Gut

Leading article

The importance of interleukin 1β in *Helicobacter pylori* associated disease

Helicobacter pylori infection is associated with divergent clinical outcomes that range from simple asymptomatic gastritis to more serious conditions such as peptic ulcer disease and gastric neoplasia. The key determinants of these outcomes are the severity and distribution of the *H pylori* induced gastritis. Gastritis that is largely confined to the antral region is associated with excessive acid secretion and a high risk of duodenal ulcer disease.[1] In contrast, gastritis that involves the acid secreting corpus region leads to hypochlorhydria, progressive gastric atrophy, and an increased risk of gastric cancer.[2] The association of *H pylori* with such variable outcome poses a fascinating scientific challenge, the unravelling of which will not only explain how ulcers and gastric cancer develop but will also act as a paradigm for gene-environment interactions in most human diseases. The proinflammatory cytokine interleukin (IL)-1β is emerging as a key mediator of many pathophysiological events that characterise host-environment interactions. In this article we discuss the role of IL-1β in *H pylori* associated disease.

The key pathophysiological event in *H pylori* infection is initiation of an inflammatory response. Bacteria or their products trigger this inflammatory process and the main mediators are cytokines. Cytokines, including interleukins, are soluble peptide molecules that mediate the interaction between immunocompetent and haematopoietic cells and between the immune and neuroendocrine systems.[3] They are produced by a variety of activated cells and exert their biological effects through binding to specific receptors on target cells. IL-1β is the archetypal pleiotropic cytokine being produced by many cells and exerting its biological effects on almost all cell types.[4] IL-1β is a potent proinflammatory cytokine and is involved in the host's response to many antigenic challenges.

Stimuli for IL-1β production

Nearly all microbes/microbial products and many non-microbial agents stimulate transcription and synthesis of IL-1β. Some of the more interesting non-microbial stimulants of IL-1β include hyperosmolarity, ischaemia-reperfusion, thermal injury, C reactive protein, urate crystals, silica/asbestos, tobacco antigen, fibrin degradation products, thrombin, oxidised low density lipoprotein, and platelet activating factor.[4] Depending on the stimulant, IL-1β mRNA levels increase rapidly within 15 minutes and then start to decline after four hours. Although large amounts of IL-1β mRNA could be produced, there is a form of dissociation between transcription and translation into the IL-1β protein. Stabilisation of IL-1β mRNA could be achieved however by exposure to bacterial endotoxin and this indeed explains why low concentrations of lipopolysaccharide induce translation of large amounts of IL-1β.[5] This observation may be relevant in the context of *H pylori* induced gastritis, for despite possessing lipopolysaccharide of relative low potency, the infection is capable of eliciting an impressive cytokine cascade with IL-1β at its centre.[6] *H pylori* infection results in a local increase in IL-1β, IL-6, and IL-2 receptor associated with high grade mucosal inflammation.[7] IL-1β in turn induces strong expression of IL-8 and the combination may explain the conspicuous recruitment, influx, and activation of neutrophils in the gastric mucosa during *H pylori* infection.[8]

Biological effects of IL-1β

Broadly speaking, the biological activities of IL-1β are targeted towards enhancing the host's inflammatory response against a variety of endogenous and exogenous stimuli. The wide spectrum of biological effects derives mainly from the ability of IL-1β to induce expression of many other genes by either initiating their transcription or stabilising their mRNA. Among these important genes are proinflammatory cytokine genes such as tumour necrosis factor α (TNF-α), IL-2, IL-6, IL-12, interferon α, β, and γ, granulocyte-colony stimulating factor and macrophage-colony stimulating factor, proinflammatory mediators such as cyclooxygenase 2, the inducible form of nitric oxide synthase, type 2 phospholipase A_2 and endothelin 1, hepatic acute phase reactants such as C reactive protein, complement C2, C3, and factor B, and growth factors such as hepatocyte growth factor and insulin-like growth factor. IL-1β also induces expression of genes for adhesion molecules such as ICAM-1, VCAM-1, and ELAM, and for some oncogenes such as *c-myc*, *c-jun*, and *c-fos*. When injected systemically, IL-1β induces fever, increased circulating nitric oxide, neutrophilia, thrombocytosis, and an increase in hepatic synthesis of acute phase reactants. Locally, IL-1β can lead to breakdown of cartilage and release of calcium from bone, it increases the release of arachidonic acid, prostanoids and eicosanoids, and it can lead to increased proliferation of fibroblasts, smooth muscle cells, and mesangial cells. These effects are thought to contribute to the healing process following damage caused by the inflammatory process.

Effects of IL-1β on gastric epithelial cells

IL-1β modulates the biological function of several gastric epithelial cell types. These include cells that produce hormonal regulators of gastric acid secretion as well as acid producing parietal cells. IL-1β has been shown to stimulate

Abbreviations used in this paper: IL, interleukin; TNF-α, tumour necrosis factor α; ECL, enterochromaffin-like; DGM, duodenal gastric metaplasia; IL-1ra, IL-1 receptor antagonist.

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gastrin release from cultured rat antral G cells.[9] Prinz *et al* showed that IL-1β can stimulate release of histamine in resting rat fundic enterochromaffin-like (ECL) cell cultures, whereas 20 minutes of preincubation of these cells with the cytokine markedly inhibited gastrin stimulated histamine secretion.[10] Mahr *et al* further showed that incubation of rat ECL cell cultures with IL-1β for 24 hours doubled the rate of apoptosis in these cells, an effect that was shown to be partially mediated by inducible nitric oxide synthase and by nitric oxide formation.[11] This modulation of the physiological function of G and ECL cells by IL-1β could explain the observed hypergastrinaemia and decreased gastric mucosal content of histamine seen in *H pylori* induced gastritis. IL-1β also has profound effects on parietal cells. Beales and Calam[12] showed that IL-1β and TNF-α inhibit acid secretion in cultured rabbit parietal cells by multiple pathways. This inhibition was shown to occur at the post-receptor level and to involve pertussis toxin and tyrosine kinase dependent and independent pathways.

IL-1β is a powerful inhibitor of gastric acid in vivo

Saperas and colleagues[13] showed that intracisternal injection of IL-1β acts centrally to induce longstanding inhibition of gastric acid secretion, and this effect requires the integrity of the prostaglandin pathways, in particular prostaglandin E2. These data suggest a possible interaction between the immune and gastrointestinal systems. The central site of IL-1β action was further defined by the same group when they showed that the cytokine acts in the medial preoptic area/anterior hypothalamus and paraventricular nucleus to inhibit acid secretion in pylorus ligated rats.[14] In yet another paper, Saperas and Tache[15] showed that IL-1β action in the CNS is mediated through interaction with specific IL-1 receptors and is selective to this cytokine. IL-1β antisecretory action could be observed under basal and pentagastrin stimulated conditions and was independent of somatostatin release in the periphery. Subsequent work by Robert *et al* has shown IL-1β to be the most potent of the known agents that are gastric cytoprotective, antiulcer, antisecretory, and an inhibitor of gastric emptying.[16] Wolfe and Nompleggi[17] estimated that on a molar basis, IL-1β is 100 times more potent than both prostaglandins and the proton pump inhibitor omeprazole and 6000 times more potent than cimetidine in inhibiting acid secretion. Yet despite its proinflammatory and acid inhibitory effects, IL-1β has been reported to reduce gastric injury produced by a wide variety of noxious stimuli, including ethanol, non-steroidal anti-inflammatory agents, cysteamine, and water immersion stress.[16 18 19] This highlights the diversity of actions of this key cytokine in defending the host against microbial pathogens while initiating a healing process that restores the integrity of the gastric mucosa.

IL-1β acts on IL-1 receptors on gastric epithelial cells

Based on their work and others, Robert and colleagues[16] suggested that IL-1 acts mostly by stimulating gastric prostaglandin synthesis. They proposed that the stomach possesses IL-1 receptors that were probably located on parietal cells, on prostaglandin producing cells, on smooth muscle cells (responsible for gastric emptying), and on as yet unidentified cells involved in gastric cytoprotection. One of the key advances in this field was the demonstration of the presence of IL-1 type I receptors on gastric epithelial cells, including parietal cells and ECL cells.[10 20] Schepp and colleagues[20] concluded that rat parietal cells express IL-1 receptors mediating inhibition of H^+ production and further speculated that the antisecretory effect of IL-1 may contribute to hypoacidity secondary to acute *H pylori* infection or during chronic colonisation by *H pylori* of the fundic gastric mucosa. This work clearly suggested that proinflammatory cytokines such as IL-1β directly influence the physiological events within the stomach and provided an insight into potential pathophysiological mechanisms that may become activated when the system is challenged by bacteria such as *H pylori*.

Two way interaction between *H pylori* infection and gastric acid secretion

There is accumulating evidence that acid secretory capacity is crucial in determining the distribution and natural history of *H pylori* infection.[21] *H pylori* infection is first established in parts of the stomach that have a higher pH, such as the antrum. High acid production by parietal cells probably protects the corpus mucosa from initial colonisation. Antral gastritis is associated with upregulation of gastrin, the acid stimulatory hormone, and downregulation of somatostatin, a universal inhibitory gastrointestinal hormone, with a net effect of increasing the drive for acid secretion. The resultant changes in the acid response are very much dependent on the state and health of the corpus mucosa and parietal cell mass. In hosts with low secretory capacity, the organism is capable of colonising a wider niche than would be possible in the presence of high volumes of acid. Colonisation of a wider niche including the corpus mucosa leads to further inhibition of acid secretion and a more aggressive gastritis that accelerates the development of gastric atrophy. Once atrophy develops, acid secretion is not only attenuated by functional inhibition caused by inflammatory mediators such as IL-1β and TNF-α, but by a more permanent morphological change that is harder to reverse. This situation is very relevant to the subgroup of humans who develop the gastric cancer phenotype in the presence of chronic *H pylori* infection. The effect of acid secretion on changing the distribution of *H pylori* colonisation and gastritis is most markedly exposed in subjects in whom acid secretion is manipulated by pharmacological means. Thus *H pylori* infected subjects on long term proton pump inhibitors undergo a shift in the pattern of gastritis from antral to corpus predominant, and they have a higher risk of developing gastric atrophy, a precursor lesion for gastric neoplasia.[22] This observation provided a clue as to the role of potential endogenous substances that could also inhibit acid secretion, such as IL-1β and TNF-α. As will be discussed later, these two cytokines were prime candidates as host genetic factors that may increase the risk of gastric cancer.

In contrast with subjects who are at risk of gastric cancer, subjects who develop duodenal ulcer disease are known to have a large parietal cell mass that is relatively free of *H pylori* induced inflammatory activity. This pattern of antral predominant gastritis with high acid output characterises the duodenal ulcer diathesis. The high acid output is associated with the development of duodenal gastric metaplasia (DGM), a protective mechanism against the persistent delivery of an increased acid load to the duodenum. The presence of gastric epithelium (DGM) in the duodenum is an invitation for antral *H pylori* infection to colonise this new niche. The ensuing gastritis with the production of proinflammatory cytokines such as IL-1β and TNF-α, greatly weakens the resistance of this mucosa, and in the presence of large volumes of acid and a reduction in duodenal mucosal bicarbonate production,[23] ulcers develop.

IL-1β, *H pylori* infection, and inhibition of gastric acid secretion

It is clear from the above that IL-1β has biological effects that qualify it as arguably the most important cytokine in

the gastrointestinal tract. Its proinflammatory properties contribute to the defence against pathogens, its antisecretory and cytoprotective effects contribute to the healing process following challenge to the integrity of the mucosa, and its acid inhibitory effects may have a profound effect on the natural history of *H pylori* infection. One of the most direct pieces of evidence of the role of IL-1β in mediating *H pylori* induced acid hyposecretion comes from an excellent paper by Takashima *et al* in this issue of *Gut*.[24] Utilising the Mongolian gerbil model of *H pylori* infection, they showed that oral inoculation of *H pylori* led to increased gastric inflammation and gastrin levels while gastric acid output was significantly decreased six and 12 weeks after inoculation. This decreased acid secretion was accompanied by elevation of IL-1β mRNA levels in the gastric mucosa. Following injection of recombinant human IL-1 receptor antagonist (IL-1ra), both serum gastrin and acid output returned to control levels. IL-1ra is the naturally occurring antagonist for both IL-1α and IL-1β and acts to attenuate their proinflammatory effects. It competes for the same receptor as IL-1α and IL-1β but occupancy of the receptor does not lead to signal transduction. The authors conclude that IL-1β induced by *H pylori* infection is the mediator of gastric acid inhibition. Another very interesting observation in the study by Takashima *et al* is the finding that the Mongolian gerbil has a low basal acid output (1/15th of that in rats). This characteristic, which is presumably determined by genetic factors, may explain why Mongolian gerbils do not develop duodenal ulcers when chronically colonised by *H pylori* infection. In contrast, gerbils have been found to develop corpus atrophy, intestinal metaplasia, and are particularly prone to developing gastric cancer.[25] This is the exact phenotype seen in human subjects who are at increased risk of gastric cancer.[2 26]

Role of IL-1β in peptic ulcer disease

IL-1β is also relevant to the pathogenesis of peptic ulcer disease. In this issue of *Gut*, Watanabe and colleagues[27] attempt to define the role of IL-1β and gastric acid secretion in gastric ulcer recurrence. They used an established rat model in which antral ulcers, induced by submucosal injection of 20% acetic acid, are known to recur on intraperitoneal injection of IL-1β. They found that 24 hours following IL-1β injection, expression of adhesion molecules and concentrations of IL-1β and TNF-α in scar tissue had increased. In nine of 11 rats treated with IL-1β, ulcers recurred while none of nine rats that also received omeprazole developed recurrence. Hydrochloric acid abolished the inhibitory effects of omeprazole but acid alone did not affect expression of adhesion molecules or cytokine concentrations, and did not cause ulcer recurrence. The key conclusion of this elegant work is that for ulcers to recur (or indeed occur), both a proinflammatory cytokine and gastric acid are essential. Although their model did not involve *H pylori* infection, it is reasonable to assume that in the human model, the stimulus for IL-1β production is infection. While the work of Watanabe *et al* focussed on gastric ulcer recurrence, it reminds us of the central role of gastric acid and IL-1β (and its associated inflammation) in the pathogenesis of peptic ulcers generally. Based on this work and that of many others, we now have a better understanding of why ulcers heal if there is adequate suppression of acid secretion despite the continuing presence of *H pylori* infection, and why they so readily recur if this acid suppression is relaxed. Equally, it explains why it is unusual for ulcers to develop in the absence of *H pylori* infection unless there is another cause of mucosal injury such as non-steroidal anti-inflammatory therapy. Finally, it is easier to understand why eradication of *H pylori* infection leads to permanent cure of ulcer diathesis as removal of the bacteria leads to downregulation of the proinflammatory cytokines such as IL-1β and reversal of the hormonal abnormalities that cause acid hypersecretion.[1]

Genetic polymorphisms in the IL-1 gene cluster increase the risk of gastric cancer and its precursors

The key question in *H pylori* research is how this infection could be associated with such divergent clinical outcomes as gastric cancer and duodenal ulcer disease. A large volume of research has focussed on the role of bacterial virulence factors in the pathogenesis of these diseases and although these factors undoubtedly contribute to the degree of tissue damage, they do not distinguish between the two key outcomes.[28] This prompted us to concentrate on the host genetic factors that may be relevant to this process. The search for the appropriate candidate genes had to stem from a profound understanding of gastric physiology and how it is disrupted by *H pylori* infection. It was immediately clear to us that the IL-1β gene is the prime candidate in the context of *H pylori* related disease. It is upregulated by infection, it is profoundly proinflammatory, and it is the most powerful acid inhibitor known. Fortunately, the gene also has a number of functionally relevant polymorphisms that could be correlated with high or low IL-1β production, setting the scene for an association study utilising a case control design. We first studied the correlation of these high IL-1β genotypes (two polymorphisms in the *IL-1B* and *IL-1RN* genes) with hypochlorhydria and gastric atrophy in a Caucasian population of gastric cancer relatives. These relatives are known to be at increased risk of developing the same cancer and have a higher prevalence of the precancerous abnormalities but only in the presence of *H pylori* infection.[26] We found that the high IL-1β genetic markers significantly increase the risk of these precancerous conditions. In a logistic regression model including both genotypes, the estimated age adjusted odds ratios for *IL-1B-511/-31T*+ and *IL-1RN***2/***2* were 7.5% (95% confidence interval (CI) 1.8–31) and 2.1% (95% CI 0.7–6.3), respectively).[29] We proceeded to examine the association between the same IL-1β genetic polymorphisms and gastric cancer itself utilising another Caucasian case control study comprising 366 gastric cancer patients and 429 population controls. We confirmed the same positive association between these genotypes and gastric cancer. In a logistic regression model including both genotypes, the estimated odds ratios for *IL-1B-511/-31T*+ and *IL-1RN***2/***2* were 1.6 (95% CI 1.2–2.2) and 2.9 (95% CI 1.9–4.4), respectively.[29]

Although IL-1β was the perfect candidate gene, other genes involved in the *H pylori* induced gastritis cascade are also legitimate targets. Our most recent search has confirmed a positive but weaker role for polymorphisms in the *TNF-A* gene that correlate with high TNF-α levels (El-Omar *et al*, unpublished data). The TNF-α polymorphism increases the risk of gastric cancer and its precursors in a similar fashion to the IL-1β polymorphisms. This proinflammatory cytokine is also upregulated in *H pylori* infection and has acid inhibitory properties, albeit weaker than IL-1β. So it is clear that the targeted and hypothesis driven search for these host genetic factors will aid in unravelling the pathogenesis of *H pylori* related diseases.

But how do these IL-1β/TNF-α polymorphisms explain the divergent outcome to *H pylori* infection? We speculate that the effect of these polymorphisms operates early in the disease process and requires the presence of *H pylori* infection. When *H pylori* infection challenges the gastric mucosa, a vigorous inflammatory response with a high IL-1β/TNF-α component may appear to be beneficial but

it has the unfortunate effect of switching acid secretion off thus allowing the infection to extend its colonisation and damaging inflammation to the corpus mucosa, an area that is usually well protected by secretion of acid. A decreased flow of acid will also undermine attempts to flush out these toxic substances causing further damage to the mucosa. More inflammation in the corpus leads to more inhibition of acid secretion and a vicious cycle that accelerates glandular loss and onset of gastric atrophy. It is apparent that this vicious cycle ultimately succeeds in driving the infection out, but at a very high price for the host. This is amply demonstrated by the finding that *H pylori* density becomes progressively lower with progression from mild gastritis through to severe gastritis, atrophy, and intestinal metaplasia. Indeed, by the time gastric cancer develops, it is extremely hard to demonstrate any evidence of the infection. An obvious question at this juncture is why only a few subjects with these polymorphisms develop gastric cancer? Why is not everyone with such a genetic makeup at risk of this outcome? The answer lies in the polygenic and multifactorial nature of most complex human diseases. These genetic factors operate only in the presence of an infectious agent and lead to the development of an atrophic phenotype. Progression of atrophy towards cancer depends on other components of the host genetic constitution acting epistatically, as well as on dietary and other factors in the environment. For example, a high intake of fresh fruits and vegetables containing antioxidants such as vitamin C may retard progression of atrophy, while smoking and a high salt intake may accelerate it.

These proinflammatory polymorphisms therefore can distinguish between subjects who will develop the hypochlorhydric atrophic phenotype in response to *H pylori* infection and those who will manage to limit the infection to a smaller area and offer relatively better protection of their corpus function. Another valid question is whether these proinflammatory polymorphisms actually offer protection against the other extreme clinical outcome, namely, duodenal ulcers. Could it be that a low IL-1β/TNF-α response to *H pylori* infection, and a subsequently lower inhibition of acid secretion, is the determinant of the antral predominant corpus sparing gastritis pattern seen in duodenal ulcer patients? To date, no reports have been published addressing this specific question. It would be tempting to speculate that this would be the case but my gut feeling is that the large parietal cell mass frequently seen in duodenal ulcer patients is determined by other genetic factors, hitherto undescribed, that relate to parietal cell development and the endocrine receptors they express. This genetically determined capacity to secrete large volumes of gastric acid will probably neutralise any subtle contribution of a genetic polymorphism in a cytokine gene.

Conclusions and a look to the future

IL-1β is an important proinflammatory cytokine with profound effects on gastric physiology. Its acid inhibitory properties uniquely qualify it as a major player in the host's response to *H pylori* infection and the diseases associated with it. Polymorphisms in the gene for IL-1β that correlate with higher levels of this cytokine have been found to increase the risks of hypochlorhydria and gastric atrophy in response to *H pylori* infection and to increase the risk of gastric cancer itself. These host genetic factors that affect IL-1β may determine why some individuals infected with *H pylori* develop gastric cancer while others do not. Future research should focus on identifying the molecular pathways that mediate this increased risk. The search for other host genetic factors that contribute to the pathogenesis of the disease should continue, particularly in view of the wonderful new opportunities made possible by the human genome project. Gastroenterology stands to benefit most from this genetic revolution and we must train our fellows to take full advantage of it. A special effort should be directed at understanding these host genetic factors in non-Caucasian populations and in populations with high and low incidences of gastric cancer. We should also target other upper gastrointestinal diseases that may be linked indirectly to these genetic polymorphisms that alter gastric physiology. Prime among these are oesophageal cancers and gastro-oesophageal reflux disease.

While *H pylori* infection is primarily a gastric disease that some may think has run its course, it is nevertheless a superb model of gene-environment interactions. It holds the key to understanding more sophisticated gastrointestinal diseases such as inflammatory bowel disease and colorectal cancer. We should not give up on it now simply because we can cure it and its associated ulcers. The challenge is to transfer the knowledge acquired in understanding it to the next frontier in gastroenterology. Our specialty has never been more exciting!

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