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ScienceDirect
Digestive and Liver Disease 40 (2008) 504–509
Digestive and Liver Disease
www.elsevier.com/locate/dld

Mini-Symposium

Helicobacter pylori infection and the pathogenesis of gastric cancer: A paradigm for host–bacterial interactions

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Received 14 February 2008; accepted 18 February 2008

Abstract

Helicobacter pylori infection is the most important acquired risk factor for gastric cancer. The infection initiates a chronic inflammatory process that eventually alters the physiology of the gastric environment and leads to achlorohydria. Gastric atrophy may be part of this process but cancer can arise without this precursor. The net effect of decades of inflammation is the establishment of a milieu awash with pro-inflammatory cytokines and characterized by the activation of signalling pathways that cross-talk between inflammation and carcinogenesis. Many of the factors involved in chronic inflammation play a dual role in the process—promoting neoplastic progression but also facilitating cancer prevention. *H. pylori* bacterial virulence factors as well as host genetic factors play a major role in orchestrating the increased risk of cancer. The study of such host–bacterial interaction is key to uncovering the molecular and cellular pathways involved and will ultimately lead to developing preventive and therapeutic strategies against this global killer.

1. Introduction

There is little doubt that *Helicobacter pylori* infection is a major factor in the pathogenesis of distal, non-cardia, gastric cancer. Since 1994, when the International Agency for Research on Cancer classified *H. pylori* as a Group 1 (definite) human carcinogen, a substantial body of evidence has been published confirming this association [1]. The possible long-term sequelae of infection, for a given individual, are diverse and there are still few markers of potential subsequent cancer formation. Indeed, the majority of infected people do not suffer significant deleterious effects. Gastritis, peptic ulcer disease and gastric cancer are all recognised outcomes. There are data suggesting that the infection may even have beneficial effects by preventing other conditions such as gastro-oesophageal reflux and its complications, although this is hotly debated. The focus of research has therefore moved from establishing the effects of infection to determining the mechanisms involved. A better understanding of these mechanisms would enable medical practitioners to move towards individual estimates of risk, or more likely, allow identification of an at risk population for gastric cancer and enable timely intervention.

The basic process that mediates *H. pylori*-induced damage is gastritis with its associated humoral and cell-mediated immune mechanisms. It is now clear that the extent and distribution of this gastritis ultimately determine the clinical outcome. Three main gastric phenotypes have been identified and each is associated with a set of pathophysiologic abnormalities that could explain why a certain outcome occurs [2]. The commonest phenotype by far, which could be termed the "simple or benign gastritis" phenotype, is characterized by mild pangastritis with little disruption of gastric acid secretion. This phenotype is commonly seen in subjects who are asymptomatic and who on the whole develop no serious GI disease. The second phenotype is the so-called duodenal ulcer phenotype and accounts for up to 15% of infected subjects, particularly in western countries where peptic ulcers were common. This phenotype is characterized by an

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doi:10.1016/j.dld.2008.02.031

antral-predominant pattern of gastritis with relative sparing of the acid producing corpus mucosa. Subjects with this phenotype have high antral-inflammatory scores, high gastrin, relatively healthy corpus mucosa and very high acid output [3]. These subjects also have defective inhibitory control of gastric acid secretion. This combination of pathophysiologic abnormalities contributes to the development of peptic ulcers, particularly duodenal and a large proportion of prepyloric ulcers. The third and most serious phenotype is the "gastric cancer phenotype", which is characterized by a corpus-predominant pattern of gastritis, multi-focal gastric atrophy, and hypo or achlorhydria [4]. The multi-step changes in the mucosa associated with carcinogenesis, which are now an accepted paradigm, were first described by Correa [5]. The presence of significant gastric atrophy and complete intestinal metaplasia with achlorhydria appears to be a key step in this pathway. Recent research has rapidly increased our understanding of the cellular mechanisms involved; in particular, it has highlighted the role of chronic sustained inflammation, the deleterious effects of an imbalance in epithelial cell kinetics and the pivotal role of bacterial virulence factors and the genetically mediated host response. These abnormalities develop as a direct result of the chronic inflammation induced by the infection and increase the risk of gastric cancer. The gastric cancer phenotype is particularly prevalent in certain parts of Asia, where this cancer is common [6]. Physiologically, the phenotype is characterized by low acid secretion, high gastrin and a low pepsinogen I and pepsinogen I/II ratio.

H. pylori infection can therefore lead to several divergent clinical outcomes. Explaining this apparent paradox is essential for understanding the pathogenesis of *H. pylori*-related disease in general and gastric cancer in particular. The last two decades have seen major advances in unraveling the contribution of bacterial virulence factors, environmental exposures and host genetic factors in the pathogenesis of *H. pylori*-induced diseases. In the following sections, we discuss the role of bacterial virulence and host genetic factors in the pathogenesis of *H. pylori*-induced gastric cancer.

2. Role of *H. pylori* virulence factors

H. pylori are specifically adapted to colonise and survive in the hostile acidic gastric environment [2]. Several factors including the urease enzyme and urea transport protein are key to maintaining a neutral pH micro-environment and survival of the organism [7,8]. Additional well-described virulence factors include the cytotoxin-associated gene A antigen (CagA), vacuolating cytotoxin (VacA), blood group antigen-binding adhesion (BabA), outer inflammatory protein (OipA) and IceA.

The 120–130 KDa protein CagA, encoded by the *cag*A gene, located on the 40 kb pathogenicity island (cag-PAI), interacts directly with host epithelial cells. A specific Type IV transporter delivers CagA, and other bacterial proteins into the epithelial cell cytoplasam. CagA induces epithelial cell proliferation and division after tyrosine phosphorylation and binding with the Src homology 2 (SH-2) domain, by activation of nuclear factor kappa B (NF-kB) and secretion of interleukin 8 (IL 8). A negative feedback system, whereby 20% of tyrosine phosphorylated CagA binds a carboxyl-terminal Src kinase (Csk) and activates Csk rather than Src family kinases, promotes persistence of infection and chronic inflammation. Additional reported effects of the Cag-PAI encoded proteins include rearrangement of the actin cytoskeleton, inhibition of apoptosis, epithelial cell DNA damage, activation of transcription factor AP-1, increased expression of the proto-oncogenes *c-fos* and *jun* and increased expression of Prostaglandin E2 [9,10–13]. The presence or extent of the complete cag-PAI present in a given strain is a major determinant of bacterial pathogenicity. CagA positive strains are associated with severe inflammation, peptic ulceration, gastric atrophy and non-cardia gastric cancer [14]. There are two distinct types of CagA described, the so-called Western and East Asian [15]. Identified polymorphisms in cagA, tyrosine phosphorylation sites, give East Asian forms a higher binding affinity for SHP-2, than western CagA varieties. The increased binding affinity has been associated with more severe and active gastritis, gastric atrophy and has been linked to gastric cancer [16].

Vacuolating cytotoxin A encoded by the vacA gene induces vacuole formation in gastric epithelial cells and stimulates apoptosis. VacA enables organic anions to enter the cell by attaching to cell membranes and acting as a voltage dependant channel. Inducing apoptosis results in a complimentary increase in cellular proliferation a key element of *H. pylori* induced gastritis. Additional reported effects of VacA include disruption of the cytoskeletal architecture, through gene modifications, damage to cell-cycle related genes and induction of the inflammatory response [17,18]. Unlike cagA, the vacA gene is present in all *H. pylori* strains, but functional expression is variable. Variations within the vacA gene have been identified, which affect expression.

The effects of other virulence factors remain less clear. BabA, an outer membrane protein is important in enabling *H. pylori* to attach and adhere to gastric epithelial cells by means of Lewis B blood group antigens [19]. Strains expressing BabA are thought to induce more severe disease. Epithelial contact induces the expression of iceA. There is evidence in other bacterial species that the iceA1 subtype acts as a restriction endonuclease. Its expression has been linked with peptic ulcer disease [20]. The outer inflammatory protein OipA, in conjunction with the cag-PAI affect gastric mucosal interleukin 8 (IL-8) levels. IL-8 is a powerful chemotactic and activating factor for neutrophils. The presence of both cagA-PAI and OipA are required to fully activate the IL-8 promoter region. Both appear to act via distinct pathways, but result in activation of the interferon regulatory factor (IRF)-1 [21,22].

Virulence factors are very important determinants of outcome in *H. pylori* infection. A better understanding of their modes of action, their interactions and genetic variations can help to identify at risk groups for gastric cancer [23,24]. Fur-