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• *REVIEW* •

Research progress on *Helicobacter pylori* outer membrane protein

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Abstract

Helicobacter pylori (*H pylori*), one of the most common bacterial pathogens on human beings, colonizes the gastric mucosa. In its 95 paralogous gene families, there is a large outer membrane protein (OMP) family. It includes 32 members. These OMP are important for the diagnosis, protective immunity, pathogenicity of *H pylori* and so on. They are significantly associated with high *H pylori* density, the damage of gastric mucosa, high mucosal IL-8 levels and severe neutrophil infiltration. We introduce their research progress on pathogenicity.

Key words: *H pylori*; Outer membrane protein; oipA; Gastric carcinoma

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INTRODUCTION

Helicobacter pylori (*H pylori*) is a noninvasive bacterium. Since Warran and Marshell isolated *H pylori* successfully in 1983, it has been identified as the major causative factor of chronic gastric and peptic ulcer disease and closely related to the occurrence and development of gastric carcinoma, mucosa-associated lymphoid tissue (MALT) lymphoma. In 1994 international cancer institute had determined it being type I carcinogen[1]. Studies regarding the *H pylori* virulence have primarily focused on urease, vacuolating cytotoxin, and cytotoxin-associated antigen. However, in its 95 paralogous gene families there is a large *H pylori* outer membrane protein (Hop) family. It includes 32 members[2,3], such as adhesin protein, proinflammatory protein, and micropore protein. Although some functions of these OMP have still been indefinite, the scholars at home and abroad have paid attention to them on diagnosis, protective immunity, pathogenicity and so on. The documents show that Hop is significantly associated with high *H pylori* colonization, the damage of gastric mucosa, high mucosal IL-8 levels, and neutrophil infiltration. We will review these aspects of OMP.

OMP AND CHRONIC GASTRITIS AND PEPTIC ULCERS

Adhesin protein

We have known that adherence to the epithelium is an important premise that bacteria settle down in the body. Adherence is believed to help protect the bacteria from gastric acidity, as well as from displacement due to peristalsis. HopZ, babA, and babB (blood-group antigen-binding gene), alpAB (adherence-associated lipoprotein) in the OMP are mainly related to adherence.

HopZ (HP9) is a vital adhesin protein. HopZ is primarily located in the bacterial surface, the number of its amino acids largely vary, ranging from 126 to 281. This is primarily because that HopZ gene suffers length-short regulation of different CT dinucleotide repetitive motif of different strains in the translational level. Birgit Peck[4] discovered that the wild-type strain ATCC43504 (HopZ negative) adhered to human gastric epithelial cells whereas a knockout mutant strain showed significantly reduced binding to the cells. Yamaoka[5] concluded: HopZ was significantly related to *H pylori* density and colonization ability in the mouse model.

babA (HP1234) and babB (HP0896) are OMP of having vital relation with adherence. Because their production binds LewisB antigen of human gastric cells, so are called blood-group-antigen-binding gene. Moreover the activity that the product of $babA_2$ (allele of babA) binds LewisB antigen is higher[6]. But because people discovered *H pylori* expresses LewisB antigen, too. Therefore, some scholars doubt whether gastric epithelial cell-LewisB is the receptor of *H pylori*[7]. Ai-Fu Tang in China[8] persistently researched and testified that LewisB antigen expressed by *H pylori* did not affect *H pylori* adherence to LewisB and summit to secretion of host (secretory people have LewisB antigen in humoral fluid). But the author thought that the $babA_2$ gene was not related to peptic ulcer, the same type of LewisB antigen expressed by *H pylori* as their host had the advantage of evading host immune system to survive, then triggered disease. Furthermore, host may trigger disease through producing autoantibody aiming at LewisB antigen. The research by Zambon[9] showed that $babA_2$ and CagA-s1 and m1(allele of Vac) in *H pylori* acted together, which could obviously worsen the degree of inflammation.

AlpAB is also concerned with adhesion of *H pylori*. At present, it is being ascertained that AlpAB are two kinds of channel-forming membrane pore: hopB and hopC, which are organized in an operon[10]. Through designing the mutant strain AlpA or AlpB, Odenbreit testified AlpAB-specific adherence and concluded that the adherence was independent of the composition of the lipopolysaccharide (LPS)[11].

Proinflammatory

oipA (outer inflammatory protein, oipA), encoding OMP gene of relative molecular mass (M_r) of 34 ku, is called HopH (HP0638). The product is called proinflammatory. As early as 1998, Yamaoka[12] discovered that M_r ranging 33 ku to 35 ku OMP were positively correlated with the level of IL-8. However, there was no relationship between other antigens including CagA and production of IL-8. The 33-35 ku antigen was present in 97.5% patients with gastric or duodenal ulcer compared to 70% those with chronic gastritis. In order to ascertain the genic position of the protein, in 2000, Yamoka[13] designed the knockout mutant strain HP0638(M_r34 ku), HP0796(M_r33 ku), HP1501(M_r32 ku), compared with wild-type about inducing to secrete the level of IL-8. The result showed HP0796 and HP1501 had no significant effect on IL-8 product. However, knockout of the HP0638 gene reduced IL-8 product approximately 50%. Cag-negative strains that contained a functional HP0638 gene produced more than three-fold greater IL-8 than Cag-negative nonfunctional HP0638 strains. So the author denoted HP0638 gene as outer inflammatory protein (oipA). The recent data[14] showed that HP0638 frame status was correlated strongly with CagA, vacA iceA genotypes. All of the strains in which HP0638 was in frame were CagA positive and vacAs1, whereas most of the strains in which HP0638 was out of frame were CagA negative (80%) and vacAs2 (70%). So the author thought it suggested that CagA positivity could affect transcription of HP0638. But Yamaoka[15] discovered in his further research that oipA status remained in the final model to discriminate duodenal ulcer from gastritis. Functional oipA was significantly associated with high *H pylori* density, severe neutrophil infiltration and high mucosal IL-8 levels and further research that polyclonal antisera to either a synthetic oipA peptide or a recombinant oipA protein detected oipA expression in *H pylori* and correlated with functional oipA status determined by PCR sequence[16]. Moreover, the recent research showed that the detecting of oipA+HP was 46.6%. But oipA was detected in patients with gastric ulcer and the rate was 100%, which was obviously higher than in patients with gastritis. Thus, it indicated that oipA was significantly more frequent in patients with gastric ulcer[17].

OMP AND GASTRIC CARCINOMAS

Before discovering *H pylori*, people believed that gastric carcinomas evolved from superficial gastritis to chronic atrophic gastritis , then intestinal metaplasia and turned into gland cancer[18]. Hop played an important role in the process. Zambon[9] research testified that coexpressed by the same *H pylori* strain, CagA, s1 and m1Vac worded synergistically, not only were worsening inflammation, but also were at higher risk for intestinal metaplasia. The scholars in Taiwan[19] discovered that a significant association was found between the serum antibodies against lower-molecular-weight proteins of *H pylori*, especially 19.5 ku and 26.5 ku, and malignant outcome of *H pylori* infection. Wei-Hong Yang[20] discovered that antibody titre of 26.5 ku protein in gastritis group was higher than that in ulcer group, in moderate, severe inflammatory gastritis was higher than that in subinflammatory gastritis. These have the advantage of the occurrence and development of tumor. Therefore some scholars believe lower-molecular-weight OMP may act as gastric carcinomas and its hypercrowd screening , it is a kind of marking antigen[21,22].

OMP AND IMMUNITY

Cytokine

When infected by *H pylori*, inflammatory cytokine induced by OMP plays an important role in *H pylori* pathopoiesis. It has been definite that oipA is positively correlated with product of IL-8 as former statement[12]. Petra[23]discovered that HpaA and OMP18(M_r18 000) induced IL-12 and IL-10 to secrete when researching their antigenicity . IL-8 is an main inflammatory promoter and regulatory factor. IL-12 was obviously positively correlated with the degree of T lymphoid infiltration in the mucous membrane and worsen gastric mucous inflammation[24].

Vaccinal research

Most OMP locates the surface of bacterial body, surface exposing, conserving relatively, inducing humoral immunity and so on. Thus, since early, people have begun researching its protective immunogenicity, but can get partial effect on protecting immunity[25,26]. Nowadays, many scholars have researched polyvalent vaccine. Zheng Jiang succeeded in constructing divalent vaccine of HpaA,OMP18 (M_r18 000) and HpaA, OMP26 (26 000), which laid the foundation of constructing *H pylori* protein vaccine[27,28].

CONCLUSIONS AND PERSPECTIVES

There are other OMP which deserve to be further studied. For example, Ping Cao[29]through researching two HopQ alleles discovered that type I HopQ alleles were found significantly more commonly in cag^+/s1-vacA strains from patients with peptic ulcer disease than in cag^-/s2-vacA strains from patients without ulcer disease. But Akihiro[30]through researching OMP29 (M_r29 000) from being isolated ATCC43504 strains discovered that OMP29 could alter its antigenicity through gene modifications mediated by nucleotide transfer. These discovers are looking forward to further probing and studying. At present, genome sequence of *H pylori* OMP have finished, but the function of many OMP has been indefinite: how on earth they induce to disease, the relation with other virulence factor: Cag pathogenicity island and VacA, which antigenicity is more. These are still not clear. However, there are many questions in former research, for example , Yamaoka thought oipA frame status was an unique index that discriminated duodenal from gastritis. But the author didn't examine gene of encoding 35 ku protein. Wei-Hong Yang[20] in China did the correlation research and discovered that in quantitative study ,the antibody titre of 35 ku protein in original duodenal bulb ulcer group was obviously higher than that in chronic superficial gastritis group.

In a word, researching virulence and pathogenicity of *H pylori* is a vital significance. This can discover new strains and further illuminate pathogenic mechanism, on the other hand, can provide basis for vaccinal screening, designing and immunity strategy. This can avail the development of a new particularity diagnosis reagent kit.

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