

## INFLAMMATION

COLITIS, MICROBIOTA  
AND MALNUTRITION

Angiotensin-converting enzyme 2 (ACE2)—an important regulator of the renin–angiotensin system—has been identified as the vital link between dietary amino acid homeostasis, intestinal immunity, microbiota composition and susceptibility to colitis in mouse models in a new study published in *Nature*. The findings provide clues as to how malnutrition leads to intestinal inflammation and diarrhoea.

Knowing that ACE2 controls the expression of the neutral amino acid transporter B<sup>0</sup>AT1 in the gut, Josef Penninger, Philip Rosenstiel and colleagues investigated the *in vivo* function of ACE2. First, they confirmed that *Ace2*-knockout mice had low serum levels of neutral amino acids (notably tryptophan), but found no morphological changes to the intestine. However, when challenged with the irritant dextran sodium sulphate (DSS; an established experimental model of colitis), *Ace2* mutant mice developed more severe colitis and diarrhoea than wild-type mice.

Next, mice were fed a protein-free diet (to eliminate dietary amino acids) and then challenged with DSS (1% dose to induce only very mild colitis). Importantly, both wild-type and *Ace2* mutant mice fed this diet developed severe colitis, indicating that protein malnutrition alters the severity of intestinal inflammation. Concentrating on a specific amino acid, the authors found that *Ace2* deficiency impaired local tryptophan homeostasis, which could be alleviated, along with the severe colitis phenotype, by tryptophan supplementation.

Further investigations revealed that *Ace2*-knockout mice, and normal mice fed a low-tryptophan diet, had reduced levels of antimicrobial peptides in the small intestine. Moreover, the composition of the gut microbiota was altered in *Ace2* mutant mice. Crucially, transplantation of gut microbiota from *Ace2*-knockout mice transferred the inflammatory phenotype and susceptibility to colitis to germ-free mice.

“The host intestinal tract and its microbes have co-evolved ... to form a balanced state that is essential for health,” notes Rosenstiel. Importantly, as tryptophan was proven to be an important amino acid, Penninger proposes that simple dietary interventions could be used to normalize gut bacteria, and potentially relieve symptoms, in people with colitis.

**Katrina Ray**

**Original article** Hashimoto, T. *et al.* ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation *Nature* **487**, 477–481 (2012)