REVIEW

Virulence of *Helicobacter pylori* outer membrane proteins: an updated review

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Abstract

Helicobacter pylori (*H. pylori*) infection is associated with some gastric diseases, such as gastritis, peptic ulcer, and gastric cancer. CagA and VacA are known virulence factors of *H. pylori*, which play a vital role in severe clinical outcomes. Additionally, the expression of outer membrane proteins (OMPs) helps *H. pylori* attach to gastric epithelial cells at the primary stage and increases the virulence of *H. pylori*. In this review, we have summarized the paralogs of *H. pylori* OMPs, their genomic loci, and the different receptors of OMPs identified so far. We focused on five OMPs, BabA (HopS), SabA (HopP), OipA (HopH), HopQ, and HopZ, and one family of OMPs: Hom. We highlight the coexpression of OMPs with other virulence factors and their relationship with clinical outcomes. In conclusion, OMPs are closely related to the pathogenic processes of adhesion, colonization, persistent infection, and severe clinical consequences. They are potential targets for the prevention and treatment of *H. pylori*–related diseases.

Keywords *Helicobacter pylori* · Outer membrane proteins · Virulence factors

Introduction

Helicobacter pylori (*H. pylori*) colonizes mainly the surface of the gastric epithelium and is an essential human pathogen that was discovered in the twentieth century. The prevalence of *H. pylori* is probably 44.3% of the entire human population [1]. According to the statistics, its prevalence is 34.7% in developed countries and 50.8% in developing countries, and the worldwide annual recurrence rate is 4.3% [2]. Although the global infection rate of *H. pylori* is high, a large proportion of infected people have no apparent symptoms and only show gastritis under an endoscope [3, 4]. However, these asymptomatic or endoscopic gastritis patients may develop changes in their condition. More severe conditions include peptic ulcer (PU), gastric cancer (GC), and mucosa-associated lymphoid tissue (MALT) lymphoma [4]. The outcome of infection depends mainly on the interactions among *H. pylori*, the stomach, and the environment [5, 6]. For developing countries with high infection rates and low economic levels, eradication of *H. pylori* with antibiotics to prevent serious diseases is the most effective and relatively cheaper method being currently applied [7].

The outer membrane is the outer barrier of Gram-negative bacteria, which consists of two highly asymmetric layers—the inner monolayer contains only phospholipids and the outer monolayer consists mainly of outer membrane proteins (OMPs) that are resistant to the external environment [8]. OMPs have a variety of biological functions, not only in maintaining the outer membrane structure and guaranteeing the material transportation but also in playing an essential role in the process of contact with the host [9]. The study of *H. pylori* OMPs will contribute to the development of vaccine and drug targets [10, 11]. OMPs in *H. pylori* mainly include lipoproteins, porins, iron-regulated proteins, efflux pump proteins, and adhesins [12]. The expression of OMPs in different strains is related to the virulence of *H. pylori*. The pathogenicity of

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the OMPs may be achieved through the following mechanisms: (1) adhesion, (2) penetration of the bacteria through the defense barrier, and (3) evasion of the immune system.

Several strains of *H. pylori* have been subjected to whole-genome sequencing, and approximately 4% of their genes were found to encode OMPs. We further divided them into five paralogous gene families according to their functions [12]. Hop (outer membrane porins) and Hor (Hop-related proteins) proteins are the best-known family. The second and third are Hof (*H. pylori* OMP) and Hom (*H. pylori* outer membrane) proteins, respectively. Iron-regulated OMPs are the fourth family, and efflux pump OMPs are the fifth family. The other types of OMPs that do not belong to any of these families have different alleles, regional distribution characteristics, and distinct correlations with other virulence factors. Allelic variation and phase variation are the most common methods used to regulate the expression of OMPs [13–15]. Usually, there are multiple alleles for each OMP, and the functions of proteins encoded by each allele are somewhat different. Additionally, due to geographical differences among strains, the expression of OMPs is also variable. In this review, we summarize recent progress in our understanding of the five best characterized OMPs: BabA (HopS), SabA (HopP), OipA (HopH), HopQ, and HopZ, and one family of OMPs: Hom and their receptors, as well as their relationship with other virulence factors and clinical outcomes.

Main OMPs

BabA (HopS)

BabA belongs to the Hop protein family, also called blood-group-antigen-binding adhesin. So far, three genomic loci have been found in *bab*, namely, *babA*, *babB*, and *babC* [16]. *BabA* and its *babB* allelic gene are irrelevant to each other according to phylogenetic analysis, and the expression of the two genes differs geographically. The multiple synonymous and nonsynonymous substitutions of the *babA* gene region indicate that it predates *babB* in phylogeny [17]. However, the *babA* diversity region may have more functional constraints, and there is a clear distinction between the US and Asian strains [3, 18].

The primary role of BabA in the pathogenesis of *H. pylori* is adhesion. Ilver et al. were the first to isolate BabA and put forward the theory that BabA adheres to the fucosylated LewisB histo-blood group antigen for host selectively [19, 20]. Backstrom found the strain 17,875 had two *babA* alleles, which were *babA1* (silence) and *babA2* (expression) [21]. *BabA2-cam* was a derivative gene of *babA2*, which was obtained by recombination of the previously silent *babA1* gene with the expressed and partially homologous *babB* locus. Then, they confirmed that *BabA2-cam* could bind to

LewisB. Similarly, the binding affinity of chimeric BabB/A adhesin to LewisB was similar to that of BabA adhesin. However, the expression level of BabB/A was low, and phase variation could occur through a slipped-strand mispairing mechanism [21, 22]. These phenomena all indicate that their transferability and heterogeneity contribute to the adaptation of the bacteria, and some strains have the potential to periodically activate and inactivate their virulence according to the host's response to infection. The expression of BabA is acid-sensitive and has nothing to do with the interpretation of LewisB or the binding affinity of LewisB [23]. Bugaytsova et al. believe that the loss expression of BabA is not related to adaptive immunity or the toll-like receptor signaling system, indicating that BabA has some other functions besides being an adhesin [24].

After the calculation and analysis of the X-ray diffraction pattern of BabA, it was found that BabA has three structural domains for combining with LewisB, including two diversity loops (DL1 and DL2) and one conserved loop (CL2) [16]. The specific binding region is the hydrogen bond network structure formed between four residues of LewisB and eight amino acids of BabA [25]. Previous research suggested that *H. pylori* had blood group binding preferences, and the specific strains only combined with O antigen residues, resulting in people with type O blood being more likely to suffer from PU than those with other blood types [16]. According to the recent study of BabA and LewisB structures, the prevalence of PU is higher in type O blood, probably because it overexpresses LewisB.

Multiple studies on the relationship between *H. pylori* and clinical diseases have shown that, compared with the control group, patients with PU and GC have higher BabA expression. This indicates that BabA is positively correlated with severe clinical diseases caused by *H. pylori* [26, 27]. Possible mechanism to explain this phenomenon is that the combination of BabA and LewisB triggers the type IV secretion system (T4SS), which helps CagA to enter the gastric mucosal epithelial cells [28]. *Cag pathogenicity island* (*cag PAI*) is a large (usually 20–100 kb) DNA fragment encoding many virulence-related genes on the *H. pylori* chromosome, which often contains repetitive or inserted sequences on both sides. *Cag PAI* mediates the expression of CagA and is closely associated with the occurrence of gastritis, PU, GC, and other diseases. *Cag PAI* also mediates the expression of T4SS [29], through which the vital virulence factor CagA is delivered into attached cells. CagA will induce the production of inflammatory factors, leading to intestinal metaplasia and precancerous lesions [28].

SabA (HopP)

The *sab* gene has two alleles, *sabA* and *sabB*. SabA is the second most commonly reported OMP in *H. pylori*. It is

named sialic-acid-binding adhesin according to its binding receptors and it belongs to the Hop family, also known as HopP or OMP17. SabB is known as HopO or OMP16 [12]. However, genomic analysis showed that the strains often both have *sabA* and *sabB* genes, which may selectively express SabA during the colonization of *H. pylori* in the host. The specific mechanism may be a phase variation caused by slipped-strand mispairing in a 5′ dinucleotide repeat region, which affects the on-off states of *sabA* and *sabB* [30]. Like BabA, the expression of SabA is rapidly regulated in response to changes in the gastric environment, such as inflammation [31]. On the one hand, the expression of SabA can be regulated at the gene level through phase variation; on the other hand, *H. pylori* can also adjust the expression of genes at the cell level through its two-component signal transduction (TCST) system. The TCST can adapt to the changes in the environment at the transcriptional level to selectively express SabA. This is also known as acid-responsive signaling because the pH of the environment is one of the factors that activates the signal [32, 33].

Pang et al. analyzed X-ray diffraction patterns after the extraction of SabA and found that the adhesion domain of SabA was highly similar to the tetratricopeptide repeat fold family, which is often gathered into multiprotein complex-mediated protein interactions. The adhesion domain of SabA is mainly a barrel transmembrane domain. Its N-terminal and C-terminal form right angles from the head domain and create a shaft together. This group also conducted experiments in vitro and found that the SabA adhesion domain could bind to sialyl-LewisX, sialyl-LewisA, and LewisX, but not to other Lewis antigens, such as LewisA, LewisB, or LewisY [34]. The expression of sialyl-LewisX can be further regulated, after the combination of SabA and sialyl-LewisX. This process relies on specific glycosyltransferase β3GlcNAcT5, which can upregulate the expression of sialyl-LewisX, enhancing the combination of SabA and sialyl-LewisX, which increases the colonization ability of *H. pylori* [35]. SabA can also combine with ganglioside in addition to sialyl-LewisX and LewisX. Benktander et al. extracted two gangliosides sialyl-neolactohexaosylceramide and sialyl-neolactooctaosylceramide that combined with SabA [36].

The expression of SabA is called its "on" state, while the nonexpression is called its "off" state. The clinical strains of *H. pylori* SabA have a frequent "on/off" state, which means that SabA can be rapidly regulated in response to the changes in the gastric ecological environment [37]. When the pH in the stomach decreases, the expression of SabA is increased, which reflects the ability of *H. pylori* to adapt to the host. Meanwhile, the combination of SabA and ganglioside also mediates the chronic infection process of *H. pylori* [38]. A study in Japan showed a close relationship between SabA and GC [39]. However, another study reported that Asian strains with SabA-positive status had little influence on the

clinical outcomes [40], so the relationship between SabA and clinical diseases is still controversial.

OipA (HopH)

Outer inflammatory protein A (OipA) is also a member of the Hop family, sometimes referred to as HopH. The location of *oipA* on the *H. pylori* chromosome is approximately 100 kb from the *cag PAI* [41]. There are no available studies on the structure of OipA and its receptors so far.

The *oip* gene also has an "on/off" state, and when OipA is expressed, CagA is usually positive, which means these two proteins have a close link [42, 43]. Except for CagA, OipA seems to have no significant interactions with the other virulence factors. Several studies have reported that OipA can increase the secretion of interleukin-8 (IL-8) and other inflammatory factors to cause neutrophil infiltration, aggravating the inflammation in the stomach and helping *H. pylori* to colonize, and this is why it is called an outer inflammatory protein [42, 44]. OipA also inhibits the apoptosis of gastric cells [45], reducing the incidence of β-catenin nuclear translocation and cancer when the *oip* gene is switched off [46]. However, an in vitro study showed that OipA did not induce an increase in IL-8 expression [42]. Therefore, a more extensive sample study is needed to confirm the relationship between OipA and IL-8. OipA also plays a vital role in the activation of focal adhesion kinase (FAK). FAK is a cytoplasmic nonreceptor tyrosine kinase that can regulate the shape of cells, mediate cell movement, and play an essential role in the occurrence and invasive growth of tumors [47–49].

Many studies have suggested that the expression of OipA was positively correlated with PU, GC, and MALT in both Asian and Western strains [50–52]. Mahboubi et al. inoculated mice with OipA vaccine and the amount of *H. pylori* colonized in the stomach was significantly reduced, as well as the inflammation after some time. Therefore, immunogenic OipA could be used as an *H. pylori* vaccine to make up for the increasing antibiotic resistance of *H. pylori* [53].

HopQ

HopQ is encoded by the *hopQ* (*omp27*) gene and also belongs to the pore protein Hop family. Studies have reported that *hopQ* has two alleles of I and II [12]. A study reported that, among *H. pylori* strains, *hopQ* I type was the most common (72.5%), followed by *hop* Q II type (15.4%), and chimeric I type and II type were the rarest [54]. Further studies on Asian and Western strains showed that the Asian strains were dominated by the *hopQ* I type, while the *hopQ* II strains were sporadic [55].

We mentioned above that BabA mediates the activation of T4SS and facilitates the translocation of virulence factor CagA. Studies have found that HopQ also plays an essential role in this process [13, 56]. HopQ can exploit the

carcinoembryonic antigen–related cell adhesion molecule family (CEACAMs) as host cell receptors, mainly CEACAM1, CEACAM3, CEACAM5, and CEACAM6 [56, 57]. HopQ I type or II type targets the β-strands G, F, and C in the N-terminal domain (C1ND) of CEACAM. It has also been reported that HopQ binds to the IgV-like domain at the N-terminal of CEACAMs to facilitate the transfer of crucial pathogenic factor CagA to host cells [57]. In vitro animal experiments have also confirmed that HopQ-CEACAM interactions provide a pathway for *H. pylori* to adhere to the host and trigger signal transduction, and then, it produces long-term effects on humans [58, 59].

At present, although there are no additional reports on the relationship between HopQ and disease, in both Western and Asian strains, the *hopQ* I type genotype was significantly linked with *vacA s1* and *m1* genotypes and *cagA*-positive status, suggesting that HopQ may be an essential virulence factor related to gastroduodenal diseases [55].

HopZ

Among the Hop family, the *hopZ* gene has also been well characterized. HopZ has two allelic variants, HopZ-I and HopZ-II. The apparent difference between HopZ-I and HopZ-II is a conserved sequence of only 20 amino acids in HopZ-I. Furthermore, the conservatism of HopZ-II is higher than that of HopZ-I, and the change frequency of the amino acid sequence is lower [60].

The host receptors of HopZ have not been well characterized yet. Nonetheless, HopZ may play a vital role in adhesion [61]. By analyzing the *hopZ* gene sequences of 15 strains of *H. pylori*, Peck found that the slipped-strand mispairing mechanism of the CT dinucleotide repeats in the signal peptide coding region of the HopZ was correlated with the expression of *hopZ* [62]. After analyzing the bacteria extracted from the stomach of infected patients, Kennemann et al. found that the expression of the gene *hopZ* also depended on the on/off switch mediated by phase variation during the early colonization of *H. pylori*, which indicated that the gene *hopZ* had a strong selectivity in vivo [13]. The *HopZ* gene can be expressed stably in the stomach without mixed infection [63]. At present, there is not enough evidence to prove that HopZ has a relationship with other virulence factors [64]. Moreover, after analysis of 63 patients with chronic infection, it was found that there was no significant correlation between HopZ and chronic atrophic gastritis, and the relationship between HopZ and other clinical diseases is not clear [13].

Hom

The Hom family consists of four OMPs: HomA, HomB, HomC, and HomD. *HomA* and *homB* are highly homologous, with 90% similarity in their nucleotide sequences, with two

identical conserved loci [12]. *HomA*, *homB*, and *homC* sequences have considerable geographic heterogeneity, but *homD* is highly conserved [65]. Oleastro et al. distinguished *homA* and *homB* at the nucleotide and amino acid levels, and found they had six allelic variants named AI–AVI [66]. Three allelic variants were observed for *homA* (AII, AIII, and AIV). In contrast, five distinct alleles were observed for *homB* (AI, AII, AIII, AV, and AVI), suggesting that *homA* has more significant heterogeneity. The expressions of the *homA* and *homB* genes are different in strains all over the world, and there are significant differences between Western and Asian strains [66]. Kim et al. found that *homC* variations in different geographical origins were related to *bab* [67]. They identified and isolated three polymorphic forms of *homC*: *homC^S*, *homC^L*, and *homC^M*. *HomC^L* was found to be most closely related to *bab* after the detection of different populations.

Similar to OipA, HomB can improve the adhesion of *H. pylori* to the host and promote the secretion of IL-8 and other inflammatory factors. A Portuguese study found that HomB had a significant positive correlation with the occurrence and development of PU in children and adolescents [68], and HomA was associated with nonulcerative gastritis [69]. At the same time, some studies also confirmed that there was no significant relationship between HomB and GC [70]. Therefore, whether HomB was positive or not could be used as an important virulence factor to distinguish GC from PU [71].

OMPs as treatment targets

The mechanism of drug resistance of bacteria mainly includes three aspects: producing corresponding hydrolytic and modifying enzymes to destroy drug activity; changing the structure of the drug target so that the drug cannot be recognized; blocking drug contact with target sites, including mechanisms of regulating membrane permeability and the antibiotic expulsion system [9]. With increasing numbers of antibiotic-resistant strains of *H. pylori*, people are devoting much effort to finding other treatments besides antibiotic treatment, and the development of an *H. pylori* vaccine is currently a hot research topic [72, 73].

The whole cell of the bacterium vaccine was first investigated in 1992. Chen et al. [74] used ultrasonic grinding of the bacteria and immunized mice with these antigens and the adjuvant cholera toxin, which provided nearly 100% of immune protection. Due to the complex antigen components of *H. pylori* and the long cycle required for whole cell of the bacterium vaccine production, low production of some strains, their ease of contamination, and poor storage stability, whole cell of the bacterium vaccines was abandoned. Then, came the development of recombinant vaccines that combined protective antigens with immune adjuvants. Immune adjuvants can enhance the body's ability to respond to antigens, especially in

**Table 1** Main OMPs and their receptors and functions

OMPs	Gene no.	Protein length (amino acids)	Receptors identified	Localization	Suggested function
BabA (HopS)	26695:1243	733	Lewis B blood group antigens [19]	Gastric epithelia	Adhesion to host cell, enhancing translocation of CagA via the T4SS
			Terminal fucose residues on blood group O (H antigen), A and B antigens salivary nonmucin glycoprotein [89, 90]	Gastric epithelia	
			Salivary mucin MUC5B and proline-rich glycoprotein [90]	Saliva	
			Proline-rich glycoprotein containing Fucα1-2Galβ motif [90]	Saliva	
			Secretory immunoglobulin A containing fucose-oligosaccharide motifs [91, 92]	Saliva	
			Salivary agglutinin DMBT1 [93]	Saliva	
			Mucin MUC5AC with N-Acetylgalactosamine-β-1, 4-nacetylglucosamine [94, 95]	Gastric mucus	
			Mucin MUC1 [96]	Gastric mucus	
			Mucin MUC2 [97]	Gastric mucus	
SabA (HopP)	26695:0725	653	Sialyl-Lewis X, sialyl-Lewis A, Lewis X [37]	Gastric epithelia	Establishment of the T4SS to enhance inflammatory response
			Salivary mucin MUC7, MUC5B [90, 98]	Saliva	
			Salivary glycoproteins (carbonic anhydrase VI, secretory component, heavy chain of secretory IgA1, parotid secretory protein, zinc α2 glycoprotein) [90]	Saliva	
			Sialylated moieties on the extracellular matrix protein laminin [98]	Gastric epithelia	
			Sialylated structures on the surface of erythrocytes [99]	Erythrocytes	
			Sialylated carbohydrates on neutrophils [100]	Neutrophils	
HopQ	26695:1177	641	CEACAMs family [58, 101]	Leukocytes, granulocytes, endothelial and epithelial cells.	Adhesion to host cell, translocation of CagA via the T4SS
OipA (HopH)	26695:0638	305	Not clear	Not clear	Adhesion, induction of inflammatory cytokine production [44]
HopZ	26695:0009	672	Not clear	Not clear	Involved in adhesion
HomB	J99:0870	669	Not clear	Not clear	HomB promotes the secretion of proinflammatory cytokine IL-8 and increases the adhesion to host cells

OMPs, outer membrane proteins; *T4SS*, type IV secretion system; *MUC*, mucin; *CEACAM*, carcinoembryonic antigen–related cell adhesion molecule; *IL-8*, interleukin-8

the early stages of immunity. Vaccines lacking adjuvants have low or no protective effects [75]. The commonly used immune adjuvants are cholera toxin [76], *E. coli* heat-labile enterotoxin [76], synthetic oligodeoxynucleotides containing unmethylated CPG motifs [77], and aluminum hydroxides [78]. The most commonly used protective antigens include CagA, VacA, urease, catalase, neutrophil-activating protein, Hsp60, BabA, SabA, and OipA [79].

Fig. 1 BabA, SabA, and HopQ bind to respective receptors on mucous layer while the receptors of OipA, HopZ, and Hom remain to be determined. These OMPs promote the adhesion of *H. pylori* to host cells
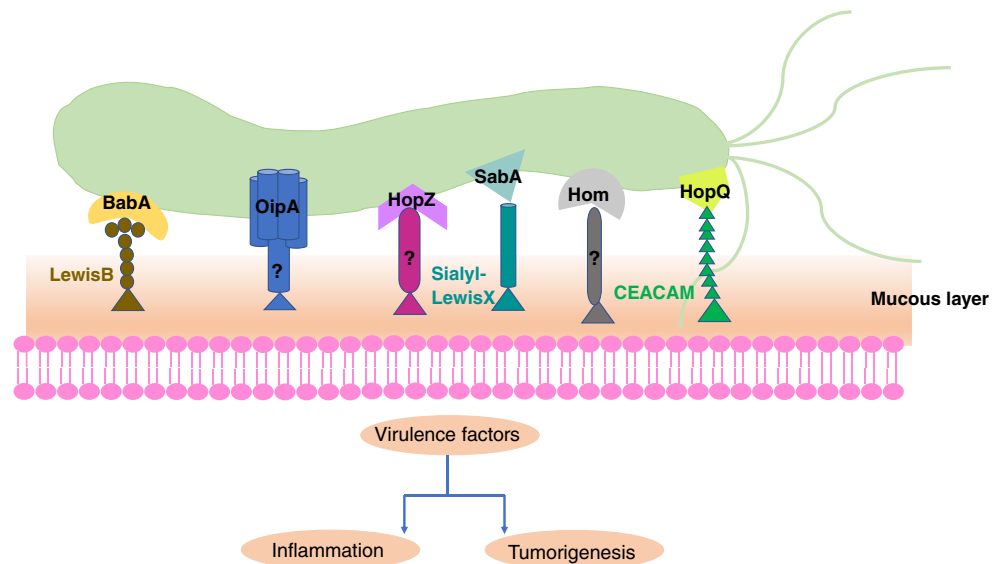
Proteomic studies on *E. coli*, *Leptospira*, and *P. aeruginosa* have proven that OMPs are related to bacterial resistance to antibiotics [80–82]. The adhesion of OMPs can stimulate the immune response of the host cell and promote the intracellular signal transduction of the proinflammatory cells, so OMPs can be used as an immunizing antigen [83]. It is also thought that mucosal immunity, rather than systemic immunity with the production of IgG, plays a greater role in adhesin-based vaccines [84]. There are also many studies using proteomics to evaluate suitable OMPs as possible candidates for vaccines [85]. BabA can be recognized as a candidate vaccine, and the recombinant BabA stimulated the humoral and cellular immunity against *H. pylori* infection [75]. OipA also plays a crucial role in the first step of *H. pylori* colonization-adhesion, so it may be considered as a suitable candidate for vaccine development [53, 86]. Other OMPs, HopB, HopC, and HopZ, are being studied further.

However, the ability of *H. pylori* to vary its OMPs limits the effectiveness of vaccines or therapeutics that target any single one of these components [87]. Peck et al. [88] found four members of OMPs, namely, HopV, HopW, HopX, and HopY. They are highly conserved in the strains analyzed, which suggests they have the potential for vaccine development. No indications of phase variation such as homopolymeric dinucleotide repeats or monomeric G or C tracts were found in the gene promoter regions corresponding to these four proteins, which means that *H. pylori* can continuously express these proteins during all stages of chronic infection, and they are stable as immune antigens. Therefore, the research direction of OMPs as immune antigens is to look for OMPs that are not prone to phase variation or to recombine OMPs with antigens such as CagA, VacA, urease, and catalase to achieve a higher immune protection rate. For asymptomatic infected patients, analyzing the strains isolated from them to determine their expression of OMPs is vital.

This will achieve individualized treatment and reduce the drug resistance rate.

Conclusion

OMPs play a vital role in the colonization of *H. pylori*. The adhesion of *H. pylori* to gastric epithelial cells is a complex process, involving a variety of adhesins and target receptors (Table 1). Diverse OMPs can also rapidly regulate themselves in response to changes in gastric inflammation and pH, to adapt to changes in their environment. OMPs not only mediate the adhesion between the bacteria and the gastric epithelial cells but also cooperate with other virulence factors such as CagA and VacA to increase the release of inflammatory factors, leading to different clinical outcomes (Fig. 1). Therefore, OMPs at least partially determine the virulence of *H. pylori* infection. Understanding the receptor interaction and mechanisms of pathogenesis of OMPs is essential for the prevention and treatment of *H. pylori* infections. Moreover, the potential of OMPs as vaccines should be further explored as an alternative therapeutic option. We expect that further investigations in this direction would help against *H. pylori*–mediated resistance and improve the clinical outcomes of *H. pylori* infections.

Compliance with ethical standards

Ethical approval   There are no ethical issues.

Informed consent   There is no informed consent required for this review article.

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