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Keynote Lecture 4

The role of *Helicobacter pylori* infection in gastric pathology

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It is now clear that *Helicobacter pylori* infection accounts for most cases of chronic gastritis and also plays a role in causing permanent changes of gastric epithelium, such as gland atrophy and intestinal metaplasia. The contribution of *H. pylori to* diseases such as peptic ulcer, cancer, lymphoma and autoimmune gastritis with its sequelae (pernicious anemia; enterochromaffin-like cell carcinoidosis) is of high clinical relevance.

Selective adhesion to the surface of gastric superficial-foveolar epithelium through specific adhesins, with or without pedestal formation, is important for permanent bacterial colonization and pathogenicity. *H. pylori* toxins (vacuolating toxin VacA, ammonia producing urease, etc.) and antigens (Gag proteins, heat shock proteins, lipopolysaccharide, etc.) are either secreted in the gastric lumen by a type II mechanism and internalized into epithelial cells by endocytosis, or directly inoculated into the epithelial cytoplasm by the adhering bacterium through a type IV system, or even released by budding of outer membrane vesicles which are endocytosed by the epithelial cells (1). Direct bacterial cytotoxicity causes epithelial cell vacuolization, cellular edema and luminal bulging (better seen at ultrastructural investigation) or micropapillary change, mucin loss and, occasionally, erosion of surface epithelium (easily recognized also under light microscopy). Epithelial transcytosis of bacterial antigens, taken up by dendritic cells and macrophages of the underlying lamina propria, as well as *de novo* or enhanced epithelial expression of immunoactive and such proinflammatory molecules as interleukin (IL)-8, human lymphocyte antigen (HLA)-DR and cathepsin E, are likely to contribute to mucosal immune-inflammatory response (2, 3). Intra- and periepithelial infiltration of neutrophils, eosinophils and macrophages contribute further to epithelial damage, especially at renewal zone level. Both direct bacterial cytotoxicity and inflammatory lesions of "active" gastritis may cause epithelial cytolysis, erosion and defective repair and are likely to promote peptic ulcer, as shown by the correlation of their presence/absence with ulcer formation/healing and, especially, by the close temporal correlation between their prompt disappearance after bacterial eradication and a parallel prevention of ulcer recurrence (4).

Epidemiological studies based on *H. pylori* serology and histological investigation of colonized gastric mucosa provided strong evidence for an important role of *H. pylori* infection in gastric carcinogenesis (5, 6). This conclusion is in keeping with early observafions on the association of severe, atrophic-metaplastic gastritis with gastric cancer (7, 8) and, in turn, is strongly supported by the development of gastric cancer in the Mongolian gerbil experimentally infected with *H. pylori (9).*

Investigation of genetic changes in early and advanced gastric cancers (10-13) suggests that at least the three following distinct carcinogenetic pathways are involved:

i) impaired DNA mismatch repair causing microsatellite instability frequently involving transforming growth factor (TGF) II receptor, insulin-like growth factor (IGE) II receptor or proapoptotic *BAX* gene. Microsatellite instability-related cancers are, as a rule, of glandular (intestinal) type and arise in metaplastic antral mucosa, with reduced rate of lymph node metastasis and better patient survival;

ii) p53 gene mutation causing dysplasia, glandular or mixed glandular to diffuse cancers; and,

ii) cadherin E gene mutation or silencing through promoter hypermethylation causing loss of cell to cell junction, cell polarity and glandular structure, thus leading to diffuse (dispersed cells) or mixed cancers.

A number of other genetic lesions have been identified, such as loss of heterozygosity at 18q21 *(DCC/DPC* genes), 11q22-23 (ATM gene), 7q31 *(c-met* gene) or 21q21-22 sites, and gene amplification/overexpression of trophic factors or their receptors, mainly as late events, are sometimes also present in early cancers (14). Less information is available on genetic changes occurring before the appearance of severe dysplasia or intramucosal cancer and on the relationship of such changes with *H.* pylori gastritis. Enhanced proliferative rate, DNA oxidative damage, and defective apoptosis, DNA repair and/or immune surveillance of transformed epithelial clones are all likely to be involved in the precancerous phase (a very long process spanning several decades) of gastric carcinogenesis and to be, directly or indirectly (via the inflammatory process) related to *H. pylori* infection (15). Investigation of the precise role of *H.* pylori gastritis in causing morphological, biochemical and genetic changes of gastric mucosa during this phase, as well as of their reversibility after bacterial eradication, seems of paramount importance to clarify the pathogenesis of gastric cancer and to plan interventional studies of cancer prevention.

In conclusion, it can be emphasized that the discovery of *H. pylori* promoted a revolution in our traditional knowledge of gastric pathology, involving epidemiology, pathogenesis, diagnosis and therapy for most clinically relevant gastric diseases with dramatic impact on patient treatment and outcome (gastritis, peptic ulcer, primary B-cell lymphoma, possibly some form of dyspepsia) or with encouraging prospectives for prevention (cancer, carcinoidosis).

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