The role of *Helicobacter pylori* infection in gastric pathology

Chairperson J. Sanz Esponera Spain

E. Solcia

Dipartimento di Patologia Umana e Ereditaria, Università di Pavia, Italy

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 carci

noidosis) 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 endocyto
tised 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 epitheli

um (easily recognized also under light microscopy). Epithelial tran

scytosis 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 proin

flammatory molecules as interleukin (IL)-8, human lymphocyte anti
gen (HLA)-DR and cathepsin E, are likely to contribute to mucosal immune-inflammatory response (2, 3). Intra- and periesophageal infiltration of neutrophils, eosinophils and macrophages contribute fur

ther to epithelial damage, especially at renewal zone level. Both direct bacterial cytotoxicity and inflammatory lesions of “active” gastritis may cause epithelial cytolsis, erosion and defective repair and are likely to promote peptic ulcer, as shown 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 carcinogenic pathways are involved:

i) impaired DNA mismatch repair causing microsatellite instabili
ty frequently involving transforming growth factor (TGF) II receptor, insulin-like growth factor (IGF) 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 glan
dular to diffuse cancers; and,

iii) cadherin E gene mutation or silencing through promoter hypermethylat

ion/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 carci

nogenesis and to be, directly or indirectly (via the inflammatory process) related to *H. pylori* infection (15). Investigation of the pre

cise 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 para

mount 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 pathol

ogy, 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).

References

1. Fiocca R, Necchi V, Sommi P el al. Release of Helicobacter pylori vacu/sting cytotoxin by both aspecific secretion pathway and budding of outer membrane