
**Helicobacter pylori** and the Cell Cycle

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In 1994, the International Agency for Research on Cancer (IARC) classified *Helicobacter pylori* infection as “carcinogenic to humans (group 1).” This conclusion was based on significant evidence in humans while recognizing that there was inadequate evidence in experimental animals (1). The strongest evidence in humans came from three independent historic cohort studies showing that serologic evidence of *H. pylori* infection (documented decades before) was statistically significantly associated with the risk of gastric carcinoma. However, laboratory data on mechanisms of carcinogenesis were lacking. Unlike some chemical and physical carcinogens evaluated by IARC, *H. pylori* may not be a “complete” carcinogen and is not expected to induce cancer in animals without the help of other etiologic factors. Suggestive evidence of interaction between biologic and chemical carcinogens is provided by the very high incidence of gastric carcinoma in ferrets infected with *Helicobacter mustelae* and given a low dose of N-methyl-N-nitro-N-nitrosoguanidine (MNNG), a potent mutagen and gastric carcinogen (2). This finding suggests that *Helicobacter* infection potentiates environmental carcinogens. The search for gastric carcinogens in humans has focused on both the luminal (3) and tissue (4) microenvironments.

Given the difficulties of inducing invasive cancer in experimental animals infected with *Helicobacter* species, attention has been directed toward intermediate biomarkers of the carcinogenic process. In this issue, Peek et al. (5) examined the effect of bacterial strain differences on two critical components of the cell cycle: cell replication and apoptosis (programmed cell death).

This report comes at an opportune time because presently there is much interest in exploring if the virulence of certain *H. pylori* strains determines the outcome of the infection. In other fields of scientific research, cell cycle alterations are being evaluated to determine their possible role in carcinogenesis, including the possible identification of checkpoints that drive the cycle, the control of which may open new avenues of treating and preventing cancer in humans (6).

The model of *Helicobacter*-induced carcinogenesis is especially appealing to researchers for several reasons. One of these reasons is illustrated by the fact that chronic, prolonged infection with *H. pylori* increases the risk of gastric cancer in some groups of individuals but not in others. In the first category are patients with multifocal atrophic gastritis, some of whom develop gastric ulcer. In the second category are patients who develop *H. pylori*-associated, predominantly antral nonatrophic gastritis and duodenal ulcer (7). Since both outcomes are a consequence of *H. pylori* infection, the study of their biologic differences may help to identify events that are, as well as those that are not, part of the carcinogenesis cascade. Bacterial strains may be different in the two contrasting outcomes, but at the present time there are no

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recognized bacterial virulence factors that separate nonatrophic (low cancer risk) from atrophic (high cancer risk) gastritis. Both types of gastritis have been associated with cagA, a marker gene of the “Pathogenicity island” (8).

Peek et al. (5) report that less virulent strains characterized as cagA negative and non s1a vacA (vacuolating cytotoxin A) increase both cell replication and apoptosis. It is proposed that such changes result in a “balanced” alteration, since more cells are being produced but simultaneously more cells are lost through programmed cell death. This is contrasted with cagA positive, vacA s1a strains that increase replication even more than vacA negatives but do not increase apoptosis, thereby resulting in an “imbalanced” excess of cells without excess loss. The differential effect on apoptosis may provide a framework for future studies of specific mediators of the apoptotic process, such as p53 and bcl-2. If more cells are being produced than lost, they should accumulate in an excessive mass, which in the gastrointestinal tract should result in mucosal hypertrophy or in polyp formation. This is rarely observed in the H. pylori-infected gastric mucosa. Cell replication in the gastric mucosa takes place in the “neck” region of the glands, followed by migration of the daughter cells toward the surface and loss by desquamation into the gastric lumen. Some desquamating cells are positively labeled for the 3’OH ends of DNA as determined with the terminal deoxynucleotide transferase-mediated digoxigenin-uridine triphosphate nick-end labeling (TUNEL) assay, indicating the DNA fragmentation characteristic of apoptosis. Although not well documented, it is possible that other desquamating cells lack such abnormal TUNEL staining. If so, then excessive cell replication without countering apoptosis does not automatically result in mucosal hypertrophy or polyp formation. However, it may result in excessive numbers of DNA-damaged cells going through repeated cell cycles. In addition to apoptosis, other types of DNA damage may result from H. pylori infection. Severe damage to DNA and cell membranes results in cell necrosis, not a frequent event in H. pylori infection. Lesser degrees of damage may be repaired, leading to total restitution of the original structure. But DNA damage that does not result in necrosis or apoptosis and is not totally repaired may lead to mutations and development of neoplasia. The gastrointestinal mucosa, like the skin, is lined by renewable epithelium, in which (most?) DNA-damaged cells are lost by desquamation.

Apoptosis in normal gastrointestinal mucosa is observed mostly near the apex of the folds, where normal desquamation takes place. In H. pylori-infected gastric mucosa, however, excessive apoptosis is observed (with the TUNEL assay) in the neck region of the glands, where replication is active. It has been suggested that this cell damage is a consequence of cytokines liberated by the neighboring inflammatory cell attracted by the bacterial infection, which will damage the “anchorage” of the epithelial cells to the basement membrane, a process called “anoikis” (homelessness) (9). It would seem, therefore, that the inflammatory process initiated by Helicobacter is damaging to the host but not to the bacteria. Has mother nature failed us? According to Blaser (10), in the context of the secular interactions between bacteria and host, becoming sick from the infection is not very harmful to the survival of Homo sapiens, especially after we have accomplished our function of procreating and preserving the species.

References

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