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SUPPLEMENT ARTICLE

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Review: Pathogenesis of *Helicobacter pylori* infection

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Abstract

In this review, we shall focus on the last year progression understanding the pathogenesis of *Helicobacter pylori* infection in the light of recent data related to adaptation of *H pylori* to the harsh acidic environment in the stomach, colonization of gastric mucosa via interaction with mucin 5 (MUC5AC) and other host cell receptors, the ability to form biofilm, interference with the host metabolic pathways, and induction of neuroimmune cross-talk as well as downregulation of gastric barrier homeostasis and its consequences for the disease development. The role of the membrane vesicles of these bacteria has been emphasized as an important source of virulence factors. Furthermore, we shall describe molecular and functional studies on new aspects of VacA and CagA virulence, including the role of urease in the upregulation of VacA toxicity, an epithelial-mesenchymal transition mediated by CagA, and the role of interaction of HopQ adhesin with carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) in CagA translocation into the host cells by the type IV secretion system (T4SS). The role of molecular mimicry between a common sequence (ATVLA) of *H pylori* heat shock protein (Hsp) B and human Hsp60 in the induction of potentially autoreactive antibodies is discussed. All these new data illustrate further progress in understanding *H pylori* pathogenicity and facilitate the search for new therapeutic targets as well as development of immunoprophylaxis methods based on new chimeric UreB and HpA proteins.

KEYWORDS
acidic environment, CagA, colonization, membrane vesicles, molecular mimicry, urease, VacA, virulence factors

1 | GASTRIC TISSUE COLONIZATION AND CHRONIC INFECTION

1.1 | Response to the harsh environment in the stomach

Jones and Zamble showed the effects of a drop in cytosolic pH on *H pylori*, exposed to external pH 2.0 mimicking the conditions in human stomach; it resulted in a nickel-responsive transcription factor (HpNikR)-dependent activation of *ure*A gene transcription illustrating the mechanism of adaptation of these bacteria to the harsh acidic environment.[1] These data allow to link acid adaptation of *H pylori* and nickel homeostasis.

Helicobacter pylori-induced reduction of mucosal bicarbonate secretion, which protects the gastric barrier against acid-induced mucosal injury, was suggested to play a role in duodenal ulcer development.[2] *Helicobacter pylori* downregulates the expression of two transporters of cellular bicarbonate in the duodenal epithelium: (a) the cystic fibrosis transmembrane conductance regulator (CFTR) and (b) the solute linked carrier 26 gene family A6 (ALC26A6), through the transforming growth factor beta (TGFβ)-mediated p38 mitogen-activated protein kinase (MAPK) signaling pathway.[2]

In a comparative transcriptomic analysis performed by Hathroubi et al, 8% of the genes studied were found to be differentially expressed between *H pylori* biofilm and planktonic cells. The genes downregulated in biofilm were involved in metabolism and translation, whereas the biofilm upregulated genes encoded the envelope proteins involved in stress response and construction of flagella.[3] The persistence of *H pylori* in the stomach is potentially promoted by this biofilm formation.

1.2 | *Helicobacter pylori* colonization and disruption of the gastric barrier

Helicobacter pylori colonization of the gastric mucosa is mediated by surface adhesins, which preferentially interact with mucin 5 (MUC5AC) and Lewis (Le) determinants. The elevated production of MUC5AC in response to *H pylori* infection could be considered as a potential mechanism facilitating bacterial adherence. Recently, by using the animal model of *Caviae porcellus* (guinea pigs), it was revealed that during *H pylori* infection the production of MUC5AC and deposition of Le^X and Le^Y determinants in the gastric mucosa were upregulated.[4] These phenomena were confirmed in vitro in cell cultures of guinea pig primary gastric epithelial cells co-cultured with the following *H pylori* components: the antigenic complex obtained by glycine acid extraction (GE), recombinant proteins such as the CagA protein, and the subunit A of urease (UreA) or lipopolysaccharide (LPS).[5] The elevated production of MUC5AC and Le deposition correlated with an increased adherence of *H pylori* to the gastric epithelial cells. Le^X/Le^Y determinants that were also present in *H pylori* LPS facilitated colonization.[4] Furthermore, Sáenz et al[5] showed that through interaction of the sialic acid binding adhesin (SabA) with sialyl-$Lewis^X$, *H pylori* penetrated deeply into spasmolytic polypeptide-expressing metaplasia (SPEM) glands induced by a high dose of tamoxifen in mice infected with the *H pylori* PMSS1 strain.

One study confirmed the role of the transferrin receptor (TFRC) in *H pylori* attachment to gastric epithelial cells, which facilitates iron capture.[6] In the same study, an overexpression of ferritin light chain (FTL) in the gastric mucosa of *H pylori*-infected patients was found to be important for the differentiation of epithelial cells into intestinal metaplasia.[6]

Zhu et al[7] analyzed the role of the aryl hydrocarbon receptor (AHR) and its suppressor (AHRR) in *H pylori* pathogenesis. For this purpose, gastric tissue specimens from *H pylori*-infected patients with gastritis or adenocarcinoma, and gastric tissue from mice were inoculated with *H pylori* during an experimental infection. In parallel, cell cultures co-cultured with *H pylori* in vitro were evaluated by immunochemistry and siRNA silencing for AHR and AHRR. The study showed that AHR and AHRR expression was negatively correlated with exposure of gastric cells to *H pylori* both in vitro and in vivo. Silencing of AHR and AHRR genes resulted in an increased production of proinflammatory cytokines, including interleukin (IL)-8, IL1-β, and tumor necrosis factor (TNF)-α, indicating that AHR and AHRR may play a role in antibacterial response and potentially in *H pylori*-related gastric disorders.[7]

Sticlaru et al[8] investigated whether chronic *H pylori* infection modulates the gastric level of neuropeptides: substance P (SP) and vasoactive intestinal peptide (VIP), in relation to the degree of bacterial colonization and the severity of inflammatory response. This study showed that both SP and VIP levels were elevated in the gastric tissue of infected individuals. Increased levels of these neuropeptides did not correlate with the degree of bacterial colonization and the severity of inflammation nor with the bacterial load; however, the SP neuronal level and myenteric ganglionitis correlated with the intensity of T-lymphocyte infiltration.[8]

Harmful conditions in the stomach increase the risk of *H pylori* DNA damage. Biochemical analysis of *H pylori* apurinic/apyrimidinic (AP) endonuclease showed its DNA substrate specificity and suggested that AP plays a protective role against the genotoxic effects due to DNA damage.[9]

In general, disintegration of the gastric barrier by *H pylori* and its soluble compounds leads to the development of inflammatory response and proliferation of gastric cells to resolve homeostasis. Nevertheless, enhanced cell proliferation may increase the risk of genetic instability of cells and the development of gastric cancer. Recently, it was shown that *H pylori* promotes the invasion and metastasis of gastric cancer by enhancing the expression of heparanase (HPA), which is involved in tissue remodeling and cell migration.[10,11] The upregulation of HPA in MKN-45 human gastric cells exposed to *H pylori* was reported in relation to increased cell proliferation on mitogen-activated protein kinase (MAPK) and nuclear factor-kappa-light-chain-enhancer of activated B cell (NF-κB)-dependent signaling pathway.[10,11]

During *H pylori* infection, elimination of mutated cells and downregulation of the inflammatory response due to cell apoptosis are beneficial to the host. However, excessive loss of epithelial cells may result in gastric barrier dysfunction. Last year, the structure of *H pylori* peptidyl-prolyl cis, trans-isomerase, which induces cell apoptosis (apo-HP0175) through its interaction with toll-like receptor 4 (TLR4), was described.[12] Structural flexibility in the apo-HP0175 was achieved through an extension of the chaperone helices. Datta et al[13] reported the association of secreted antigen HP0175 with upregulation of miR-29b-1-5p, regulation of matrix metalloproteinase (MMP)-2 and 9 activity, and migration of gastric epithelial AGS cells.

2 | VIRULENCE FACTORS

2.1 | Outer membrane vesicles

Helicobacter pylori virulence factors are soluble, cell-surface-bound, or injected into the host cells via the type IV secretion system (T4SS). Recently, the central role of outer membrane vesicles (OMVs) produced by *H pylori* on the distribution of bacterial antigens was suggested. Various biologically active compounds of *H pylori*, which are present in OMVs, can be internalized into host cells, and

consequently influence signaling pathways and promote apoptosis of gastric epithelial cells as well as immunocompetent cells, and thus strengthen or downregulate the immune responses leading to disease development.[14]

By using protonography and mass spectrometry, Ronci et al[15] confirmed the presence of α-carbonic anhydrase (CA) in OMVs generated by planktonic and biofilm phenotypes of *H pylori* strains. This work suggested that CA, together with urease, may play a pivotal role in decreasing gastric juice acidity by *H pylori*.[15]

According to Turner et al,[16] the size of OMVs determines the protein content, immunogenicity, and mechanisms of entrance into the host cells, which can occur via caveolin-dependent endocytosis (OMVs 20-100 nm) or macropinocytosis and endocytosis (OMVs 90-150 nm). These findings suggest the role of OMVs in the pathogenesis of *H pylori* and the potential use of OMVs in vaccine development.

2.2 | VacA, CagA, and related virulence factors

Foegeding et al[17] tested the hypothesis that ammonium chloride (NH_4Cl) increases the toxicity of vacuolating cytotoxin A (VacA). This study showed that it did not occur by altering toxin trafficking to lysosomes or autophagosomes but by increasing the intracellular VacA stability. This study also confirmed that ammonia, which is generated by a bacterial urease during *H pylori* infection, enhances VacA toxicity.

By using histopathological examination and real-time PCR-(RT-PCR), gastric biopsy specimens from a southwestern Asian region, Saudi Arabia, were analyzed for *vac*A, *cag*A, and *ice*A genes.[18] The *vac*A subtypes: s1as1bm2, s1a1b, and s2m2, correlated with chronic gastritis in 90.0%, 8.01%, and 84.2%, respectively. Molecular characterization of the *vac*A gene in *H pylori* clinical isolates from patients with gastroduodenal diseases was also carried out in Assam, India.[19] The *vac*A signal sequence and mid-region were amplified by PCR and then sequenced for phylogenetical analysis. The most prevalent variant was s1m1 regardless of clinical outcomes of *H pylori* infection.

Liu et al[20] reported the CagA-dependent downregulation of cathepsin C (CtsC) via Src/ERK and Janus kinase (JAK) and activation of transcription 3 (STAT 3) pathways, leading to impairment of neutrophil activation and thus promoting the persistence of bacteria in the gastric mucosa.

The involvement of CagA in regulation of the Hippo tumor suppressor pathway via effector Yes-associated protein (YAP) was investigated by Li et al[21] For this purpose, gastric epithelial cells were co-cultured in vitro with *H pylori* PMSS1 *cag*A-isogenic mutant strains, wild-type *cag*A+ strains, or recombinant *cag*A. *Helicobacter pylori* recombinant *cag*A and *cag*A+ strains, but not *cag*A− mutants, promoted activation of the YAP pathway indicating an increased risk of gastric cancer in relation to *H pylori* strains producing CagA.[21] They also demonstrated that *H pylori* CagA+VacA+ strains are able to induce differentiation of fibroblasts into cells with characteristics of cancer-associated fibroblasts (CAFs), which induce epithelial-mesenchymal transition (EMT) of normal rat gastric epithelial cells. This process allows polarized epithelial cells to differentiate into a mesenchymal phenotype with enhanced migration activity and invasiveness.[22] The study by Noto et al,[23] on gerbil and human gastric epithelium models, revealed that *H pylori* $CagA^+$ strains induced gastric proteomic changes, which were correlated with upregulation of Rab/Ras signaling proteins: RABEP2 and G3BP2, and the severity of malignant lesions in vivo.

The exact mechanism of CagA translocation into the host cells by the T4SS is unclear. Recently, certain carcinoembryonic antigen-related cell adhesion molecules (CECAMs), which capture *H pylori* outer membrane adhesin HopQ, were found to participate in CagA translocation.[24] For this purpose, a CRISP/Cas9-knockout technology was applied to generate human gastric CEACAM integrin knockout AGS and Kato III cells. Neither β1 integrin heterodimers (α1β1, α2β2, α5β1) nor any other αβ integrin heterodimers on the cell surface were involved in CagA translocation. However, deletion of the HopQ or simultaneous deletion of CEACAM1, CEACAM5, and CEACAM6 in Kato III cells totally blocked translocation of CagA.[24]

2.3 | New aspects of other virulence factors

Interaction of *H pylori* with gastric epithelial cells induces different signal transduction pathways within the host. The gas chromatography-mass spectrometry (GC/MS) technique was used to analyze the metabolites of human AGS cells, which were co-cultured with the *H pylori* strain ATCC 43504.[25] Short exposure of AGS cells to *H pylori* resulted in low levels of metabolites of the tricarboxylic acid (TCA) cycle and amino acid metabolism, whereas these metabolites were elevated during prolonged co-culture of gastric cells with *H pylori*. Furthermore, the role of *H pylori* in the regulation of isocitrate dehydrogenase- and asparagine synthetase-dependent pathways was demonstrated.[25]

Zhao et al[26] demonstrated by molecular docking that seven residues of UreA, located on two interfaces, participated in the UreA/Hsp60 interaction confirming the chaperone activity of Hsp60 during urease maturation.

Helicobacter pylori urease and neuraminyllactose-binding hemagglutinin (HpaA) sequences were screened by combining in silico tools and immunoinformatic web servers for the ability of preparing fusion and then recombinant protein with chimeric sequence: $UreB_{229\text{-}561}$-HpaA covering the most important antigenic determinants of these bacteria.[27] This protein induces antibody production and stimulates T lymphocytes indicating its vaccination potential.

The role of *H pylori* virulence genes such as *cag*A and *vac*A in the development of gastric diseases is well known, whereas the significance of *hom*A and *hom*B genes is still uncertain. The study carried out by Šterbenc et al[28] on a young Slovenian population infected with *H pylori* showed that *hom*A and *hom*B genes were not independent markers of *H pylori* virulence; however, they may act synergistically with other known virulence genes, including *cag*A *and vac*A, in the development of gastric disorders in children.

The gastric tissue biopsy specimens from healthy individuals and from patients with chronic gastritis or gastric cancer were analyzed for the presence of the *oip*A gene encoding outer membrane inflammatory protein A (*oip*A) and its functional status, which can be "on" or "off" due to CT dinucleotide slippage that modifies the reading frame leading to a functional or non-functional gene status.[29] In this study, the status "on" was most frequently found in gastric cancer patients from Western countries.

Gonciarz et al,[4] by using *H pylori*-infected *Cavia porcellus* and primary gastric epithelial cells of these animals, showed the role of Le^X and Le^Y determinants of *H pylori* LPS in binding these bacteria to gastric epithelial cells. Another study revealed that the LPS of Western and Asian *H pylori* strains was different in the type of linker between the core oligosaccharide (Glc-Gal-Hep-III-Hep-II-Hep-I-KDO) and attached trisaccharide (GlcNAc-Fuc-Hep).[30] In Western but not Asian *H pylori* strains, a linear glucan-heptan linker between these two parts of LPS was identified. The presence of an alternative linker in LPS of Asian strains and its role in *H pylori* pathogenesis were suggested because *H pylori* infection is more severe and symptomatic in Asia than it is in Western countries.

The study carried out by Gonciarz et al,[31] on a common epitope (ATVLA sequence) of *H pylori* heat shock protein (Hsp)B and human Hsp60, revealed its immunogenicity. IgG class antibodies to synthetic P1 peptide containing ATVLA were detected in patients with gastritis or coronary heart disease (CHD) infected with *H pylori* as well as in *Cavia porcellus* inoculated with *H pylori*, but not in uninfected individuals or asymptomatic *H pylori* carriers, suggesting a potential role of such antibodies, possibly autoreactive, in the development of *H pylori*-related disease. This dependence was also shown by the stimulation by ATVLA of human THP-1Blue™ monocytes for the secretion of proinflammatory cytokines.[31]

Posselt et al[32] reported that, during *H pylori* infection, c-Abl non-receptor tyrosine kinase called Abelson murine leukemia viral oncogene homolog 1 kinase (c-Abl), implicated in cell division, differentiation, cell adherence, and stress response, which is activated by CagA, can be also activated in a CagA-independent pathway. This pathway was mediated by the T4SS effector D-glycero-β-D-manno-heptose-1,7-bisphosphate (βHBP) and protein kinase C (PKC). Furthermore, it was shown that the *H pylori* genetic region, known as integrating conjugative elements of *H pylori* T4SS, contains a novel type of T4SS, which is considered as a *H pylori* virulence factor.[33] However, the structure containing genes encoding components of this system, and the interactions between this T4SS and other virulence factors remain unknown.

The p38 mitogen-activated protein kinase (MAPK) signaling pathway has been suggested to play a role in the development of chronic inflammatory response due to *H pylori* infection. Wang et al[34] identified a new pathway of p38 nuclear translocation, in response to *H pylori* infection independent on the p38 phosphorylation status, which engaged small ubiquitin-related modifier (SUMO), especially SUMO-2. Furthermore, they showed that SUMO-dependent nuclear transfer of p38 was decreased upon mutation of its SUMO-interacting motifs (SIMs).[34] By using NMR and biophysical techniques, Jaiswal et al[35] suggested a potential interaction between the human SUMO-1 and the histone-like DNA binding protein of *H pylori* (Hup), which presents two SIMs.

Morey et al[36] reported that *H pylori* cholesterol-α-glucosyltransferase (cgt) blocked IFN-γ-induced cell signaling via JAK/STAT by reducing the cholesterol level, allowing the bacteria to escape the inflammatory response of the host.

In conclusion, all of the data published over the last year illustrate the huge progress in understanding the pathogenicity of *H pylori* and pave the way for future research in the field.

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The authors declare no conflict of interests.

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