Host susceptibility of *H. pylori*-related gastrointestinal disorders

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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 cancer. The key determinants of these outcomes are the severity and distribution of the *H. pylori*-induced gastritis. Cancer occurs in a gastric milieu characterised by severe inflammation, hypochlorhydria and atrophy, all of which precede malignant transformation by decades. Host genetic factors are emerging as key determinants of disease risk for many cancers. Identifying candidate genes is a major challenge that has to stem from a profound understanding of the pathophysiology of the disease. In the case of *H. pylori*-induced gastric cancer, we speculated that the candidate genes would influence both gastric physiology and the inflammatory response to the infection. We initially targeted the pro-inflammatory cytokines interleukin-1β (IL-1β) and tumour necrosis factor-α (TNFα), both of which are inhibitors of acid secretion and key mediators of the host's response to the infection. We reported that pro-inflammatory polymorphisms in the *IL-1* gene cluster and the TNF-α gene (*TNF-A*) increase the risk of gastric cancer and its precursors in Caucasian populations. Our findings have since been expanded to include other candidate genes such as *IL-10*, and confirmed independently in other Caucasian and non-Caucasian populations. More recently, we have shown that genetic polymorphisms of the innate immune response genes such as *TLR4* and mannose binding lectin are also risk factors for gastric cancer and its precursors. The pro-inflammatory genetic constitution seems to increase the risk of non-cardia gastric cancer while protecting against gastro-oesophageal disease. In summary, infected subjects with a pro-inflammatory host genetic makeup have an increased risk of developing severe gastritis, progressive gastric atrophy, hypochlorhydria and finally gastric cancer. Other gene-environment interactions clearly influence the rate of progression of these lesions and the ultimate malignant transformation.