Helicobacter pylori HopH (OipA) and Bacterial Pathogenicity: Genetic and Functional Genomic Analysis of hopH Gene Polymorphisms

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Background. Expression of the Helicobacter pylori outer membrane protein HopH is regulated by phase variation within a CT dinucleotide repeat motif of the hopH gene.

Methods. To investigate the importance of HopH for bacterial pathogenicity, we performed a detailed functional genomic and population-based genetic characterization of this contingency locus.

Results. Sequencing of hopH in H. pylori strains from 58 patients revealed that the hopH “on” genotype is linked to bacterial virulence determinants, such as the vacAs1, vacAm1, babA2, and, most strongly, cagA genotypes. hopH mutagenesis resulted in reduced bacterial adherence to gastric epithelia in vitro. Complementation of hopH in trans restored the adherence properties of hopH mutants. Although HopH has been previously linked to proinflammatory epithelial signaling, hopH mutagenesis did not alter epithelial interleukin-8 secretion in vitro. Comparative epithelial gene-expression profiling by cDNA microarrays revealed no significant differences between the wild-type–specific and hopH mutant–specific transcriptomes. By contrast, a large set of genes was differentially regulated in a cag pathogenicity island–dependent manner.

Conclusion. An in-frame hopH gene may be linked to gastroduodenal diseases because of its association with other virulence factors or increased bacterial adherence and colonization. The strong linkage with cagA indicates that HopH may contribute to the fitness of cagA-positive strains in vivo.

Helicobacter pylori chronically infects approximately one-half of the world’s population, and it has been recognized as the primary cause of peptic ulceration, gastric cancer, and mucosa-associated lymphoid tissue lymphoma [1, 2]. In the past 2 decades, many aspects of the pathogenicity of H. pylori have been determined at the molecular level. However, it is still not fully understood why only 10%–15% of infected patients develop disease during the course of their lives. The development of H. pylori–associated disease is thought to be affected by bacterial virulence factors, as well as by genetic predisposition and the immunological response of the host. Several bacterial virulence factors, including the cag pathogenicity island (cagPAI), the vacuolating cytotoxin (VacA), and the blood group antigen–binding adhesin (BabA), have been associated with a more-severe clinical outcome [3–5]. The cagPAI is a 40-kb genomic fragment that consists of >30 genes [6]. Most of these genes encode a type IV secretion system (T4SS) that translocates bacterial macromolecules, including CagA and peptidoglycan, into host cells [7, 8]. The interaction of these translocated molecules with signal transduction pathways ultimately results in a number of cellular and molecular changes, as well as in proinflammatory host cell responses, which thus links CagA to disease development [7, 9].

The vacA gene, which encodes the vacuolating cytotoxin, is naturally polymorphic, particularly near the
5′-terminal region (the s-region) and in the midregion [10].
Two main families of s-region sequences (s1 and s2) and 2
main families of midregion sequences (m1 and m2) have
been described. Mature VacA from toxigenic vacAs1 strains has a
hydrophobic N-terminal region that can insert into mem-
branes, leading to the vacuolation of target cells. In nontox-
igenic vacAs2 strains, this region is preceded by a hydrophilic
N-terminal extension that blocks vacuolating activity [11]. The
m-region of the vacA gene encodes for the p58 VacA subunit,
which is involved in binding of VacA to host cells [10]. Mo-
saicism in the m-region confers the cell specificity of vacu-
olation. In clinical H. pylori isolates, vacA signal and midregion
alleles and their combinations vary, and certain subtypes have
a geographically restricted distribution [10].

Approximately 4% of the H. pylori genome, significantly
more than that of any other known bacterial species, is com-
posed of genes encoding integral outer membrane proteins
(OMPs) [12–14]. In a systematic analysis of H. pylori OMPs,
Alm et al. [14] identified 5 paralogous gene families with
H. pylori (OMPs) [12–14]. The m-region of the vacA gene encodes for the p58 VacA subunit,
which is involved in binding of VacA to host cells [10]. Mo-

Patients and methods.

Patients and biopsy samples. Five antral biopsy samples were
collected from each of 58 H. pylori–infected German patients
with chronic gastritis who provided informed consent. Patients
receiving nonsteroidal anti-inflammatory drugs or antisecretory
therapy and those with ulcer disease or gastric carcinoma were
excluded from the study. Two antral and corpus sections were
stained with hematoxylin-eosin. Histopathological evaluation
was performed using the Sydney classification system. The
remaining biopsy samples were stored in liquid nitrogen and
homogenized before the isolation of DNA or RNA, as described
elsewhere [27].

Bacterial culture, generation of H. pylori hopH/cagE
mutants, and genetic complementation of hopH in trans.
Bacterial culture, hopH/cagE mutagenesis, and genetic comple-
mentation were performed in accordance with standard tech-
niques and are described in detail in the Appendix, which
is available at the Journal’s Web site (http://www.journals.
uchicago.edu/JID/journal/home.html).

Adherence assays and fluorescence/confocal microscopy.
Bacterial adherence to the gastric cancer cell lines KATO-III
and AGS was analyzed semiquantitatively in adherence assays.
A detailed description of the methodology is provided in the
Appendix.

Real-time quantitative polymerase chain reaction (PCR)
and reverse transcription (RT)–PCR. Quantitative PCR was
used to determine the bacterial colonization density in gastric-
biopsy samples. Therefore, genomic DNA from gastric-biopsy
samples was isolated and subjected to real-time PCR. Amounts
of H. pylori ureB DNA were determined quantitatively and
normalized to amounts of β-actin DNA. Primer and probe
sequences are provided in the Appendix. Amounts of IL-8
mRNA were determined in gastric cancer cell lines by quan-
titative TaqMan PCR (Applied Biosystems), as described else-
where [28].

Coculture of H. pylori with gastric epithelial cells, deter-
mination of IL-8 protein/mRNA levels, SDS-PAGE, and
immunoblot analysis.

A total of 3 × 10^5 KATO-III or AGS cells were plated into 6-well plates and cultured for 24 h in 2 mL
of RPMI 1640 medium supplemented with 20% fetal calf serum and 1% antibiotics (all Sigma-Aldrich) in a humidified
incubator that contained 5% CO₂. After 24 h, cells were washed
once with PBS, and 2 mL of antibiotic-free medium was added
to each dish. Different bacterial concentrations (bacteria:cell
ratios, 1:100, 1:50, and 1:10) were then cocultured with the
cells. For IL-8 mRNA measurements, mRNA was isolated after
6 h of incubation. IL-8 protein levels were assayed from the supernatant after 24 h of incubation using a commercially avail-
able ELISA kit (BD Biosciences), in accordance with the man-
ufacturer’s instructions. SDS-PAGE and immunoblot analysis
is described in the Appendix.
Gene-expression profiling and microarray data analysis. KATO-III cells were stimulated with B128 wild-type (wt) \( H. \) pylori and its isogenic \( cagE \) and \( hopH \) mutant strains at an MOI of 50 for 6 h. Total RNA was prepared using Trizol reagent (Life Technologies). Then, 5 \( \mu g \) of RNA was labeled and hybridized to Affymetrix HG U133A 2.0 GeneChips in accordance with Affymetrix protocols. Microarrays were initially analyzed for general assay quality using the Simpleaffy package for R (Free Software Foundation). The average background was \(<55\%\) for all 8 microarrays. Two biological replicates per condition were analyzed. CEL files were called “present” was 55%–58% for all 8 microarrays. Two scaling factors were 0.56–0.88, and the percentage of transcripts were processed for global normalization and generation of expression values using the RMA algorithm in the R Affy package [29]. The list of significantly regulated genes was achieved by applying the SAM multiclass algorithm [30] in the SAMR package for R (false discovery rate, <1%; 1546 probe sets). Further data preparation was done using Spotfire DecisionSite software (Spotfire). The complete data set will be submitted to Gene Expression Omnibus, the National Center for Biotechnology Information repository of gene-expression data, and it will be available on the corresponding Web site (available at: http://www.ncbi.nlm.nih.gov/projects/geo/).

RESULTS

Sequence analysis in the signal-peptide coding region of the \( hopH \) gene. The functional status of \( hopH \) is regulated by a slipped-strand repair mechanism based on the number of CT dinucleotide repeats in the signal sequence coding region of the gene [21]. In the present study, the corresponding \( hopH \) locus was sequenced in strains from 58 patients with chronic gastritis. Figure 1 shows the nucleotide sequences of the signal peptide coding region in the \( hopH \) gene. The number of CT repeats ranged from 5 to 11, which is distinct from East Asian \( H. \) pylori strains, which have been shown to harbor \( \leq 5 \) CT repeats [31]. Some 59% (\( n = 34 \)) of strains had an in-frame \( hopH \) gene, with the 6 CT (50%; 17/34) and the 5+2 CT (26.5%; 9/34) repeat patterns being most frequently associated with the “on” status of the gene. Seven or 8 CT repeats were the most common genetic basis for a nonfunctional (“off”) \( hopH \) gene, leading to premature termination of translation (8 CT repeats, 45.8% [11/24]; 7 CT repeats, 20.8% [5/24]).

Association of \( hopH \) switch status with other \( H. \) pylori virulence and adherence factors. Figure 1 shows the association of the \( hopH \) switch status with different \( H. \) pylori virulence factors. The \( hopH \) frame status was most closely correlated with the presence of \( cagA \). Most \( H. \) pylori strains with an in-frame \( hopH \) gene were \( cagA \) positive, whereas the majority of strains with a \( hopH \)-off gene were \( cagA \) negative (84.5% overall concordance). Furthermore, the \( hopH \) in-frame status was associated with the \( vacA \) and \( vacA\) allelic subtypes and with presence of the \( babA \) gene encoding the adhesin BabA. Conversely, the \( hopH \)-off status was more often present in \( babA \)-negative strains or strains harboring the \( vacAs2 \) or \( vacAm2 \) genotypes (figure 1, bottom). Thus, the functional \( hopH \) gene is associated with the expression of known virulence factors of \( H. \) pylori.

Effect of \( hopH \) on the adherence properties of \( H. \) pylori to gastric epithelial cells. Several \( H. \) pylori OMPs, including \( BabA \), \( SabA \), \( AlpA/B \), and \( HopZ \), have been implicated in bacterial adherence [15–18]. Therefore, we investigated whether \( hopH \) influences bacterial binding. Bacterial adherence to gastric cancer cell lines (KATO-III and AGS) was assessed using the B128 and G27 wt strains, which have a functional \( hopH \) gene, and different independent isogenic \( hopH \) mutants. Both the wt and \( hopH \) mutant strains were able to bind to KATO-III cells (not shown). However, the adherence of \( hopH \) mutant strains to gastric cells was significantly lower than that of wt strains (\( P<.001 \)) (figure 2B). To exclude possible artifacts, \( hopH \) mutants were carefully checked, and multiple integrations of the knockout plasmid into the \( H. \) pylori genome were excluded by Southern hybridization (figure 2A). Adherence is thought to facilitate bacterial colonization [32]. To analyze bacterial colonization in patients infected with \( hopH \)-on versus -off strains, we quantified bacterial \( ureB \) DNA in gastric-biopsy samples and normalized the values to levels of \( \beta \)-actin DNA. As shown in figure 2C, bacterial colonization densities were lower in patients infected with \( hopH \)-off strains than in those infected with \( hopH \)-on strains. It could be therefore speculated that \( HopH \) expression may affect bacterial colonization in vivo. However, given that the \( hopH \)-on status is associated with other virulence factors, our data do not provide definitive evidence about which virulence factors are directly responsible for the increased bacterial colonization densities in vivo.

Complementation of the \( hopH \) gene and restoration of the adherence properties of \( hopH \) mutant strains. To further confirm the influence of \( HopH \) on bacterial adherence, we complemented our \( hopH \) mutant strains with \( hopH \) in trans. For this purpose, the functional \( hopH \) gene under its own promoter was introduced into the \( vacA \) locus of the \( hopH \) mutant strain. The corresponding vector containing parts of the \( cysS \) and \( vacA \) genes (\( HP0886 \) and \( HP0887 \), respectively) was constructed and termed “pCV1” (figure 2D). Subsequently, a chloramphenical resistance cassette and the \( hopH \) gene, including its promoter region, were cloned into pCV1, to yield pCV2 (figure 2E). The construct was transformed into \( hopH \) mutant strains. Subsequently, adherence assays were performed to test the binding capacity of complemented strains. Figure 2F shows that complementation of the \( hopH \) gene completely restored the adherence properties of the mutants. The \( hopH \) mutant strains with the complemented genotype behaved similarly to the wt strain with respect to binding to gastric epithelial cells.

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Figure 1. Variations of hopH CT repeat region sequences in Helicobacter pylori strains from 58 German patients and the association with different virulence factors. Top, nucleotide and deduced amino acid sequences of the hopH signal peptide coding region from all H. pylori strains. Phase variation renders the gene in or out of frame (gene “on” or “off”). Asterisks denote stop codons. Bottom, association of the hopH-on or hopH-off status with other virulence factors. The no. of strains in each group is indicated in the circles.
Figure 2. HopH effects on bacterial adherence and colonization. A, Southern hybridization analysis after construction of *Helicobacter pylori* hopH mutant strains to exclude multiple integrations of the kanamycin resistance (Km<sup>R</sup>) cassette in the *H. pylori* genome. Chromosomal DNA from *H. pylori* B128 wild-type (wt) and hopH mutant strains was digested with BglII (cutting sites in HP0637 and HP0638), fractionated by agarose gel electrophoresis, and transferred to nitrocellulose sheets. The membrane was hybridized to a <sup>32</sup>P-labeled probe corresponding to the *apha-A3* Km<sup>R</sup> cassette sequence consisting of the *EcoRV* 1.0-kb fragment from pJM30. The *aphA3* probe hybridized to a 3.6-kb BglII fragment from chromosomal DNA of the hopH mutants but did not hybridize with wt chromosomal DNA from wt bacteria. B, Quantitative assessment of *H. pylori* binding to KATO-III cells. Cells were cocultured with B128 wt and its isogenic hopH mutant strain at an MOI of 10. *H. pylori* B128 wt and hopH mutant were added to the cells and incubated for 40 min under continuous shaking. Cells were then washed 3 times with PBS, and adherent bacteria were counted after bacterial staining. Statistical analysis was performed using Student’s *t* test. *P* < .001. One of 5 independent experiments yielding similar results is shown. Experiments are shown using the *H. pylori* strain B128. Similar results were obtained with the G27 strain and when AGS cells were used. C, *H. pylori* colonization densities in patients infected with hopH-on or hopH-off strains, as assessed by quantification of amounts of bacterial *ureB* DNA in the gastric mucosa. Copies of *H. pylori* *ureB* DNA were determined by real-time PCR and normalized to *β*-actin DNA copies. Bars within the box plots represent median values (50th percentile). The ends of the bars indicate the 25th and 75th percentiles, the 10th and 90th percentiles are represented by error bars, and the 5th and 95th percentiles are shown by black circles. *P* values were calculated using the Mann-Whitney *U* test. D and E, Construction of the replacement vector for complementation of hopH at the vacA locus, as described in the Appendix. F, Restoration of the adherence properties of hopH mutant strains by complementation of the hopH gene; experiments were conducted as described for panel B. Amp<sup>R</sup>, ampicillin resistance; Cm<sup>R</sup>, chloramphenicol resistance; KO, knockout; MCS, multiple cloning site.
Influence of HopH on CagA translocation and tyrosine phosphorylation. Bacterial attachment is required for CagA translocation into host cells. To analyze the influence of HopH on the function of the T4SS, we investigated the translocation and phosphorylation of CagA into gastric epithelial cells. For this purpose, KATO-III cells were infected for 4 h with the B128 wt or hopH mutant strains, and CagA translocation and tyrosine phosphorylation were assessed by Western blotting. Figure 3 shows that both strains were able to translocate CagA protein to a similar extent. CagA was then tyrosine phosphorylated intracellularly, which was accompanied by cortactin dephosphorylation, as described elsewhere [33]. Similar results were obtained when H. pylori G27 and its isogenic hopH mutant or AGS cell lines were used (data not shown). These data indicate that HopH does not interfere with known functions of the cagPAI and the CagA protein.

Effect of HopH on IL-8 secretion by epithelial cells in vitro. It is still being debated whether HopH is directly involved in the induction of IL-8 secretion by gastric epithelial cells [21, 23–25]. To investigate whether the expression of HopH in our strains interferes with the ability to induce IL-8 in infections, we stimulated KATO-III and AGS cells with different H. pylori strains and determined IL-8 mRNA levels by RT-PCR and protein levels by standard ELISA. As shown in figure 4, H. pylori B128 wt and the hopH mutant strain induced IL-8 expression and secretion by KATO-III cells in a dose-dependent manner. However, there were no significant differences in IL-8 expression and secretion between the 2 strains. Despite using several independent hopH mutants of the H. pylori strains B128 and G27, we could not detect an influence of HopH on IL-8 expression and secretion from KATO-III and AGS cells (data not shown). As a control, we constructed cagE mutant strains, which exhibited a T4SS defect. As expected, cagE mutant strains induced significantly lower levels of IL-8 than the wt or hopH mutant strains (figure 4).

Comparison of strain type-specific transcriptomes in gastric epithelial cells after infection with wt and mutant H. pylori. To obtain a more global picture of the interaction between H. pylori and epithelia, we performed gene-expression profiling of KATO-III cells that were either unstimulated or stimulated with different H. pylori strain types (B128 wt and its isogenic hopH and cagE mutant strains). Figure 5A–5C shows the epithelial
Figure 5. Gene-chip analysis of KATO-III epithelial cells stimulated or not stimulated with different Helicobacter pylori strain types. Cells were left unstimulated (basal) or were stimulated for 6 h with the H. pylori strain B128 wild-type (wt) and its isogenic cagE and hopH mutants at an MOI of 50. RNA was used to probe Affymetrix HG U133A 2.0 chips. Expression values were calculated as the average of 2 independent experiments. Scatter plots show expression values of all 22,270 probe sets present on the array, with each circle representing 1 probe set. Expression of each gene in the condition of the Y-axis is plotted against expression of the same gene in the condition on the X-axis. The diagonal lines indicate 2-fold differential gene expression between the 2 conditions. Red circles, genes that are increased or decreased >2 fold. Genes located on a hypothetical diagonal middle line of identity that crosses the lower left and upper right X/Y intersections are equally expressed in conditions of both the vertical and horizontal axes. A–C, gene expression of noninfected cells plotted against gene expression of cells infected with different H. pylori strain types. D–F, transcriptomes of cells infected with different H. pylori strain types plotted against each other.

transcriptomes after stimulation with the different strain types in relation to basal gene expression. Although all strains induced a remarkable change in gene expression, the transcriptional response of epithelial cells to the cagE mutant strain was weaker. Figure 5C shows that the number of genes regulated in response to incubation with the cagE mutant strain was clearly lower than that regulated by the wt or the hopH mutant strain. To explore differences in gene expression induced by different strain types, strain type–specific transcriptomes were plotted against each other (figure 5D–5F). The gene-expression profiles of both the wt and the hopH mutant strain differed significantly from that of the cagE mutant–specific transcriptome (figure 5D and 5E). SAM 2-class unpaired statistical analysis revealed that 1172 probe sets were statistically significantly regulated between cells stimulated with the wt and those stimulated with the cagE mutant strain. By contrast, the transcriptomes induced by the wt and hopH mutant strains were remarkably similar. Figure 1E shows that all probe sets were located around the virtual diagonal “middle line of identity,” which indicates equal expression in conditions of both the vertical and horizontal axes. Of note, none of the 22,277 probe sets were statistically significantly regulated between cells stimulated with the wt and those stimulated with the hopH mutant strain (SAM 2-class unpaired statistical analysis; minimal false discovery rate, >80%). Thus, HopH expressed by the strains used in the study does not interfere with intracellular signaling events.

DISCUSSION

Microbial fitness and survival are dependent on a balance between genome maintenance and genetic diversity. H. pylori faces the challenge of maintaining its fitness in dynamic and often hostile environments. Multiple mutational and recombintatorial mechanisms allow bacteria a rapid generation of genetic diversity as a mechanism of adaptation to environmental fluc-
tutions [34, 35]. Simple sequence repeats are hypermutable DNA sequences that act as an important source of functional genetic diversity for many bacterial pathogens [34, 35]. The H. pylori genome contains close to 30 genes with simple sequence repeats (dinucleotide repeats or homopolymeric tracts), which are located either within coding or upstream regulatory DNA regions [12, 13, 20]. The largest group of potentially phase-variable genes identified in the H. pylori genome constitutes cell surface–associated proteins, which are likely to be involved in microbe-host interactions [20]. This suggests that phenotypic and phase variation contributes to the maintenance of bacterial fitness.

Simple sequence repeats in the hopH gene have been shown to regulate the expression of this OMP [21, 31]. We found that the functional status of hopH influences bacterial adherence. hopH mutant strains had significantly lower adherence to gastric epithelial cells than did wt strains, and complementation of the hopH gene restored the adherence properties of hopH mutant H. pylori. Bacterial adherence plays an important role in the colonization of mucosal surfaces [32, 36]. The proximity to the epithelium protects bacteria from the extreme acidity of the gastric lumen and displacement from the stomach by peristaltic movements and washout with the luminal fluid. Therefore, bacteria with better adherence characteristics are supposed to colonize at higher densities [32, 36]. Indeed, previous studies showed that HopH influences the colonization properties of H. pylori in animal models [22, 25, 37].

Whether HopH directly affects proinflammatory signaling is still under debate. In several studies, one group of researchers showed that HopH expression is associated with increased IL-8 secretion by gastric epithelial cells [21]. The authors further showed that HopH is involved in signal transducer and activator of transcription factor 1 (STAT1) phosphorylation and induces IL-8 expression via the STAT1–interferon regulatory factor 1 (IRF1) pathway [38]. In agreement with several other reports, however, we were not able to find an influence of HopH on IL-8 secretion and expression in vitro [23–26]. One possible explanation for the discrepancies between the studies may be the use of different H. pylori strains.

The identification of genetic events related to host-pathogen interactions is important for the understanding of microbe-induced biological processes. Transcriptional profiling allows us to comprehensively analyze proinflammatory signaling events in H. pylori–stimulated epithelia and provided a global view of strain type–dependent regulation of gene expression. On the basis of previous results [38], we expected to identify a set of genes that was differentially induced by wt and hopH mutant strains, depending on the presence of STAT1 and IRF1 binding sites in the promoter regions of the genes. However, the epithelial transcriptomes induced by wt and hopH mutant strains were remarkably similar. Whereas a large set of genes was significantly differentially regulated by wt and cagE mutant strains, there were no significant differences between the wt-specific and hopH mutant–specific transcriptomes. Thus, in the strains used in our study, HopH does not seem to have a direct influence on proinflammatory signaling. Nevertheless, HopH may influence disease outcome in vivo. The dense colonization of HopH-expressing strains may lead to increased gastric inflammatory responses and may explain the association of HopH with gastric diseases [22, 39]. Because of the strong concordance between HopH and CagA expression, the independent influence of HopH on the gastric inflammatory response could not be evaluated in our study.

Only 5% of all H. pylori strains obtained from German patients had an in-frame hopH gene. Among these strains, a 6, 5+2, or 9 CT dinucleotide repeat pattern was dominant, whereas a pattern of 7 or 8 CT repeats was most common in hopH-off strains. All strains from our patient population had ≥5 CT repeats. By contrast, H. pylori strains from Asian countries, such as Japan and China, have ≤5 CT repeats [31]. Furthermore, almost all East Asian H. pylori strains harbor an in-frame hopH status, with a 3+1 repeat pattern being most common [31]. Thus, the CT dinucleotide pattern in the hopH signal sequence has geographic characteristics. The length of simple sequence–repeat tracts may influence the rate of phase variation, with longer tracts probably having higher mutation rates [40].

Localized hypermutation in contingency loci has a major influence on bacterial adaptation and on the evasion of immune defences in diverse species of bacterial pathogens [41, 42]. Similarly to other bacteria that persistently colonize mucosal surfaces, such as Haemophilus influenzae or Neisseria gonorrhoeae [35], H. pylori is able to alter OMP expression in vivo, probably as a mechanism of adaptation to different persons or to changing environmental conditions within one host [18, 43–45]. For HopH, it has been shown that strains obtained 10 years apart from the same host can vary in hopH frame status [31].

The hopH in-frame status was associated with vacAs1, vacAm1, cagA, and babA2 genotypes. The strongest association was found between HopH and CagA expression, with 85% concordance. The reason for this strong association is not understood. However, because there is no obvious common genetic mechanism controlling expression of the 2 genes, linkage of hopH and cagA seems to be based on selection in the host. It is conceivable that HopH offers a selective advantage for cagPAI-positive bacteria that may, for example, prefer a gastric microenvironment in which HopH expression is beneficial. This idea is supported by the observation that oipA-mutated cagPAI-positive H. pylori strains are impaired in their ability to colonize Mongolian gerbils [25]. Thus, differential regulation of HopH expression by
phase variation may contribute to the fitness of cagPA1-positive or -negative strains in vivo.

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References

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