

Impact of *Helicobacter Pylori* on Mucus Rheology

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Why does the stomach not digest itself? The food we put in our stomach is efficiently broken down in this harsh acidic environment and yet somehow the acid does not damage the stomach itself. The answer is that the mucus gel layer lining the inside of the stomach serves as a protective barrier. For the past several years we have been engaged in a collaborative research program (with the groups of Drs Thomas Lamont and Nezam Afdhal of Beth Israel Deaconess Medical Center, Harvard Medical School) examining the biophysical mechanism that causes the mucus to form a gel. We have unlocked many clues toward obtaining a detailed molecular picture. Our research is now at the stage where we can meaningfully address the biophysics of a gastric mucus related disease, i.e. ulcers.

Mucus secretions form a protective layer on many tissues that are exposed to the external environment but it is perhaps in the stomach where the mucus layer faces the harshest conditions. In order to understand how this protection is achieved we have been studying gastric mucin, a large polymeric glycoprotein in gastric mucus that is primarily responsible for the mucus layer's protective properties. This molecule, similar to other mucins, is comprised of a long protein backbone with carbohydrates side chains arrayed like the bristles of a bottle-brush. The key to the protective function of gastric mucin lies in its ability to change from a viscous solution at neutral pH to a gel when in an acidic environment (below a pH of about 4), thus effectively providing a barrier.

Based on observations from Dynamic Light Scattering (DLS) and Atomic Force Microscopy (AFM) experiments we developed a molecular model of gelation, involving a complex interplay between electrostatic and hydrophobic interactions from specific domains of the mucin molecules. We have also shown that, *in vitro*, gastric juice is able to go through the mucus layer as if in a finger-like "channel." As the pH in the vicinity of the acid finger becomes very low (close to about 2) the mucin forms a gel confining the acid. However, since the gelation is reversible, after the acid has passed through, it returns from its gel state to its more fluid solution state and the "channels" close up once again. In addition, the surface of the mucus layer exposed to the interior of the stomach gels, thus preventing back diffusion of the hydrochloric acid.

Do our studies of gastric mucin gelation have any bearing on the problem of ulcers? This is particularly timely, as this year, Drs. Warren and Marshall, were awarded the Nobel Prize for establishing that many ulcers are caused by *Helicobacter Pylori*, a bacterium commonly found in the gut. While biochemical studies of *Helicobacter Pylori* show that it secretes enzymes that hydrolyze urea producing ammonia and carbon dioxide which neutralize hydrochloric acid allowing it to colonize the stomach, the physical mechanisms, and dynamics of how the flagellated helical bacterium "bores" its way like a cork-screw through the mucus gel, or its

effects on the physical properties of the mucus layer are not well understood. We have recently initiated a collaboration with the group of Dr. Ciaran Kelly of Beth Israel Deaconess Hospital, who are studying signaling pathways and vaccines for *Helicobacter Pylori*. They also make mutants that lack flagella, or the ability to produce the enzyme urease. Using video microscopy we are examining the motility of the bacteria and its mutants in mucin gels at different pH, urea concentration, and the presence of chemo-attractants. Similar experiments have been carried out by other researchers on *Helicobacter Pylori* in a viscous solution (Yoshiyama et al, Karim et al) but to the best of our knowledge, there have not been any motility studies in actual mucin or mucus gels. Previous studies of the bacteria's effect on mucus and mucin seem to be somewhat inconclusive. Infection with *Helicobacter Pylori* has been said to damage the mucus layer (Slomiany et al, Sarosiek et al, Sidebotham et al) but it has also been reported that the overall integrity of the mucus layer in vivo is not disrupted (Allen et al, Markesich et al). Our preliminary results show that *Helicobacter Pylori* is highly motile in porcine gastric mucin at neutral pH. It remains unclear whether the bacteria has any reproducible impact on the rheology of gastric mucin until more data is obtained.

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