Commentary

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“Déjà vu all over again”

(Yogi Berra)

A quick examination of the history of scientific discovery related to microbial pathogenesis confirms that scientists follow a predictable pattern of investigation. Typically, key virulence factors are identified and vaccines or therapies are designed to neutralise them. The characterisation of cholera toxin serves as an example of the potential benefits of being able to identify a single molecular entity that contributes to so much of humanity’s suffering. The understanding of the biological function of this molecule has yielded important insights into cell signalling, cytokine networks and mucosal immune regulation. Yamaoka and colleagues, in this issue (see page 442) have applied this time honoured approach in their studies of potential virulence factors associated with Helicobacter pylori. They show that isolates of *H pylori* bearing the *cagA* gene higher levels of cytokines and inflammation in the gastric mucosa than *cagA*– strains.

Studies to define virulence factors of *H pylori* included the work of Leunk and colleagues who showed that *H pylori* produced a soluble factor that induced vacuolisation of epithelial cell lines.1 Shortly thereafter, the cytotoxin associated gene (*cagA*) and the vacuolating cytotoxin gene (*vacA*) were cloned and characterised. The link between virulence factors and disease was supported by Crabtree *et al* who astutely observed that a disproportionate number of patients with peptic ulceration had mucosal antibodies to a protein of approximately 120 kDa.2 This is the approximate size of the *cagA* gene product. The *cagA*+ strains were shown preferentially to induce IL-8 production by gastric epithelial cell lines.3 In addition, Peek and co-workers showed that patients infected with *cagA*+ strains of *H pylori* expressed increased levels of mRNA or protein, or both, for a variety of cytokines.4 These studies are but a portion of numerous reports documenting the increased production of interleukin (IL) 1, IL-6, IL-8, and/or tumour necrosis factor α (TNFα) in the mucosa of *H pylori* infected patients (reviewed in5 ). As most patients are infected with strains of *H pylori* that express *cagA*, one might have expected these strains to correlate with the increased levels of cytokines. Indeed, Yamaoka and colleagues have now confirmed this association.

However, the wheels began to come off the band wagon promoting *cagA* as a virulence factor when isogenic mutants lacking the *cagA* gene were shown to still be capable of stimulating IL-8 production in vitro.6 Moreover, another recent study has shown virtually no association between antibodies to cagA protein and inflammation or gastroduodenal disease.7 One development worth noting is the identification of a cluster of genes in some strains and not others.8 This cluster or “pathogenicity island” encompasses many genes including *cagA* as well as the genes that are directly responsible for IL-8 induction.9 Thus, despite the lack of any known function for *cagA* in the induction of IL-8, its genetic linkage to genes within the “pathogenicity island” make it a reasonable surrogate marker of the potential for *H pylori* to induce IL-8 in vitro. Although strains lacking this genetic cluster may still play a role in the pathogenesis of disease, the presence of a “pathogenicity island” is so striking that it seems unlikely that strains lacking all of these genes will induce as much inflammation and carry the same risk of gastroduodenal disease. However, from the practical point of view if a patient has a duodenal ulcer associated with *H pylori* infection, there is no debate about the prescribed treatment. Regardless of the expression of *cagA*, *vacA* or any other gene, the patient will receive antimicrobial treatment.

The association of certain strains of *H pylori* with an increased inflammatory response raises the possibility that gastroduodenal disease is enhanced by the host response. For example, the link between *cagA*, *picB*, IL-8 production, neutrophil accumulation, and gastroduodenal disease all point to a role for increased amounts of neutrophil mediated tissue damage.

Other studies suggested tissue damage may also be mediated by gastric lymphocytes. This notion is supported by the observation that the antibody response generated during *H pylori* infection cross-reacts with antigens on host cells.10 These autoantibodies are in the proximity of activated complement in the gastric noose suggesting that at least some of the epithelial damage is mediated by immune complex formation. In addition, freshly isolated gastric T cells produce cytokines that select for cytotoxic responses capable of damaging the gastric epithelium (Kathleen Bamford *et al*, manuscript submitted). However, these autoimmune-like lymphocyte responses have generally not been linked to *cagA* and in fact, the autoantibody response seems to be driven by *H pylori* lipopolysaccharide.11 At this time, one cannot say with certainty which host responses contribute to tissue damage nor is it clear which virulence factors may be driving these responses.

Attempts to explain microbial pathogenesis by studying one gene can also be a disservice as fashion in science often overwhelms curiosity and originality. A quick review of the investigative directions into the pathogenesis of HIV illustrates how novel scientific discoveries may be inhibited by the magnetism of a trendy area of research. For several years, the binding of viral gp 120 to CD4 on host cells was perceived as being responsible for governing invasion. However, recent studies have shown that some chemokine receptors on host cell surfaces play an important role in virus entry.12 This confusion emerged from investigations of a pathogen with a mere handful of genes that have been studied at huge expense. One can only wonder how the hundreds of gene products expressed by *H pylori* can be understood with a more modest international research effort.

With the recent cloning of the entire *H pylori* genome, several hundred genes have been identified including the subset associated with the “pathogenicity island”. It will take substantial effort to dissect out which ones code for products that promote gastroduodenal disease and how the
pathogenesis of these diseases is linked to the virulence factors. We all eagerly await the outcome of innovative studies that examine other gene products that may better explain the vagaries of the host response to this infection.

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood and I –
I took the one less traveled by
And that has made all the difference

Robert Frost, “The Road Not Taken”

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