The twists and turns in the life of Helicobacter pylori

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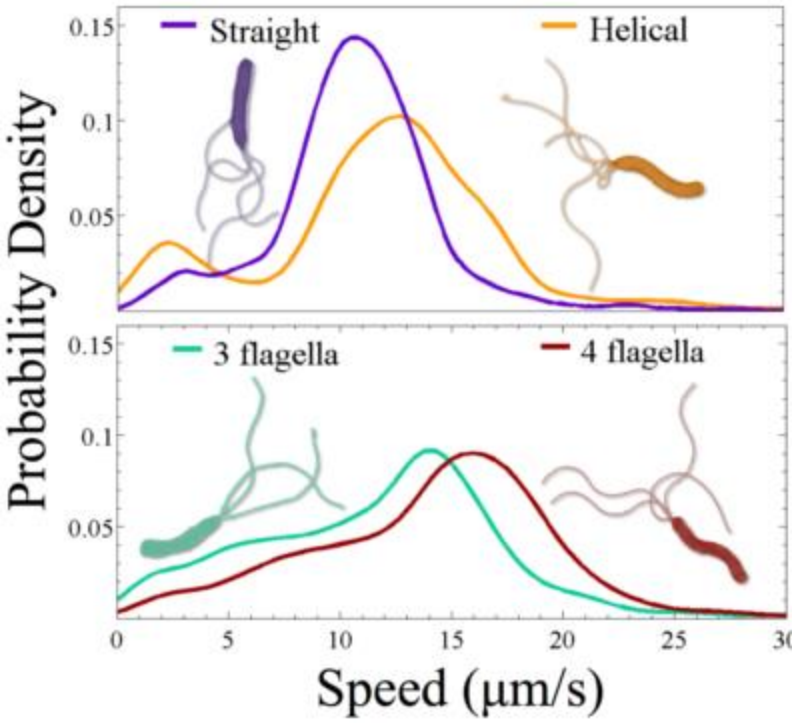

Smooth histograms summarizing speed distributions of bacteria in viscous solutions of gastric mucin. Top histogram: straight rod mutants show reduced swimming speeds (8-13%) in viscous solutions of gastric mucin. Bottom histogram: mutational perturbation of flagellum number shows a 19% increase in speed with 4 versus 3 flagella. Histograms include representative colorized tem images of each h. pylori strain analyzed.

Image provided by Ms. Laura Martinez.

Roughly half of the world's population is infected with the bacterium *Helicobacter pylori* (*H. pylori)* yet the vast majority of infections remain asymptomatic. However, chronic *H. pylori* infection significantly increases the risk for number of diseases, including gastric ulcers and gastric cancers. *H. pylori* is shaped like a corkscrew (helical shape) and it has been proposed that this helical shape is important for the bacteria to burrow through the protective mucus layer of the stomach. Consistent with this notion, previous work from the Fred Hutch Laboratory of Dr. Nina Salama (Human Biology, Public Health Sciences and Basic Sciences Divisions) not only identified genes required for *H. pylori's* helical shape (*csd* genes) but also showed that *csd* mutants were less efficient in colonizing the stomach in a mouse model. However, to directly test the role of cell shape, one would have to compare motile behaviors of helical rod with straight rod *H.pylori* strains, as well as determine the extent of shape variation in wild-type isolates of *H. pylori.* A new study from the Salama Lab, led by graduate student Laura Martinez and published in *Molecular Microbiology*, combined live-cell imaging with mathematical modeling to demonstrate that cell shape and flagellum number contribute independently to promote *H. pylori* motility in viscous environments.

The authors first chose three wild-type *H. pylori* strains from symptomatic patients and then used imaging software to determine that all three displayed marked variation in all morphological parameters examined, including: cell length, side curvature, flagellum number, and flagellum length. Next, the investigators imaged hundreds of live individual bacteria in environments designed to mimic the gel-like consistency of the human gastric mucus. This analysis revealed that all three strains not only exhibited overlapping distributions of swimming speeds but also that the trajectory of individual bacteria was complex, wherein forward swimming bouts were punctuated by reorientations and reversals. To assess which aspects of motility, if any, were dependent on helical shape, the authors compared motile behaviors of a wild-type H. pylori strain with its straight rod mutant counterpart (*Δcsd6*) generated in the same genetic background. Their results showed that the *Δcsd6* mutant displayed a significant reduction in both the maximum speed and in the fraction of motile bacteria. Because flagella-dependent motility is important for infection in other species, the researchers queried the role of flagellum number on motility. To this end, they measured several motility parameters in *H.pylori* strains that had either more, less, or normal number of flagella. This analysis revealed that swimming speed, but not other aspects of motility, correlated with flagellum number. Finally, a mathematical modeling algorithm known as resistive force theory (RFT) was used to compare the relative contributions of helical cell shape and flagellum number on swimming speed. Their RFT model first assumed constant motor torque and then varied the motor torque dependent on flagellum number. The RFT analysis showed that a combination of cell shape and flagellum number were required to explain the difference observed experimentally. Said Ms. Martinez: "The helical shape of *H. pylori* is a defining feature of this bacterium. Efficient motility is essential for *H. pylori* to persistently colonize the gastric mucus layer and to reach its niche adhered to stomach epithelial cells and in the proximal mucus overlying these cells. Our lab has previously shown that *H. pylori* mutants with altered shape do not colonize well. In this study, we experimentally confirmed the long held hypothesis that helical shape promotes faster swimming speeds in viscous solutions like gastric mucus, where *H. pylori* lives. Surprisingly, the differences in speed we measured are pretty subtle. We also showed that you could get a similar speed boost by inducing expression of 4 instead of 3 flagella. The fact that changing flagellum number could compensate for loss of helical shape makes us wonder if there are other selective pressures beyond swimming speed impacting morphology. Current work is focusing on localizing wild-type and mutant bacteria within infected tissue to further explore how cell shape impacts colonization". In summary, this study demonstrated that cell shape and flagellum number make important contributions to *H. pylori* motility, but there are likely to be other selective pressures that sculpt these morphological parameters *in vivo*.

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Martinez LE, Hardcastle JM, Wang J, Pincus Z, Tsang J, Hoover TR, Bansil R, Salama NR. 2016. Helicobacter pylori strains vary cell shape and flagellum number to maintain robust motility in viscous environments. Mol Microbiol. 99(1):88-110. doi: 10.1111/mmi.13218.