*Nature Reviews Microbiology* | Published online 30 Dec 2015; doi:10.1038/nrmicro.2015.23

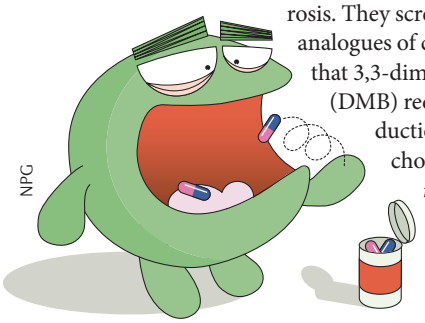
MICROBIOME

# Drugs for your bugs

> DMB treatment reduced ... the development of atherosclerotic plaques

The gut microbiota has a crucial role in the metabolism of trimethylamine (TMA)-containing nutrients that are present in some foods, which ultimately results in the generation of TMA *N*-oxide (TMAO), a metabolite that has been linked to the development of atherosclerosis. Now, Wang *et al.* show that targeting the microbial enzymes that are involved in this process reduces the levels of TMAO and is a potential therapeutic strategy for cardiovascular disease.

The generation of TMAO is a two-step process that involves both the gut microbiota and the host: following ingestion of TMA-containing foods (such as those rich in choline, phosphatidylcholine and carnitine), microbial TMA lyases generate TMA, which is then processed by host liver enzymes into TMAO. Therefore, Wang *et al.* sought to identify inhibitors of microbial TMA lyases as potential therapeutics for atherosclerosis. They screened structural analogues of choline and found that 3,3-dimethyl-1-butanol (DMB) reduced the production of TMA from choline in *Proteus mirabilis* and in recombinant *Escherichia coli* cells expressing the CutC–CutD enzymatic complex of *P. mirabilis* that is responsible for the production of TMA. Furthermore, microorganisms from mouse caecal contents and human faeces could produce TMA when grown in the presence of choline, phosphatidylcholine or carnitine, and TMA production from all of these substrates was inhibited in the presence of DMB. Importantly, DMB was able to inhibit the production of TMA by the commensals *P. mirabilis*, *Proteus penneri* or *Escherichia fergusonii* in a rich nutrient broth without affecting the growth of these bacteria, which may reduce the development of drug-resistant bacterial mutants.



NPG

To examine the impact of DMB treatment *in vivo*, the authors fed wild-type mice and atherosclerosis-prone mice (lacking apolipoprotein E; *Apoe*$^{-/-}$) either a regular diet or a diet supplemented with choline or carnitine (known to raise levels of TMAO in the plasma), in the presence or absence of DMB in the drinking water. Indeed, choline or carnitine supplementation resulted in increased levels of TMAO in the plasma, but treatment with DMB reduced these levels. Furthermore, DMB treatment reduced the formation of macrophage foam cells and the development of atherosclerotic plaques in *Apoe*$^{-/-}$ mice that had been fed the choline-rich diet.

Finally, the authors sequenced the caecal microbiota of the different groups of *Apoe*$^{-/-}$ mice, which revealed that the abundance of the taxa *Clostridiaceae* (in male mice) and the order *Clostridiales* and the genus *Ruminococcus* (in female mice) positively correlated with levels of TMA and TMAO and with the size of atherosclerotic plaques, whereas DMB treatment decreased the proportion of these taxa in mice fed a choline-rich diet. By contrast, the abundance of the *Bacteroidetes* family *S24-7* in female mice negatively correlated with levels of TMA and TMAO and with the size of atherosclerotic plaques, and increased following treatment with DMB.

Collectively, these data suggest that altering the gut microbiota and inhibiting microbial production of TMA is a potential therapeutic strategy for atherosclerosis.

*Cláudio Nunes-Alves*

**ORIGINAL ARTICLE** Wang, Z. *et al.* Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell* **163**, 1585–1595 (2015)
**FURTHER READING** Sommer, F. & Bäckhed, F. The gut microbiota — masters of host development and physiology. *Nat. Rev. Microbiol.* **11**, 227–238 (2013)