Commentary

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Cytokines and *Helicobacter pylori* – a growth area

Yasunaga and coworkers describe their experiments, which examine the relation between *Helicobacter pylori* colonisation, mucosal production of various cytokines and growth factors, and enlarged fold gastritis. They find that *H pylori* colonisation was associated with increased release of hepatocyte growth factor (HGF) and interleukin 1β (IL1β) and that the release of HGF by mucosal biopsy specimens in vitro was reduced by the addition of an IL1β receptor antagonist, suggesting that changes in these two factors were linked. Samples taken from patients with enlarged fold gastritis (all were *H pylori*+ve) had the highest amounts of HGF immunoreactivity and HGF and IL1β release of all the groups studied. Importantly, after *H pylori* eradication, the size of the enlarged folds reduced in parallel with reduction in IL1β and HGF levels, further supporting the idea that a close link exists between *H pylori* colonisation, cytokine release, growth factor production, and mucosal growth.

Their paper therefore begins to examine the complex interrelation between colonisation with *H pylori,* cytokine release, growth factor production, and mucosal growth. Hitherto, individual studies in this area have tended only to examine the relation between two of these four variables.

Cytokines and *H pylori* colonisation

It is now accepted that there is a close relation between colonisation with *H pylori* and the development of chronic active gastritis and peptic ulceration. The details of how the presence of *H pylori* causes these effects are less clear but it is probable that cytokine production by the organism itself or by the patient in respone to the presence of the organism, is relevant to this process. Several pro-inflammatory agents have been implicated in these responses. Those originating from the bacterium itself include the membrane lipopolysaccharide, urease (which acts as a chemotactic agent for monocytes and neutrophils in vitro), vacuolating cytotoxin, and the heat shock proteins.

The lipopolysaccharides and water soluble surface proteins of *H pylori* increase the production of IL1β, tumour necrosis factor (TNF), and the reactive superoxide anion by activated monocytes/macrophages.[1] Tissue levels of IL8 also appear to be raised in *H pylori* infected people. A close link between *H pylori* colonisation and IL8 and TNFα levels is supported by the finding that tissue levels of mRNA for IL8 and TNFα decrease after eradication of the organism.[2] Interestingly, Gionchetti and coworkers,[3] found no significant differences in IL1β levels between *H pylori*+ve and –ve subjects, a result which differs from the findings presented in this issue.

The main rationale for looking at these relations was that the presence of increased cytokine concentrations might well be important in perpetuating the inflammatory process (by direct toxic effects on the epithelium as well as recruiting additional inflammatory cells). In addition, the production of these cytokines might directly stimulate the G cells to secrete gastrin, thereby explaining the hypergastrinaemia and increased acid production usually seen in patients with duodenal ulceration.

Growth factor production and *H pylori* colonisation

Several early studies reported that peptic ulceration was associated with decreased epidermal growth factor (EGF) levels in gastric juice and saliva.[4 5] *H pylori* status was not examined (although it is reasonable to presume that there was a high carriage rate of *H pylori* in these patients). A recent study in *Gut,* however, did not find reduced levels of EGF in peptic ulcer patients.[6]

Gastric mucosal EGF immunoreactivity[7] and messenger RNA levels are generally considered to be extremely low under non-damaged conditions, with the vast majority of gastric juice EGF being derived from swallowed saliva. It is important to note however, that this idea has recently been questioned.[6]

Transforming growth factor α (TGFα) is a potent mitogen and binds to the same receptor as EGF. In contrast with the low levels of mucosal EGF seen in the normal stomach, mucosal levels of TGFα are high.[7] Studies suggesting that TGFα might play an important part in controlling growth of the gastric mucosa include the finding that transgenic animals, which overexpress TGFα in the gastric mucosa have marked mucosal hyperplasia resembling Menetrier's disease. Changes in the concentration of TGFα within the mucosa and in gastric juice in various pathophysiological states are also being examined by various groups, at present there is no general consensus regarding whether any consistent changes in TGFα levels occur. In the paper published in this issue, no difference in tissue TGFα levels were found between *H pylori*+ve and –ve subjects whereas a preliminary study by Persico *et al,* found that *H pylori* colonisation of the stomach was associated with reduced mucosal TGFα tissue concentrations.[8] Interestingly, Stachura and coworkers found that continued administration of aspirin to volunteers increased mucosal TGFα levels, suggesting TGFα might be important in the adaptive response to noxious agents.[9]

HGF, also known as scatter factor, binds to the C-met receptor and is a potent stimulant of proliferation and cell migration in epithelial cells. Kondo and coworkers have previously reported that *H pylori* colonisation is associated with increased levels of HGF messenger RNA in gastric mucosa and suggested that this effect was probably mediated through 'the mucosal inflammation'.[10] The present study by Yasunaga showing that IL1β antagonists reduced the production of HGF suggests a much closer link between cytokine and growth factor production than was previously recognised. Their findings that HGF levels were highest in patients with large fold gastritis and that HGF levels fall in parallel with changes in fold thickness (after *H pylori* eradication) also implicates this growth factor in the trophic response.

H pylori colonisation is undoubtedly important in the production of gastritis and peptic ulceration. The inflam-

matory process is probably due to a combination of toxic pro-inflammatory agents produced directly by the organism and by the patient's immune system in its efforts to eradicate the organism. Until recently the major focus has been on cytokine production in response to this infection. The finding that IL1β antagonists reduce the production of the growth factor HGF, however, suggests that we should pay closer attention to the link between pro-inflammatory cytokines and growth factor production including examination of the molecular mechanism(s) involved. Examination of this area might provide new insights into why only a small subpopulation of *H pylori* colonised subjects go on to develop peptic ulceration and might also be relevant to the apparent link between *H pylori* colonisation and abnormal mucosal growth in conditions such as large fold gastritis and gastric carcinoma.

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