The clinical and biological significance of the *Helicobacter pylori cag* pathogenicity island

Richard Peek

Helicobacter pylori induces inflammation in virtually all hosts, a persistent process that increases the risk of developing peptic ulcer disease, distal gastric adenocarcinoma, and mucosal lymphoproliferative disease, yet only a minority of colonized persons develop clinically apparent sequelae. Propensity to develop disease may be related to differences in expression of specific bacterial products, to differences in host response to the bacteria, or to the interaction between host and microbe. *Helicobacter pylori* strains that possess the *cag* pathogenicity island induce more severe gastritis and augment the risk for developing peptic ulcer disease and distal gastric cancer. A specific mechanism by which *cag*$^+$ strains may enhance gastritis is strain-selective regulation of IL-8, a pro-inflammatory cytokine. Upon contact with gastric epithelial cells, *H. pylori* activates multiple signal transduction cascades that regulate IL-8 secretion, and these events are dependent upon genes within the *cag* island. An independent effect of *cag*-mediated cellular contact is translocation and phosphorylation of *H. pylori* proteins (i.e. CagA) within the host epithelial cell, and these events induce changes in cellular morphology and alterations in the actin cytoskeleton. *H. pylori* also modulates epithelial cellular turnover in a strain-specific manner. Persons infected with *cag*$^+$ *H. pylori* strains have significantly higher proliferation rates, but lower apoptosis

scores, than either *cag*$^-$ or uninfected persons. Increases in proliferation that are not balanced by concordant increases in apoptosis over years of colonization may influence the ability of *cag*$^+$ strains to augment the risk for gastric cancer. The redundancy of intracellular signaling cascades activated by *H. pylori* and the divergent epithelial cell responses induced by components of the *cag* island likely contribute to the diverse spectrum of diseases associated with colonization as well as the ability of this organism to persist for decades within the gastric niche. Serologic detection for the presence of *cag*$^+$ strains is currently the best practical test for virulence. However, prior to recommending such a strategy of screening and selective intervention, it is critical to determine whether *cagA*$^-$ strains are completely non-pathogenic.