Immunological aspects of *Helicobacter pylori* infection

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**INTRODUCTION**

Prior to the discovery of *Helicobacter pylori* it was considered unlikely that bacterial pathogens could colonise the stomach due to the arid environment created by acid secretion and other defensive factors. Microbial infection of the gastric mucosa is prevented in part by the production of mucus and several proteins with antibacterial actions, such as lysozyme and lactoferrin, as well as structurally by the tight junctions at the apical border of the epithelial cells. *H. pylori*, cultured for the first time from human gastric mucosa in 1983 (1), not only colonises human gastric epithelium but is also currently considered as the major aetiological agent in the pathogenesis of chronic gastritis and peptic ulcer disease (2, 3). Development of gastric cancer (4, 5) and lymphoma (6, 7) have also been related to *H. pylori* colonisation. It is now generally accepted that *H. pylori* infection is acquired in childhood from other infected individuals.

Possession of an active urease enzyme permits *H. pylori* to overcome the gastric acidity during the colonisation process by creating a surrounding alkaline microenvironment (8). *H. pylori* normally resides between the mucus layer and the epithelial cells, protected from the gastric lumen hostility, and only rarely has been found intracellularly (9). The colonisation of the gastric epithelium elicits an immune reaction consisting of both humoral and cellular components. A series of inflammatory changes take place with release of cytokine and products of arachidonic acid metabolism, which recruit and
activate polymorphonuclear cells and monocytes. In other mucosal tissues this primary response may be beneficial and protective, while in the stomach *H. pylori* infection becomes chronic in the absence of treatment due to the inability of the host's immune response to eliminate the bacteria.

Although *H. pylori* infection almost invariably causes chronic gastritis, only a proportion of the infected subjects develop peptic ulcer (10). In addition to the possibility that some *H. pylori* strains might be more ulcerogenic than others, the nature of the host immune response may partly explain the different outcomes of infection by this organism. For example, the presence of autoantibodies (11), the degree of acid secretion and the gastric cytokine profile (12) have all been suggested as variables which may account for the variation in the clinical manifestation of disease.

**INITIATION OF THE INFLAMMATORY RESPONSE**

**Role of chemokines and acute response in *H. pylori* infection**

The epithelium is the first barrier to the organism and therefore the first to initiate a response. After penetration of the mucus layer the bacteria adhere to the epithelial cells via bacterial adhesins (13) which may induce direct cell damage or the liberation of epithelial-derived pro-inflammatory cytokines. Epithelial cell activation is evidenced by actin polymerisation (14), inositol phosphate induction (15) or phosphorylation of intracellular protein (16). Adherence of the organism to gastric epithelial cells is accompanied by loss of microvilli, irregularity of the luminal border and intracellular changes including loss of cytoplasm, oedema and vacuolation (17).

Peptides belonging to the chemokine family are involved in the recruitment and activation of immune cells. These chemokines [RANTES (regulated upon activation, normal T cell expressed and secreted), GRO alpha (growth-related oncogene protein-alpha), ENA-78 (epithelial-cell-derived neutrophil attractant-78), MIP-1α (macrophage inflammatory protein-1 alpha), IL-8 (interleukin-8)] are released by the epithelium both in response to *H. pylori* (18) and on exposure to endogenous pro-inflammatory mediators (19). Recent data indicate that induction of ENA-78, in comparison with IL-8, appears later but is not secreted, and its expression is not related to CagA-positivity (20). Bacterial induction of epithelial chemokines involves a protein tyrosine pathway and NF-κB activation (21). In *H. pylori* infection there is a marked increase in IL-8 in gastric epithelial cells relative to uninfected mucosa (22) and *in vitro* studies have clearly indicated that lipopolysaccharide (LPS) and LPS-free components such as urease will induce monocyte secretion of IL-1 and TNF-α (23). These mediators can modify epithelial cell differentiation by upregulating the expression of chemokines. Finally IL-16, a recently described cytokine that