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REVIEW

Helicobacter pylori BabA in adaptation for gastric colonization

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Abstract

Helicobacter pylori (*H. pylori*) as a causative agent of gastric complications, is well adapted for the colonization of gastric mucosa. Although the infectious process depends on several factors, the adhesion to the gastric mucosa is the first and important step. Among several outer membrane proteins, BabA is one of the significant protein involving in many inflammatory processes in addition to its role in the attachment for the persistent colonization. We performed a PubMed search using the key words: "*babA*", "pylori", "gastric complications", "homologous recombination", "slipped strand mispairing"; a total of 249 articles were displayed. Of these we mainly focused on articles with the full text in English and published between 2005 and 2016. *H. pylori* BabA is involved in binding with receptors; however, its synthesis is regulated by phase variation. In this review we confirm that *H. pylori babA* can be modulated at the molecular and functional levels to adapt to the stress within the gastro-intestinal tract.

Key words: BabA; Gastric complications; *Helicobacter pylori*; Homologous recombination; Slipped strand mispairing

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Core tip: *Helicobacter pylori* are well adapted to colonize the gastric mucosa. Although the infectious process depends on several factors, adhesion to the gastric mucosa is the first and critical step. Among outer membrane proteins, BabA is an important protein involved in many inflammatory processes in addition to playing a role in the aforementioned attachment process. In this review, we have summarized the current, published knowledge regarding its functional and molecular aspects by which the pathogen can attach to the host cell receptors.

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INTRODUCTION

The *Helicobacter pylori* (*H. pylori*) is a helical, Gram-negative bacterium that chronically infects the stomach of half of the world's population[1]. Since this bacterium is strongly associated with the development of duodenal ulcer and gastric cancer, International Agency for Research on Cancer categorized this bacterium under strong carcinogen (group I carcinogen) in 1994[2,3]. The global burden of gastric cancer is high which accounts for 6.2% of cancer burden worldwide[4]. However, the appearance of new cases of gastric cancer has been found variable in developing (8.4%) and developed countries (4.5%)[5]. Mortality rate due to the gastric cancer is the third most common cause among all cancer related deaths[6,7].

Although the exact means of transmission of this bacterium is not understood clearly the evidences suggest that this bacterium is transmitted from person to person contact between family members *via* fecal-oral or oral-oral route and mostly the infections are acquired in childhood[8-10]. The data from epidemiological studies conducted support the transmission of infection by exposure to contaminated water or food as well[11,12]. The socio-economic status of family highly reflects the infection rate among peoples as the infection rate tends to be higher in peoples belonging to family with low socio-economic status[13]. This contribution highly suggests the higher prevalence rate of *H. pylori* infection in developing countries than the developed countries. The infection rate ranging from 70%-90% and 25%-50% in developing and developed countries respectively[14].

H. pylori related clinical outcomes also depend on the ancestral relation between human and bacterium as suggested recently. The individuals infected with non-ancestral strains that are not evolutionarily adapted to their host develop severe histo-pathological damage and clinical outcomes than infected with co-evolutionarily developed strains[15]. However, being a truly opportunistic pathogen, the *H. pylori* utilizes the various virulence factors such as CagA and VacA as the effector protein for the development of gastric diseases[16] and the outer membrane proteins (OMPs) such as blood group antigen binding adhesion (BabA), sialic acid binding adhesin (SabA), and outer inflammatory protein (OipA) found on the surface (adhesins) of bacterial cell envelop for the attachment to the mucus layer of the gastric epithelium playing an important and initial step for the colonization and development of persistent infection for decades or for entire life time[17-19].

LITERATURE SEARCH

We conducted a PubMed search using the key terms "*babA*", "pylori", "gastric complications", "homologous recombination", "slipped strand mispairing"; 249 articles were found during the search. We focused on, but did not limit ourselves to, articles with the full text in English and published between 2005 and December 2016. For greater clarity and insight we considered few articles published between 1989 and 2005. We retrieved a total of 98 articles that studied BabA and its paralogs, presence, function, production, and role in the development of gastric complications, attachment to host cells, and adaptation. Abstract only publications, case reports, editorials, and review articles were excluded. While performing the search, irrelevant articles with authors' family names as 'Baba' were also excluded. We also performed a literature search in Google using the terms: "pylori", "gastric cancer", and "slipped strand mispairing". Through this, we selected three reports that were not indexed in PubMed.

bab paralogous genes and their chromosomal location

H. pylori colonization elicits humoral and cellular immune responses although, ineffective in the bacterial clearance. However, despite of the peristaltic movement of the intestinal tract and movement of the chyme, the bacterium establishes the strong interaction with the epithelial surfaces. The bacterial attachment on the epithelial surface is the interaction between the receptor molecules on the host cell surface and adhesin molecules found on the bacterial cell envelope and this interaction is the first and important step of the *H. pylori* related pathogenicity. The Gram-negative bacterial cell envelope consists of two concentric lipid bilayers, the inner membrane (cytoplasmic membrane) and the outer membrane. More than 50% of the outer membrane mass consists of OMPs. *H. pylori* genome encodes a large number of OMPs and most of them are surface exposed and consists of transport channels (porins), and adhesins. The closely related (at least partially redundant)

Table 1 Chromosomal location of *babA*, *babB* and *babC* genes in different strains

Strain	Locus A	Locus B	Locus C
26695	*babB*	*babA*	*babC*
J99	*babA*	*babB*	No corresponding gene
HPAG1	*babA*	*babC*	*babB*
G27	*babC*	No corresponding gene	*babA*
51	*babA*	*babB*	No corresponding gene
Shi470	*babA*	*babB*	No corresponding gene
P12	*babA*	*babB*	*babB* homolog[1]
52	*babA*	*babB*	No corresponding gene
B38	*babA*	No corresponding gene	No corresponding gene
v225d	*babA*	*babB*	No corresponding gene
SJM180	*babB*	*babC*	*babA*
PeCan4	*babA*	*babB*	No corresponding gene
Sat464	*babA*	*babB*	No corresponding gene
35A	*babA*	*babB*	No corresponding gene
India7	*babA*	*babB*	No corresponding gene
Gambia94/24	*babA*	*babB*	No corresponding gene
SouthAfrica7	*babA*	*babA*	No corresponding gene
Oki112	*babA*	*babA*	No corresponding gene
Oki154	*babA*	*babB*	No corresponding gene
Oki828	*babA*	*babA*	No corresponding gene
J166	*babA*	*babB*	No corresponding gene
SNT49	*babA*	*babB*	No corresponding gene
Puno120	*babA*	*babB*	No corresponding gene
Puno135	*babA*	*babB*	No corresponding gene
B8	*babA*	*babA*	No corresponding gene
83	*babA*	*babB*	No corresponding gene
ELS37	*babB*	*babA*	No corresponding gene
HUP-B14	*babA*	*babC*	No corresponding gene
F16	*babA*	*babB*	No corresponding gene
F30	*babA*	*babB*	No corresponding gene
Hp238	*babA*	*babB*	No corresponding gene
BM013A	*babB*	*babB*	No corresponding gene
29CaP	*babA*	*babA*	No corresponding gene

[1]Although the gene is homologous to babB but due to the insertion of adenine (A) caused the formation of stop codon and premature termination.

proteins are grouped into paralogous families[20].

Among the large group of adhesins identified BabA, SabA, adherence associated lipoprotein A and B (AlpA/B), OipA, and HopZ[17,18,21-24], BabA (or HopS or OMP28) is around 75-80 kDa major OMP which was the first identified member of adhesin family[25]. Two other closely related paralogs to BabA has been found, the BabB (HopT or OMP19) and BabC (HopU or OMP9)[26]. The function of BabB and BabC is not known yet and needs to be determined. The *bab* gene sequence analysis revealed that there is extensive 5' and 3' region homology particularly between *babA* and *babB* but the variability in middle region of sequence suggests that the middle divergent region of *babA* likely mediates the binding function[26,27].

The *babA, babB* and *babC* genes can be located in at least 3 different chromosomal loci. The three marker genes *hypD, s18* and heme oxygenase gene *hp0318* represent the chromosomal location of *bab* genes. The *bab* gene found downstream of *hypD*, *s18* and *hp0318* is said to be located at locus A, locus B and locus C respectively[28]. For example; in strain J99 (where *babC* is absent), *babA* (*jhp0833*) and *babB* (*jhp1164*) are located downstream of *hypD* and *s18* (locus A and locus B) respectively whereas in strain 26695, the locations for *babA* and *babB* are reversed; *babA* (*hp1243*), *babB* (*hp0896*) and *babC* (*hp0317*) are located downstream of *s18, hypD* and *hp0318* (locus B, locus A and locus C) respectively. Similarly, in strain HPAG1, the *babA, babB* and *babC* are located downstream of *hypD*, *hp0318* and *s18* (locus A, locus C and locus B) respectively whereas in strain G27 (where *babB* is absent), *babA* and *babC* are located downstream of *hp0318* and *hypD* (locus C and locus A) respectively and in strain 51 (where *babC* is absent), the *babA* and *babB* are located downstream of *hypD* and *s18* (locus A and locus B) respectively[29-31] as shown in Table 1. We made an attempt to find the *bab* genes in respective to their genomic locus in different strains deposited in gene bank. Among *H. pylori* deposited in gene bank by 30 November 2016, we randomly selected the 33 strains for the characterization of chromosomal locations of *bab* genes *(babA, babB and babC)* (Table 1). Although, the chromosomal locations of *babA, babB* and *babC* in few strains such as J99, 26695, HPAG1, G27 and 51 already have been described yet in other strains we made an effort to document the chromosomal location of these genes. In strain P12 there is a *babB* homologous gene at locus C but due to the insertion of one adenine (A) at position 679 resulted the shift in the nucleotide frame and the stop codon at position 230 and premature termination of the amino acid sequence. The reports of several studies from various parts of the world depicts that in majority of the strains *babA* and *babB* prefers to be located at locus A and locus B respectively[28-30,32]. Despite of the three identified loci there can be an unidentified locus. In a study, Hennig *et al*[29] found *babA* sequences from 2 strains not located at locus A, B or C and they hypothesized that there may be a yet not identified chromosomal locus for *babA*.

Production of BabA

As discussed in previous section, the *babA* can be located in at least three different identified loci. The BabA production has been claimed to be influenced by its genomic location. In strain J99, *babA* located at locus A is expressed and binds with Lewis blood group (Leb) antigen whereas in strain 26695; *babA* located at locus B is not expressed and does not bind to Leb antigen[33,34]. The detailed mechanisms involved in the expression of *babA* have not been depicted in detail. However, we have summarized the possible mechanisms published in several literatures.

The strain CCUG17875 was reported to possess two alleles of *babA* denoted as *babA1* found at locus B and *babA2* found at locus A[34]. The allelic form *babA1*

does not contain the translation initiation codon ATG because of the deletion of 10 bp including start codon in its signal sequence and is not expressed whereas the *babA2* containing the translation initiation codon ATG is expressed and involved in the Leb binding activity[34]. The expression of *babA* can be influenced on transcriptional as well as translational level. The absence of translation initiation codon ATG in *babA1* influence the translation, but this phenomenon is quite uncommon. Nonetheless, unfortunately, several epidemiological studies still use the methods to characterize *babA2* as the functional status of *babA* by using primers specific for the signal region to differentiate *babA1* and *babA2*. The presence of variable number of cytosine-thiamidine (CT) dinucleotide in the 5'-region of the *babA* sequence due to the intra-genomic recombination with *babB* leads to the phase variation and affects the expression of *babA* (discussed in latter section). The characteristics of the promoter sequence also play a critical role in the expression of *babA*. During protein expression all mRNAs are not synthesized in the same amount because of the promoter characteristics which controls the expression on transcriptional level. In a study, the presence of additional 4 adenines between the -10 and -35 motif in *babA* located at locus B could diminished the strength of the promoter of *babA*[34]. The nucleotide structure of -10 and -35 motifs sequence and the characteristics of nucleotides present between the -10 and -35 motifs tend to make the promoter strong or weak. For example, the promoter region of one of the OMP gene *sabA* contains a thymidine (T) nucleotide repeat tract adjacent to the -35 motif and the length of this T-tract varies between strain to strain and this variation have been suggested to affect the expression of *sabA*[35-37]. Recently it has been also suggested that the T-tract modulates the binding of RNA polymerase σ-factor and α-factor resulting in the alteration of SabA expression[38]. The nucleotide repeat motifs located between the -35 and -10 promoter motifs influence the docking of RNA polymerase σ-factor and the nucleotide repeat motif located upstream of -35 motif alters the binding of regulatory factors of RNA polymerase[38]. However, the detailed studies are needed to evaluate the characteristics of promoter regions responsible for the variation in expression of *babA* in loci A/B/C.

H. pylori babA is highly polymorphic being susceptible for the changes in their regulatory and coding sequence that leads to the loss of BabA expression in multiple animal models including mice, gerbils and macaques; therefore, it is difficult to study the role of BabA contribution in the development of gastric damages[39]. However, it has been shown that in *H. pylori* isolated from the chronically infected persons, the BabA expression was maintained in three quarter of the isolates surveyed over time and it suggests that there is selective advantage for BabA expression in human host[40].

Occurrences of babA containing H. pylori

Most epidemiological studies have reported the *babA* functional status using the *babA2* specific primers designed to detect the 10-bp deletion in the signal region of the *babA1* allele and its association with increased risk for gastric inflammation[41]. The reported prevalence of *H. pylori* containing *babA* shows great variation across different parts of the world[28,32,42-55] as shown in Table 2. However, we previously reported the BabA expression level by immunoblotting and Leb binding in diverse collection of *H. pylori* strains and divided in to high, low, and non BabA expressing strains[52]. The strains expressing low level of BabA were associated with higher incidence of gastrointestinal damages as compared to BabA with high expression and BabA negative strains. It was concluded that although, the *babA*2 detection provides an indication of functional *babA* status, it may not reliably reflect the complete information of genetic variants for *babA* expression.

BabA and its binding receptors

Adherence of *H. pylori* to the host cell receptor provides several benefits to the bacteria such as protection from the washing out during mucus shedding, provides nutrient access from damaged host epithelial cells, promotes delivery of the bacterial toxins and other effector molecules to the host cells for development of pathogenicity and facilitates the development of persistent infections[56-58]. The attachment of bacteria to the host cells also elicits immune response; however, no longer protective in *H. pylori* infection. Several functional molecules serving as a receptor for the binding of *H. pylori* through BabA has been reported (Table 3).

Since the postulated transmission for the *H. pylori* infection takes place through oral route, the possible initial attachment could be occurred with the salivary proteins. The BabA mediates the attachment by binding with difucosylated glycans found on Leb antigens of the salivary mucin MUC5B serving as a receptor for BabA[59,60]. The surface immobilized salivary agglutinin; glycoproteins-340 (gp-340) also provides the platform for the attachment of BabA[61]. Salivary prolin rich glycoprotein (PRG) is the major component of parotid and submandibular saliva containing several repeats of short prolin rich sequence. Salivary PRG containing Fucα1-2Galβ motif also provides the access for the attachment of BabA[59]. The secretory immunoglobulin A (s-IgA) is the major immunoglobulin found in the mucus secretions which protects the mucus membrane from invading organisms. However, the fucose-containing oligosaccharide motifs on s-IgA could play a role in the binding phenomena of BabA[17]. However, in a study this phenomenon was not confirmed suggesting that the variation in the glycosylation and sialylation between the salivary and gastric s-IgA or the proportions of s-IgA1 and s-IgA2 subclasses

Table 2 Prevalence of *babA* in different Asian and other countries

Ref.	Countries	Criteria for *babA* positive	Prevalence	Year
	Asia			
Abdullah *et al*[43]	Iraq	Positive with *babA2* specific primers	33.7% in NUD and 58.8% in PUD	2012
Karabiber *et al*[44]	Turkey	Positive with *babA2* specific primers	49% in gastritis	2014
Abadi *et al*[45]	Iran	Positive with *babA2* specific primers	Overall-40.6% 95%-GC, 18.1-DU, 26.1-NUD	2013
Yadegar *et al*[46]	Iran	Positive with *babA2* specific primers	Overall-96.7% 94.4%-NUD, 100%-PUD, 100%-GE, 100%-GC	2014
Saberi *et al*[42]	Iran	BabA expression	Overall-62%	2016
Osman *et al*[47]	Malaysia	Positive with *babA2* specific primers	41%-NUD	2015
Boonyanugomol *et al*[48]	Thailand	Positive with *babA2* specific primers	Overall-66.2%, 70.7%-CCA, 54.5%-Cholelithiasis	2012
Chomvarin *et al*[49]	Thailand	Positive with *babA2* specific primers	Overall-92% 92%-NUD, 85%-GU, 100%-DU, 94%-GC	2008
Ghosh *et al*[50]	India	Positive with *babA2* specific primers	Overall-67.5% 65.6%-NUD, 70%-DU	2016
Con *et al*[51]	Japan	Positive with *babA2* specific primers	Overall-96.8%	2010
Fujimoto *et al*[52]	Japan	Leb binding activity	Over all-88.0%	2007
Kim *et al*[32]	South Korea	Positive with *babA* specific primers	Overall-47.5%	2015
	Other countries			
Kim *et al*[32]	United States	Positive with *babA* specific primers	Overall-90%	2015
Biernat *et al*[53]	Poland	Positive with *babA2* specific primers	Overall-23.1% 18%-NUD, 30%-PUD, 31.8%-GERD	2014
Homan *et al*[54]	Slovenia	Positive with *babA2* specific primers	Overall-47.9%	2014
Boyanova *et al*[55]	Bulgaria	Positive with *babA2* specific primers	Overall-48.8% 59.3%-PUD, 43.5%-NUD	2010
Matteo *et al*[28]	Argentina	Positive with *babA* specific primers	Overall-67%	2011
Con *et al*[51]	Costa-Rica	Positive with *babA2* specific primers	Overall-73.7%	2010
Fujimoto *et al*[52]	Colombia	Leb binding activity	Overall-83.0%	2007

NUD: Non-ulcer disease; PUD: Peptic ulcer disease; GC: Gastric cancer; DU: Duodenal ulcer; GE: Gastric erosion; CCA: Cholangiocarcinoma; GERD: Gastroesophageal reflux disease; GU: Gastric ulcer.

Table 3 BabA receptors found on oral cavity and in stomach

Receptors identified	Localization	Ref.
Mucin MUC5B	Saliva	Walz *et al*[59] and Prakobphol *et al*[60]
Agglutinin glycoprotein-340 (gp-340)	Saliva	Prakobphol *et al*[61]
Prolin rich glycoprotein containing Fucα1-2Galβ motif	Saliva	Walz *et al*[59]
Secretory immunoglobulin A containing fucose-oligosaccharide motifs	Saliva	Borén *et al*[17] and Royle *et al*[62]
Salivary agglutinin DMBT1	Saliva	Issa *et al*[63]
Lewis b blood group antigen (Leb) and terminal fucose, H1-antigen, A-antigen and B-antigen	Gastric epithelia	Borén *et al*[17] and McGuckin *et al*[64]
Mucin MUC5AC with N-acetylgalactosamine-β-1,4-N-acetylglucosamine	Gastric mucus	Lindén *et al*[68] and Kenny *et al*[69]
Mucin MUC1	Gastric mucus	Lindén *et al*[71]
Mucin MUC2	Gastric mucus	Cohen *et al*[72]

which are known to be differently glycosylated may play this role[62]. Similarly, a salivary agglutinin called the deleted in malignant brain tumors 1 (DMBT1) is expressed in saliva and composed of highly fucosylated oligosaccharide. The salivary DMBT1 was found to act as the receptor to interact with BabA[63].

After transit to the stomach, the bacterium localizes to the specific locations and mediates adaptation through several ways. The gastrointestinal epithelium is covered by a semi-permeable mucus layer primarily consists of secreted mucins that protects the gastric epithelial surface by trapping the invading materials[64]. However, the attachment of bacteria to the epithelial surface mediates the survival adaptation and persistent infections. The di-fucosylated glycan found on Leb and mono-fucosylated glycans found on H1-antigen, A-antigen and B-antigen of blood group O, A and B respectively binds with BabA[17,33,65]. However, the binding affinity of BabA with H1 antigen is low because it lacks the Leb Fuc4 residue that forms a hydrogen bond with amino acid asparagine (N) at 206 position of BabA[66] as described below in next section. These antigens are expressed on the mucus surface and gastric epithelial surface of which the Leb antigen is the dominant antigen found on the surface of gastric epithelial cells and it is also the most studied receptor

Table 4 Oligosaccharides found in Leb involving in binding with amino acid of BabA

Oligosaccharide in Leb	Amino acid in BabA	Position of amino acid in BabA
Fuc1	Cysteine (C)	189
Fuc1	Glycine (G)	191
Fuc1	Asparagine (N)	194
Fuc4	Asparagine (N)	206
GlcNAc3 or Gal5	Aspartic acid (D)	233
Gal5	Serine (S)	234
GlcNAc3 or Gal5	Serine (S)	244
Fuc1	Threonine (T)	246

for BabA attachment[67].

Similarly, other molecules have also been reported to play a crucial role in the binding of BabA. The gastric mucin MUC5AC with N-acetylgalactosamine-β-1,4-N-acetylglucosamine residues on O-linked oligosaccharides from gastric MUC5AC has also been reported to act as receptor for BabA[68,69]. Most recent immunohistochemistry laden tissue profiling assay using mice model showed that the expression of Leb structure is a mucin α 1,2-fucosyltransferase (FUT2) enzyme dependent and consequently identified MUC5AC as the carrier molecule of the Leb structure[70].

The MUC1 is also notable to discuss. In case when bacteria do not bind to MUC1, an extracellular mucin domain of 200-500 nm long appears that physically distances the bacteria from the host cell surface and in case when it does bind MUC1, the extracellular mucin domain is released from the epithelial surface[71]. In another study by Cohen *et al*[72] conducted in children, the gastric mucin MUC2 was reported to be expressed in few foleolar cells and it was shown to participate in binding with BabA but only in 11.11% of children. Therefore, fucosylated glycans found on several glycoprotein molecules serve as the receptor.

Insight into BabA binding with receptors

The detailed molecular determination of BabA binding with its receptor Leb was studied recently by Hage *et al*[66]. They depicted that the Leb oligosaccharide molecules involving in the binding with BabA consists of two fucose residues (Fuc1 and Fuc4), two galactose residues (Gal2 and Gal5), an N-acetylglucosamine residue (GlcNAc3), and a glucose residue (Glc6). Using strain J99 as an experimental model they found that 8 highly conserved amino-acids of BabA involved in the interaction with Leb by hydrogen bond formation. The bond formation occurs between amino acid cysteine (C) at position 189 and Fuc1 (C189:Fuc1), glycine (G) at position 191 and Fuc1 (G191:Fuc1), asparagine (N) at position 194 and Fuc1 (N194:Fuc1), asparagine (N) at position 206 and Fuc4 (N206:Fuc4), aspartic acid (D) at position 233 and GlcNAc3 (D233:GlcNAc3), aspartic acid (D) at position 233 and Gal5 (D233:Gal5), serine (S) at position 234 and Gal5 (S234:Gal5), serine (S) at position 244 and GlcNAc3 (S244:GlcNAc3, Gal5), serine (S) at position 244 and Gal5 (S244:Gal5) and threonine (T) at position 246 and Fuc1 (T246:Fuc1) (Table 4). They also elaborated that the binding of N at position 206 with Fuc4 determines the binding affinity and substitution of N with alanine (A) at position 206 resulted in the reduction of binding affinity by about 2.3-fold and the binding of BabA with H-1 which lacks Fuc4 residue of Leb showed about 2.4 fold reduction in binding affinity[66]. Despite of the role of Leb for providing the binding receptor and enhancing the colonization, the several reports indicate the antagonistic effect of Leb. In a study led by Lindén *et al*[73] found that the individuals with Leb-negative showed significantly higher *H. pylori* density than Leb-positive, which is in accordance with the result obtained in a study using Rhesus monkey[74]. Therefore, it can be said that although, the attachment of bacterium *via* BabA-Leb is important but not elusive.

Based on their ABO blood group antigen binding preferences, BabA bearing *H. pylori* strains can be classified as "specialists" and "generalists". The specialist strains prefer to bind only on blood group O specific glycans whereas generalist strains bind blood group O as well as blood group A and B specific glycans[65]. Till recently the detailed insight concept about the binding of specialists and generalists with the mono-fucosylated glycan on A, B and O blood group was unknown. However, recently the X-ray structures of the BabA specialist and generalist adhesins have been revealed according to the O and ABO blood group preferences[75]. The preference shifting was found to be due to the single amino acid substitution in its carbohydrate binding domain. The carbohydrate binding domain contains one conserved loop (CL2) and two diversity loop (DL1 and DL2). The loop DL1 is responsible for making the BabA to be either specialist or generalist. Binding of specialists with blood group O antigen involves only CL2 and DL2 loops while the binding of generalists involve CL2, DL2 as well as DL1 loops. In specialists BabA, the domain DL1 contains the amino acid leucin (L) at 198 position which makes the DL1 to be inaccessible for binding with larger glycans present on blood group A and B. The replacement of L to serine (S) in generalists makes the DL1 to be accessible for the glycans found on blood group A and B as well as O (Figure 1). In this way the generalists can bind with glycans found on blood group A, B as well as O antigen whereas the specialists can bind the glycan found on blood group O antigen only[75]. Therefore, this capability of binding explains why the peoples of blood group O are more prone to develop duodenal ulcers[65]. The fucosylated oligosaccharide residue found on the H1 antigen is abundantly expressed by the healthy gastric mucosa of most Western peoples which makes them more susceptible to colonize by generalists as well as specialists and for the development of peptic ulcer[17,76].

The binding of BabA to the Leb receptor is severely affected by the level of BabA production which is

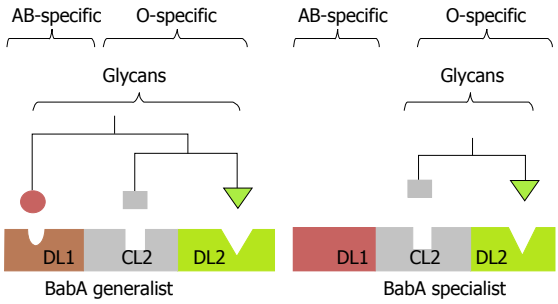

Figure 1 In BabA generalists the serine (S) at position 198 makes the DL1 domain to be accessible for the glycan found on blood group A, B as well as O antigen whereas in BabA specialists the replacement of S to leucine (L) makes DL1 to be inaccessible for binding with larger glycans present on blood group A and B antigen.

mediated on transcriptional and translational level. We detected that the strains expressing low levels (less than 10% to that of J99) of BabA protein did not mediate the enough Leb binding activity whereas, the strains expressing high level (more than 20% to that of J99) of BabA did enough Leb binding[52]. However, Saberi *et al*[42] categorized the *H. pylori* strains in four types depending on the BabA expression and Leb-binding, strains expressing high level BabA showed high Leb-binding, strains expressing low level BabA showed low Leb-binding whereas strains with no BabA expression showed no Leb-binding (8%) as well as low Leb-binding (30%) activity.

Homologous recombination and bab chimera formation

Recombination between similar sequences is called the homologous recombination. Homologous recombination takes part in the double strand DNA repair caused by environmental stress and it aids adaptation advantage for the development of persistent colonization to *H. pylori* to the changing gastric environment within a single host or to the new host[77-79]. *H. pylori* exhibits the highest genetic recombination rate than any other known bacterial species[80] and it suggests that the bacteria has a selective advantage of genetic recombination for long term survival and colonization in human stomach[81].

The allelic diversity in *H. pylori* is remarkable and it exhibits high transformation mediated homologous recombination[77]. Recent analyses of sequential sampling of *H. pylori* from the same individual elaborated the OMPs *futB, babA* and *hopZ* to be the genes with high recombination events whereas the *hopQ* with low recombination[82,83]. Although the function of the most closely related *babA* paralogs; the *babB* and *babC*, is unknown yet but extensive sequence similarity shows the intra-genomic recombination between these genes and the evolution of *bab* chimera[35]. The RecA-dependent intragenomic recombination between homologous genes causing fusion of portions of two or more coding regions results in the formation of chimeric genes. In *H. pylori* the recombinational gene conversion occurs in homologous genes *babA, babB* and *babC*. The formation of chimeric *babB/A* can lead to a non Leb binding strains regain Leb binding activity or it can abolish *babA*-dependent adhesion[35,84]. Varying proportions of chimeras have been reported from different studies across the world. In a study by Matteo *et al*[28], the chimeric *babA/B* gene was observed in 20% whereas chimeric *babB/A* gene was observed in 15%. Similarly, in another study among American and Korean strains, the *babA/B* chimera, *babB/A* chimera and *babB/C* chimera was identified in 28.7%, 2.5% and 1.25% respectively among American strains whereas *babA/B* chimera and *babB/A* chimera was identified from 6.25% and 1.25% respectively from Korean strains. The *babA/B* was most prevalent type of *bab* chimera among all types of chimera reported[32].

Slipped strand mispairing and phase variation

Slipped strand mispairing (SSM) is a phenomenon of either deletion or insertion of nucleotides during DNA replication because of the short, contiguous homogenous or heterogeneous repetitive DNA sequence of 6 base pairs or less. This repetitive sequence, susceptible for mispairing is designated as short sequence repeats (SSR), microsatellites or variable number of tandem repeats (VNTR)[85,86]. SSM is one of the mechanisms resulting in the phase variation that produces nucleotide mispairing between the mother and daughter strand during the DNA replication[87,88]. The OMP genes such as *babB, hopZ, oipA* that possess the dinucleotide CT-repeats in the 5'-coding region, likely undergo SSM to regulate their expression by phase variation[18,89,90]. Nucleotide slippage can be occurred in replicating or template strand. If slippage occurs in replicating strand, there is insertion of one CT-dinuleotide and if slippage occurs in template strand, there is deletion of one CT-dinucleotide (Figure 2)[91]. This phenomenon leading to the variation in the number of CT-dinucleotides over time may provide certain advantages for adaptation to different niches and stomach micro-environments *via* immune evasion or adhesion. In *H. pylori*, the fragments of *babB* containing CT repeats may recombine with *babA* or *babC* resulting in the formation of chimeric genes. According to the Bäckström *et al*[34] the strains with in-frame protein expression (ON) status contain 8-CT repeats whereas out of frame protein expression (OFF) phenotypes contained 7 or 9 CT repeats. The gain or loss of one CT-dinucleotide creates frame shifts and loss of expression of *babA*.

The number of CT-repeats in the 5'coding region of nucleotide sequence decides whether the protein expression is ON or OFF. The protein expression becomes in-frame if the number of CT-repeats is 5, 8, 11 and 14 whereas if the number of CT-repeats is 6, 7, 9, 10, 12, 13 it makes protein expression out of frame[30,34,84]. Out of frame status of protein

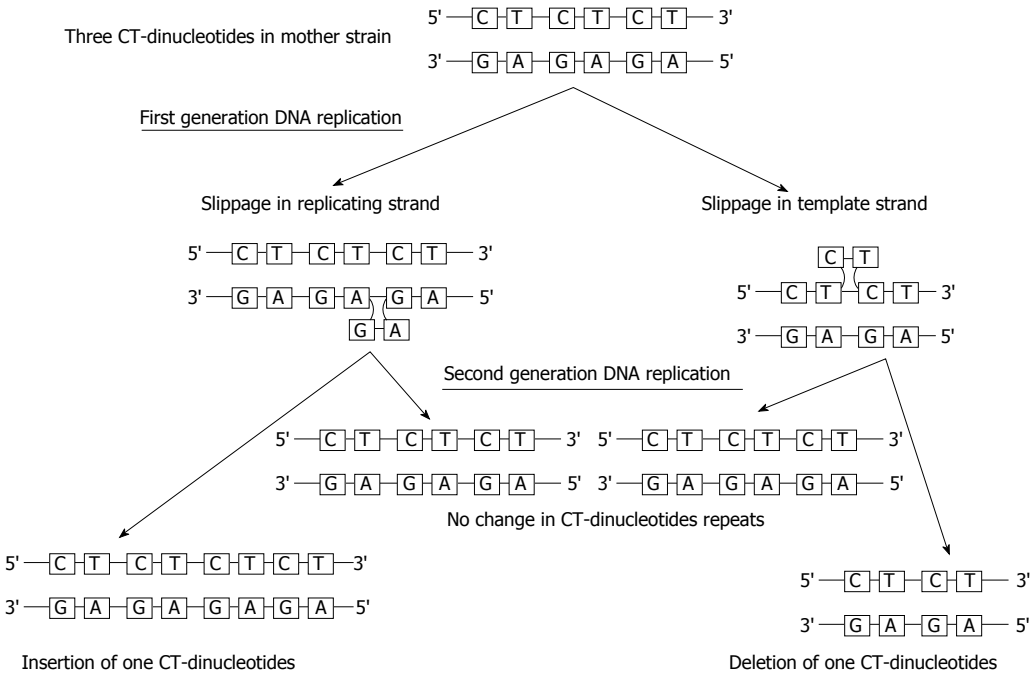

Figure 2 Cytosine-thiamidine-dinucleotide repeats and slipped strand mis-pairing. Both replicating and template strands are prone to undergo for slippage mis-pairing. Slippage occurring in replicating strand during first generation of replication causes insertion of one CT-dinucleotide in replicating strand whereas the template strand contains original number of CT-dinucleotide. If slippage occurs in template strand during first generation replication, one CT-dinucleotide is deleted in replicating strand to make base paring. During second generation of DNA replication, out of two progeny generating from slippage in replicating strand, one progeny contains DNA with one CT-dinucleotide more than the mother strain while the other progeny contains same number of CT-dinucleotide as mother strain. During second generation of DNA replication, out of two progeny generating from slippage in template strand, one progeny contains DNA with one CT-dinucleotide less than the mother strain while other progeny contains DNA with same number of CT-dinucleotide as do mother strain. CT: Cytosine-thiamidine.

expression evolved due to the insertion or deletion of one nucleotide resulting in the truncated (immature) proteins whereas if the status is in-frame it results in the full-length protein expression[92].

The genes containing variable number of nucleotide repeats may go to the phase variation. Phase variation is an adaptation mechanism that provides advantages for colonization[93]. In a study, the BabA expression was lost during the experimental infection in rhesus macaques by phase variation or allele replacement with BabB and in subsequent follow up study in mouse, the BabA expression was found to be lost due to phase variation in 5'-CT repeat regions of *H. pylori* strain J166[39]. The Leb binding clones from OFF to ON phase conversion express BabA adhesin that are functionally equivalent to the wild type but the quantity of BabA adhesin less abundant than the wild type[34].

Other clinical significance of BabA mediated attachment

The attachment of *H. pylori via* BabA mediates several outcomes. *H. pylori* BabA binds with Leb and induces the double strand breaks in the host cells, which is thought to be independent of VacA, γ-glutamyl transpeptidase and the *cag* PAI[94]. However, it has been also confirmed that BabA-positive status of infecting strains is associated with CagA-positive, OipA-positive (*oipA* "on") and *vacA* s1 genotype for the development of intestinal metaplasia[95]. The infection with BabA-positive strains has been associated with the increased risk for development of peptic ulcer diseases in Western countries[41,96]. However, the association of BabA with peptic ulcer diseases has not been confirmed in patients from East Asian or some other Western countries[97-99]. It has been claimed that the BabA-mediated attachment to gastric epithelial cells might enhance CagA translocation and the enhancement of inflammation[100]. Furthermore, the triple-positive (BabA, CagA and *vacA* s1-positive) strains of *H. pylori* shows greater colonization densities, elevated levels of gastric inflammation and a higher incidence of intestinal metaplasia in patients in contrast with the only CagA and *vacA*s1 positive strains[101,41]. Despite of the association of high level BabA with severe clinical outcomes, surprisingly, it has been also found that low level BabA expressing strains could more likely be associated with increased mucosal inflammation and severe clinical outcomes compared to that of high level BabA-positive and Leb binding strains[42,52]. Although, the underlying mechanisms remains unclear, it has been hypothesized that during adulthood, the induced hyperacidity may enhance the development of gastric metaplastic patches in the duodenum and the *H. pylori* expressing low levels of BabA and Leb attachment are able to detach from the gastric niche and reattached to the gastric metaplastic patches in the duodenum and develop the ulcers at the gastric-duodenal tissue border[42]. The BabA adhesin expression also seems tightly associated

with the onset of type 4 secretory system (T4SS)-related host response *in vivo*[100]. In an *in vivo* study, using the Mongolian gerbils, the BabA-mediated adherence of *H. pylori* to the epithelial cells has been shown to augment the *cag* PAI dependent *H. pylori* pathogenicity. The BabA-Leb interaction can trigger the production of pro-inflammatory cytokines and some factors that can enhance the cancer development[101].

CONCLUSION

H. pylori infection is a major cause of gastric complications including gastric cancer which is the third leading cause for mortality among all cancer related deaths. *H. pylori* being a Gram-negative organism, the OMP present in the cell envelope provides the initial step binding with the Leb antigen for the persistent colonization. BabA is capable of binding with receptors found on the oral mucosa and gastric mucus layer. The closer insight of *bab* genes revealed the presence of dinucleotide (CT) repeats in 5'-region which causes SSM leading to the phase variation. The formation of chimera with the homologous genes *babB* and *babC* causes the regulation of protein expression on transcriptional level. In addition to the high level BabA expression associated with the severe clinical outcomes many reports have also suggested the low level expression with severe outcomes where the underlying mechanism is not clear yet. Even though many roles of BabA in disease process have been evaluated, the role of BabB and BabC has not been assessed yet. Further study is under demand for the assessment of the role of BabB and BabC as well as to elaborate the underlying mechanism of low expression BabA and severe clinical outcomes.

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