Helicobacter pylori and Gastric Atrophy—Cancer Paradoxes

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It has long been recognized that chronic gastritis is a precursor of gastric cancer only when atrophy is part of the spectrum of lesions (1). These observations are paradoxical, since atrophy is characterized by the loss of glandular epithelium, whereas cancer represents its excessive and anarchic replication. The phenomena that give rise to atrophy in the chronic gastritis complex are presently a source of considerable interest; they may help us to understand the mechanisms of carcinogenesis, especially those related to biological agents such as bacteria. Environmental factors have been implicated in gastric carcinogenesis: Populations and individuals at high risk of gastric cancer consume excessive amounts of irritants, such as NaCl, as well as inadequate amounts of fresh fruits and vegetables (2). The latter appear to play a protective role in carcinogenesis in several organ systems (3).

Helicobacter pylori is the overriding cause of chronic gastritis. Infection with this bacterium is the main cause of duodenal ulcers as well as gastric ulcers. Paradoxically, the former are associated with a decreased risk of gastric cancer, while the latter increase such risk (4,5). Many factors have been proposed to explain the divergent pathways of H. pylori infection, possibly involving the genetic makeup of the host, diet, and virulence factors of the bacterium (6).

No carcinogens or mutagens have been identified in H. pylori, but several bacterial toxins and products are known. Some strains of bacteria induce vacuolization of epithelial cells. Strains producing the vacuolating cytotoxin, VacA, were found to be overrepresented in isolates from patients with duodenal ulcers (who are not at increased risk of gastric cancer) (7). A new paradoxical observation was made when similar excessive representation of cytotoxin-producing strains was reported for patients with gastric atrophy (which does increase gastric cancer risk) (8). A second cytotoxin-associated protein (CagA, product of the cagA gene) has been identified and linked to tissue injury (9) and to increase in gastric cancer risk (10). Recently, new genes have been identified that also may be involved in the pathogenesis of gastric injury, such as cagII or cagC (11,12). Strains expressing both VacA and CagA were shown to induce gastric pathologic abnormalities in mice similar to those observed in human infections: loss of glands, erosions, ulceration, and inflammatory infiltration. Strains not expressing vacA or cagA induced only mild inflammation (13).

This background emphasizes the importance of the report by Kuipers et al. (14) in this issue of the Journal, documenting the role of cagA-positive bacteria in the development of gastric atrophy in humans. The mechanisms by which cagA-positive H. pylori strains induce both atrophy and cancer are not clear. A clue might be provided by the fact that such strains enhance the expression of several proinflammatory cytokines (interleukin 1α, interleukin 1β, and interleukin 8) in the host (15,16). Infection with cagA-positive strains results in a more intense gastritis. Certainly, various inflammatory mediators, including reactive oxygen and nitrogen species, are mutagenic and are released in large amounts during persistent inflammation. Thus, one possibility is that the degree of inflammation determines the degree of DNA damage and point mutations. However, this does not explain why atrophy is part of the precancerous process.

One explanation may be provided by new insights on how cells handle DNA damage, specifically the induction of programmed cell death, or apoptosis, in cells that are injured but do not die of necrosis. While, traditionally, apoptosis and necrosis are polarized events, it is becoming evident that, in inflammation, both may be represented in the spectrum of cell responses to the barrage of inflammatory mediators. Following DNA damage, a cell may arrest its reproductive cycle and repair the damaged DNA, or, alternatively, if the damage is more severe, the cell may undergo apoptosis and eliminate the risk of replicating mutated DNA. If the damage is too extensive, then the cell dies by necrosis mechanisms, since it loses control of membrane integrity and organelle function. This spectrum of reactions can be demonstrated in cultured epithelial cells: Nitric oxide at low doses induces apoptosis; however, at higher doses, cell death occurs via necrosis (17). In atrophic gastritis, inducible nitric oxide synthase (the isoformal of the enzyme associated with inflammation) is expressed, particularly in infiltrating neutrophils and macrophages in the neck region of the gastric glands where cell replication normally takes place.

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We have provided evidence for apoptosis in *H. pylori* gastritis, with a reduction in the apoptosis index after clearance of the infection or antioxidant administration (18). Thus, the loss of glands in atrophic gastritis may represent a large-scale induction of apoptosis as the result of oxidant- or nitric oxide-mediated DNA damage. The failure to execute apoptosis of transformed cells may allow the process to enter the next stage toward an eventual cancer end point.

It may be that atrophy is a marker of cell injury that possibly increases cancer risk via hypochlorhydia (diminished secretion of hydrochloric acid) and changes in the microenvironment. Obviously, cells dying of apoptosis do not provide carcinogenic clones, but those that escape apoptosis after having experienced DNA damage may create such clones. Nitric oxide and related species released by white blood cells may induce apoptosis in some epithelial cells, leading to atrophy, and also may induce nonlethal DNA damage in other target epithelial cells.

References


Note

1. Authors' note: Recent work has shown that the so called cagC gene permits induction of cytokines and has been renamed p1B (19).

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A New Brochure to Increase Patient Awareness of the Importance of Treating Cancer Pain

- Patients have a right to pain control.
- Patients have a role in communicating their pain.
- Patients should talk to their doctors or nurses as soon as pain begins.
- Patients should not let fears keep them in pain.

Get Relief From Cancer Pain is written at a 5th grade reading level and is available through the American Cancer Institute's Cancer Information Service at 1-800-ACS-2345 or the American Cancer Society at 1-800-ACS-2345.

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