Nature Reviews Gastroenterology & Hepatology **12**, 550 (2015); published online 1 September 2015; doi:10.1038/nrgastro.2015.154

HELICOBACTER PYLORI

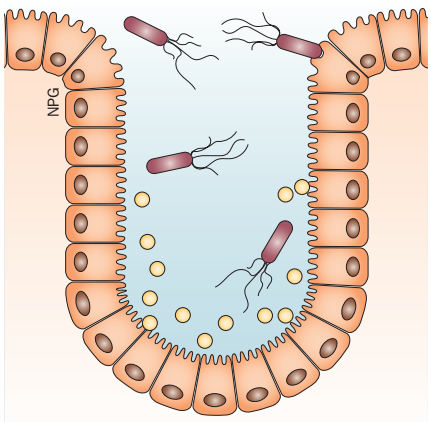
Lessons in bacterial attraction

By secreting urea, the gastric epithelium attracts *Helicobacter pylori*, which can sense the metabolite as it binds to the bacterial receptor TlpB, according to a study published in *Cell Host & Microbe*.

During many millennia of colonization and co-evolution in humans, *H. pylori* has become remarkably competent at recognizing and exploiting its host's resources for survival. To protect itself from the acidic environment in the stomach, *H. pylori* actively avoids the acidic lumen, hides in the mucus layer and can buffer its local environment by secreting urease, an enzyme that degrades urea into ammonia and bicarbonate. This latter skill makes *H. pylori* somewhat dependent on urea, a resource produced by the gastric epithelium, as Huang *et al.* could show when they analysed media conditioned by gastric cells in an *ex vivo* human gastric organoid system. The media was loaded into a micropipette and presented to a culture of motile *H. pylori* in a microgradient assay.

"To our surprise, *H. pylori* rapidly responded and were attracted to the tip of the needle releasing organoid-conditioned media, indicating that *H. pylori* have very sensitive mechanisms to detect and respond to host metabolites from the gastric epithelium," explains corresponding author Manuel Amieva. When the organoid-conditioned media was replaced with a solution of urea in water (1 mM), wild-type *H. pylori* were equally responsive (water alone did not attract them). "Our findings show that indeed urea is a dominant chemoattractant released by host cells," summarizes Amieva.

By engineering isogenic *H. pylori* mutants that lack each of the four known chemoreceptors (TlpA–D), the investigators were able to identify TlpB as the main chemotactic sensor, which can directly bind urea (and similar analogues) with high affinity and detects even nanomolar amounts.



The authors suggest that innate expression of urease by *H. pylori* prevents the sensitive TlpB receptor from getting saturated by the substantially higher concentration of urea present in the stomach (1–5 mM), as it keeps metabolite concentrations in the immediate surroundings of the bacterium at a level in which TlpB can function. In line with this argument, a genetically engineered *H. pylori* strain that lacked functional urease was unable to respond to urea (concentration range: 25 nM–1 M) in the microgradient assay.

In addition, Huang *et al.* could confirm that TlpB is required for long-term persistence of *H. pylori* in the stomach. When C57BL/6J mice were infected with wild-type and TlpB-deficient *H. pylori*, the number of bacteria lacking the receptor substantially decreased after 6 weeks compared with wild-type. However, the finding that mutated bacteria still establish colonization indicates that multiple signals might initially help *H. pylori* to find its home in the stomach.

Future work of the group will now aim at clarifying some of the underlying details in the interaction between *H. pylori* and host cells. Whereas in most cases the bacterium lives undetected and without interfering in the stomach of the human host, its presence can sometimes also lead to serious pathology such as gastric cancer and ulcers.

"We would like to identify other host metabolites that *H. pylori* senses and determine the host signals *in vivo* that are important for *H. pylori* in establishing infection. In particular, we are interested in how *H. pylori* colonizes and interacts with the progenitor and stem cell epithelium deep in the gastric glands, since these interactions might be important in the development of cancer," concludes Amieva.

Christine Weber

Original article Huang, J. Y. *et al.* Chemodetection and destruction of host urea allows *Helicobacter pylori* to locate the epithelium. *Cell Host Microbe* **18**, 147–156 (2015)