BACTERIAL PATHOGENESIS

Natural defences

Recent research published in *Science* has shown that a glycoprotein produced by cells in the stomach acts as an antibacterial and protects against infection with *Helicobacter pylori*.

H. pylori first 'hit the headlines' in the 1980s when researchers in Australia identified this Gram-negative microorganism as a cause of peptic ulcer disease and gastritis. However, so far, many aspects of *H. pylori* infection remain an enigma. Importantly, about half of the world's population harbour *H. pylori*, but only 20% of those infected develop related illness, indicating that most people can protect themselves against invasive disease. Jun Nakayama and colleagues have now shed some light on these defence mechanisms.

As *H. pylori* is rarely found in deeper parts of the gastric mucosa, this anatomical location seems to be hostile to colonization by this organism. Unlike surface epithelium, cells in the inner layers of the stomach secrete a mucin glycoprotein that comprises a specific carbohydrate moiety — α1,4-linked *N*-acetylglucosamine (α1,4-GlcNAc). The authors therefore suspected that *O*-glycans with this modification might protect against infection with *H. pylori*. To test this hypothesis, Nakayama and colleagues made recombinant glycoproteins containing the terminal α1,4-GlcNAc residue. When *H. pylori* was co-cultured with these recombinant molecules, bacterial growth was severely inhibited, the bacteria looked abnormal and motility was reduced. Human pyloric gland cells secrete glycoproteins containing the terminal α1,4-GlcNAc, and so, the authors co-cultured *H. pylori* with mucin produced by these cells. Similar to the recombinant molecules, *H. pylori* growth was severely repressed by this mucin. By contrast, when *H. pylori* was co-cultured with mucin derived from surface gastric mucosal cells — which lacks the specific carbohydrate residue — the bacteria flourished.

So, what is the mechanism of action of these α1,4-GlcNAc-capped *O*-glycans? Mass spectrometry showed that a cholesterol component of the bacterial cell wall, cholesteryl-α-D-glucopyranoside (CGL), was reduced in bacteria that had been cultured with α1,4-GlcNAc- capped *O*-glycans. CGL, similar to the α-linked *O*-glycans, comprises an α-linked sugar residue, and its glycosylation is catalysed by a carbohydrate-transferring enzyme. *In vitro* assays showed that recombinant *O*-glycans with α1,4-GlcNAc inhibited the activity of this enzyme, as the production of CGL from cholesterol and UDP-Glc precursors was decreased in the presence of the α1,4-GlcNAc-capped proteins. The authors reasoned that the α1,4-GlcNAc moiety might inhibit glycosylation of the structurally analogous CGL.

These studies provide a fascinating insight into the antibacterial armoury of the gastric mucosa. As the authors note, the next challenge will be to harness this natural antibiotic for use in human therapy.

Shannon Amoils

References and links

ORIGINAL RESEARCH PAPER Kawabuko, M. *et al*. Natural antibiotic function of a human gastric mucin against *Helicobacter pylori* infection. *Science* **305**, 1003–1006 (2004)