Helicobacter pylori-epithelial cell interactions: From adhesion to apoptosis

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NL Jones, PM Sherman. *Helicobacter pylori*-epithelial cell interactions: From adhesion to apoptosis. Can J Gastroenterol 1999;13(7):563-566. Studies suggest that host cell signal transduction cascades are manipulated during infection with microbes, including the gastric pathogen *Helicobacter pylori*. Several putative adhesins have been proposed to mediate the attachment of *H pylori* to gastric epithelial cells. Following bacterial binding, a series of signalling pathways are activated in the infected gastric epithelial cell. These signals include both cytoplasmic (such as vacuolization, tyrosine phosphorylation and elevation of cytosolic calcium) and nuclear (proliferation, apoptosis and chemokine transcription) events. Research aimed at elucidating the interactions that occur between the host cell and the bacterium during infection should improve the limited knowledge of disease pathogenesis.

Key Words: *Adhesion; Apoptosis;* Helicobacter pylori*; Signal transduction; Vacuolation*

Les interactions entre les cellules épithéliales et *Helicobacter pylori* : de l'adhésion à l'apoptose

RÉSUMÉ : Des études laissent à penser que les cascades du signal de transduction de la cellule hôte sont manipulées pendant une infection par des microbes, y compris le pathogène gastrique *Helicobacter pylori*. Plusieurs mécanismes putatifs d'adhésion ont été proposés pour médier l'adhésion de *H. pylori* aux cellules épithéliales gastriques. À la suite de l'adhésion bactérienne, une série de voies de signalisation sont activées dans la cellule épithéliale gastrique infectée. Ces signaux comprennent à la fois des événements cytoplasmiques (tels que la vacuolisation, la phosphorylation de la tyrosine et l'augmentation du calcium cytosolique) et nucléaires (prolifération, apoptose et transcription des chimiokines). Les recherches visant à élucider les interactions qui surviennent entre la cellule hôte et la bactérie pendant une infection devraient accroître les connaissances sur la pathogénie de la maladie.

A new research field termed 'cellular microbiology' merges the disciplines of cellular biology and microbiology and is yielding important new information (1). Investigators in this discipline study the cross talk that occurs between pathogens, or their products, and the target eukaryotic cell to advance understanding of both disease pathophysiology and cell biology (2).

The consequences of the interactions between the gastric pathogen *Helicobacter pylori* and epithelial cells during infection of humans include a manipulation of host cell signalling that is likely to play a role in disease pathogenesis. Following adhesion, cytoplasmic signal transduction pathways, vacuolar trafficking and nuclear signalling events are exploited by the bacterium. In addition to enhancing our knowledge of how bacterial pathogens interact with host cells to mediate disease, the investigation of these virulence factors provides novel tools to study aspects of cellular biology.

MICROBIAL ADHESION AND THE INDUCTION OF EUKARYOTIC CELL SIGNAL TRANSDUCTION PATHWAYS

H pylori exhibits tropism for gastric epithelial cells (3). During infection, the bacteria binds specifically to gastric epithelial cells lining the stomach or in areas of gastric metaplasia. The underlying mechanisms responsible for this tissue tropism remain unclear but likely are related to specific bacterial adhesins. The precise adhesin(s) responsible for *H pylori* binding to gastric epithelial cells are unknown. However, a number of putative attachment factors for the organism have been investigated and are discussed (Table 1).

A role for microenvironmental pH in the modification of bacterial binding has been suggested. Huesca et al (4) demonstrated that a brief period of acid shock altered *H pylori* binding specificity with an increase in bacterial adherence to sulfogalactosyl ceramide as assessed by using thin-layer chromatography overlay. This effect was abro-

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TABLE 1
Putative adhesins of *Helicobacter pylori*

Adhesin	Reference
Flagellin	3
Lipopolysaccharide	50
Exoenzyme H	51
Heat shock proteins	4
Urease	6,7
Hemagglutinins	52
BabA (Le^b binding adhesin)	10
Outer membrane proteins	12

gated by incubation with inhibitors of protein synthesis or antiheat shock protein antibodies, suggesting a possible role of heat shock proteins in mediating adhesion. In support of a role for pH in altering adherence in vitro, Corthesy-Theulaz et al (5) identified an increase in *H pylori* binding to the intestinal T84 cell line at pH 5.4 compared with pH 7.4.

Although urease previously was proposed to mediate bacterial attachment (6), more recent studies suggest that this surface-exposed enzyme does not play a role in the adhesion of *H pylori* to gastric epithelia. Comparison of binding between an isogenic urease-negative mutant and the parent strain to either primary gastric epithelial cells or a gastric epithelial cell line in vitro showed no demonstrable difference (7). Similarly, a lack of correlation between the expression of hemagglutinins and *H pylori* binding in vitro suggests that hemagglutinins do not play a major role in adherence (8).

In situ studies suggest that the fucosylated blood group antigen Lewis b mediates binding of *H pylori* to gastric epithelial cells (9). The putative *H pylori* adhesin, which binds to the Lewis b blood group antigen, has been identified. Using a receptor activity-directed affinity tagging method, Ilver et al (10) purified and cloned blood group antigen-binding adhesin (BabA). The presence of the Le^b binding phenotype was associated with the presence of the *cag* pathogenicity island. The possible role of the pathogenicity island in regulating binding to Le^b is unclear because deletion of the entire pathogenicity island did not reduce binding to the Le^b antigen in vitro. The importance of Le^b as a receptor for *H pylori* has recently been questioned because in vitro studies demonstrate that adhesion of *H pylori* to isolated human gastric epithelial cells is independent of the expression of Lewis antigens (11).

Although the precise factors mediating *H pylori* adherence are unclear, it is likely that multiple adhesins are involved. The recent sequencing of the entire genome of one *H pylori* strain allowed the identification of the presence of a large proportion of outer membrane proteins and lipoproteins, which may serve as putative adhesins (12). It is also possible that the outer membrane proteins are involved in antigenic variation, leading to immune evasion and persistence of infection by the bacterium (13).

In addition to allowing binding to specific receptors on host gastric epithelial cells, adhesins can mediate a cascade of signals within the eukaryotic cell. Following intimate adherence of *H pylori* to epithelial cells in vitro, there is an elevation in the second messenger inositol trisphosphate (IP3) (14,15). It is uncertain whether bacterial adherence is necessary for activation of this signal transduction pathway because poorly adherent or nonadherent strains also generate IP3 production in infected epithelial cells (15).

The activation of IP3 signalling is similar to the cascade of events associated with infection with the gastrointestinal pathogen enteropathogenic *Escherichia coli* (EPEC) (14). EPEC infection of eukaryotic cells induces the elevation of inositol phosphate, calcium flux and tyrosine phosphorylation of a 90 kDa protein in association with rearrangements of the cytoskeleton underneath the adherent bacteria (known as the attaching and effacing lesion) (16). However, it remains controversial whether tyrosine phosphorylation of host proteins and alteration of the cytoskeleton to form the attaching and effacing lesion occur during *H pylori* infection. Smoot et al (17) and Segal et al (18) identified F-actin accumulation and pedestal formation in gastric epithelial cells infected with *H pylori* in association with tyrosine phosphorylation of two host proteins differing in size from the 90 kDa phosphorylated protein during EPEC infection. Isogenic mutants generated in the *cag* pathogenicity island abrogated host cell phosphorylation (19). In contrast, Dytoc et al (14) and Pucciarelli et al (15) observed the effacement of microvilli in infected epithelial cells in the absence of redistribution of host cell cytoskeletal elements.

The significance of bacterial adhesion in mediating disease was recently demonstrated in a murine model (20). *H pylori*-infected transgenic mice genetically engineered to express the putative receptor Le^b in the gastric pit and mucous cells showed an altered pattern of bacterial adhesion and disease manifestations compared with normal littermates. Both groups of mice displayed an equivalent degree of colonization. However, bacteria bound to the mucous layer in normal mice, whereas bacteria adhered to both the mucous layer and the pit, and surface epithelial cells of Le^b-expressing mice. A higher proportion of transgenic mice developed more severe gastritis with the presence of mucosal-associated lymphoid tissue (53% versus 20%, $P<0.05$). In addition, parietal cell autoantibodies were detected more frequently in the transgenic mice (87% versus 26%) at 16 weeks after infection. The presence of autoantibodies was associated with more pronounced reactive atypia and parietal cell loss. Although the factors involved in adhesion-mediated injury have yet to be determined, these studies highlight the importance of bacterial binding in disease pathogenesis.

VACUOLATING CYTOTOXIN-STIMULATED SIGNAL TRANSDUCTION

Approximately half of all *H pylori* strains produce a cytotoxin, referred to as VacA, which induces the vacuolation of epithelial cells in vitro (21). Recent evidence suggests that allelic variation of *vacA* determines the cytotoxin-producing phenotype of a given strain (22). The gene encoding the vacuolating cytotoxin (*vacA*) is present in all *H pylori* strains

outside the *cag* pathogenicity island. However, only strains with the s1, m1 alleles express toxin protein (22).

Elegant studies using VacA as a probe are defining the cellular mechanisms involved in cytotoxin-mediated vacuolation. Papini et al (23) identified markers of the late endosomal compartments, including the vacuolar-ATPase and the GTPase rab7 on the vacuolar membranes. In addition, cells overexpressing activated rab7 stimulate vacuole formation when exposed to VacA (24). In contrast, vacuole formation is inhibited in cells expressing a dominant negative mutant rab7. These findings indicate that the toxin-induced disruption in endocytic trafficking occurs at a late stage and is mediated by rab7.

Lysosomal markers have also been identified on the vacuolar membranes (25), suggesting that the vacuoles are comprised of a mixed endosomal-lysosomal compartment. In support of this contention, processing and sorting of proteins normally targeted to the lysosome are altered by VacA (26). A recent study suggests that one possible sequelae of VacA-altered organellar trafficking includes the interruption of the li-dependent pathway of antigen presentation by newly synthesized major histocompatibility complex (MHC) class II molecules (27).

In addition to vacuole formation, the toxin stimulates host cell signal transduction pathways in vitro, including stimulation of inositol phosphates and cytosolic free calcium (28). Increases in adenosine 3′5′-cyclic monophosphate in association with phosphorylation of 31 kDa and 22 kDa proteins are present following eukaryotic cell exposure to VacA (28).

H PYLORI-MEDIATED NUCLEAR SIGNALLING AND APOPTOSIS

H pylori infection of gastric epithelial cell lines causes activation and nuclear translocation of the transcription factor nuclear factor-kappaB (NF-κB) that results in increased transcription of chemokines, including interleukin-8 (IL-8) (29,30). Studies of *H pylori*-infected human gastric biopsy specimens confirm both an enhanced IL-8 production (31) and activation of NF-κB (29). Using transfection experiments with reporter gene constructs, Aihara et al (30) demonstrated that NF-κB and activator protein-1 binding to the IL-8 promotor region both upregulate production of IL-8 (30). Recent studies suggest that direct bacterial contact is needed to induce gastric epithelial cell IL-8 secretion (32). Mutational analysis provides evidence for a role of picB (named for 'promote the induction of cytokines', also known as cagE) in mediating IL-8 secretion (33,34). It is unclear whether picB directly upregulates IL-8 or is involved in the export or secretion of another activator.

In addition to NF-κB activation, *H pylori* infection alters the gastric epithelial cell cycle, enhancing both proliferation and programmed cell death of gastric epithelial cells (35,36). These changes in cell turnover are identified in both *H pylori*-infected children (Table 2) (37) and adults (38). Studies have identified enhanced expression of the tumour suppressor *p53* during *H pylori* infection both in vitro (39) and in vivo (37). Enhanced expression of the proapoptotic protein Bak is also seen during *H pylori* infection (40). These studies suggest that *H pylori* may activate the apoptotic pathway by more than one mechanism.

TABLE 2
Cell cycle alterations during *H pylori* infection in children

	Control	*H pylori*-negative gastritis	*H pylori*-positive gastritis	P
Apoptotic index	40±10	50±10	120±10	<0.005
Proliferative index	13.7±3.1	18.9±2.8	32.4±3.5	<0.01
p53 expression	3.7±0.9	2.4±0.9	19.9±3.7	<0.005

Results are expressed as means ± SE. Data from reference 37

In vitro experiments indicate that the bacterium can directly induce apoptosis (41,42) and that bacterial-epithelial cell contact is required (40). The exact bacterial factors involved are an area of intense investigation. Fan et al (43) reported that bacterial binding to gastric epithelial cells that express MHC class II is capable of inducing apoptosis. Studies in *H pylori*-infected adults suggest that the presence of infection with a CagA-positive strain is associated with an enhanced proliferative rate of gastric epithelial cells in the absence of an accompanying increase in apoptosis (44). In vitro studies provide conflicting results regarding the role of CagA in abrogating apoptosis (45).

In addition to a direct effect of the bacterium, recent studies implicate a role of immune-mediated apoptosis of gastric epithelial cells. Among *H pylori*-infected children, gastric epithelial cell apoptosis returned to baseline only following both eradication of the bacterium and resolution of gastritis (37). One mechanism by which immune cells trigger apoptosis of target cells occurs through binding of the Fas receptor to the Fas ligand (46). In vitro experiments suggest that Fas receptor expression is upregulated on gastric epithelial cells during *H pylori* infection (41). In addition, Rudi et al (47) detected an increase in Fas receptor-expressing gastric epithelial cells and Fas ligand-expressing infiltrating cells in gastric biopsy specimens obtained from *H pylori*-infected adults.

In vivo studies using animal models of helicobacter infection should clarify the factors involved in the observed alterations in cell turnover in infected humans. For instance, in a recent study of three inbred mouse strains (BALB/c, C3H/HeJ and C57BL/6), *Helicobacter felis* infection increased gastric cell apoptosis only in the C57BL/6 strain (48). The authors suggested that one explanation for the observed findings is a lack of secretory phospholipase A_2 (recently indentified as the locus responsible for influencing polyposis in the Min mouse (49) in the C57BL/6 strain.

CONCLUSIONS

Evidence suggests that *H pylori* can be included among the growing list of microbes that alter host signal transduction cascades during infection. The studies summarized in this review document that the bacterium, and its products, mediate both cytoplasmic and nuclear signalling events. Investiga-

tion of the interactions between the bacterium and the host cell should elucidate the mechanisms involved in disease pathogenesis.

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