome has been observed in a range of autoinflammatory diseases, but a selective treatment has so far proven elusive.

A team led by Matthew Cooper synthesized a small-molecule compound, MCC950, that had previously been described in a large library of IL-1 $\beta$  inhibitors. The investigators then tested this agent *in vitro*, using multiple cultures derived from mouse and human cells. These tests revealed MCC950 to be a highly potent and selective inhibitor of NLRP3.

Cooper and colleagues then administered MCC950 to mice with experimental autoimmune encephalomyelitis (EAE), a model of MS. The compound delayed onset of EAE and reduced disease severity relative to control mice.

“In several animal models and *ex vivo* human samples, we found that we can block inflammation with this potent small molecule,” Cooper explains. “The really exciting next steps will be to look at cerebral inflammation in diseases such as AD, Parkinson disease, amyotrophic lateral sclerosis and others.”

An increasingly popular nonpharmacological strategy for managing inflammation is

the ketogenic diet, which has also proved to be an effective treatment for epilepsy. However, the mechanisms by which ketones yield these effects are not clear.

Vishwa Deep Dixit and co-workers isolated two major ketone bodies produced by the ketogenic diet,  $\beta$ -hydroxybutyrate (BHB) and acetoacetate. The investigators then treated macrophages derived from mouse bone marrow with these ketones, and recorded inflammatory responses to lipopolysaccharide, monosodium urate and other challenges.

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“BHB, but not structurally related ketone bodies, substantially blocked NLRP3 inflammasome activation in response to multiple proinflammatory factors,” explains Dixit. The macrophages treated with BHB responded normally to factors that provoke other pathways, such as NLRC4 activation after *Salmonella* infection, suggesting that BHB selectively targets NLRP3.

“Ketogenic diets could be relevant against several inflammatory disorders just as they have been used in people with drug-resistant epilepsy,” concludes Dixit. Pharmacological manipulation of BHB might also be a viable approach to the amelioration of inflammation.

Alex Chase

**Original articles** Coll, R. C. *et al.* A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. *Nat. Med.* doi:10.1038/nm.3806 | Youm, Y.-H. *et al.* The ketone metabolite  $\beta$ -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat. Med.* doi:10.1038/nm.3804