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Mini Review

The Tall Tale of the *Helicobacter pylori* Blood Group Antigen Binding Proteins

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The features of *Helicobacter pylori* adhesins, their interactions with their host counterparts, regulated and selective gene expressions are amongst the many clever strategies this microorganism undertakes to survive the otherwise sterile gastric milieu. The ingenious crafting of these interactions and the respective host reactions govern, in part, an array of consequences ranging from asymptomatic infections to varying degrees of gastric inflammation, ulcer formation, atrophic, metaplastic and dysplastic changes and ultimately gastric cancer. The most well studied *H. pylori* adhesins include those which bind host blood group antigens; namely BabA and SabA. In this review, I attempt to tell the historical tale of how these moieties and their respective interactions with the host were discovered and characterized. The details of the subsequent applications of these findings in further genotyping studies will be later reviewed to avoid disruption of this crafty tale. *J Med Microbiol Infec Dis, 2014, 2 (1): 11-15.*

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Helicobacter pylori (Hp), is a highly heterogeneous microorganism, which can regulate and manipulate its own, as well as host's gene expression in an attempt to remain colonized in the otherwise sterile acidic environment of the stomach [1, 2]. The co-existence of Hp and its human hosts dates back to a minimum of 50,000 years [3]. Despite the fact that the majority of Hp infections remain asymptomatic, a fraction of the infecting strains have evolved to the more pathogenic forms which are, in essence, associated with the more severe clinical outcomes of infection; including peptic ulcers and gastric cancer. Therefore, the virulence factors of Hp, including its vacuolating toxin (VacA) [4, 5] and its associated gene (CagA) [6, 7] have claimed decisive roles in determining the Hp-induced GI complications. In addition to these two major virulence moieties, which describe the level of Hp toxicity, other virulence determinants [2, 8-10], as well as host [11] and environmental [12] factors, join in to create susceptibility toward development of the more severe clinical outcomes.

Keeping these in mind, the key contributing factor in survival of Hp in the harsh acidic environment of the stomach, is its capacity in colonization and avoidance of mucosal clearance. In this regard, the characteristics of Hp adhesins and their interactions with gastric epithelial cells play a decisive role in determining the chronicity of infection, likelihood of transmission, and ultimately the severity of the resulting histopathologic damages.

In this regard, it was previously established that Hp colonizes gastric epithelial cells by binding to fucosylated Lewis b (Leb) histo-blood group antigen. But for the first time in 1998, Ilver and colleagues [13] used receptor activity-directed affinity tagging to purify the Hp adhesin, which binds to Leb and named it the blood group antigen binding protein A (BabA).

The epithelial binding capacity of Hp strains was found more prevalent amongst the otherwise virulent strains of Hp.

Accordingly, a year later, Gerhard *et al.* [14] used PCR and RT-PCR to investigate the prevalence of babA2 gene in a German population. They found that babA2-positive strains are highly associated with the more severe Hp-induced GI disorders, including duodenal ulcers and gastric cancer. The effect of which was further amplified when co-resided with the vacA s1 and cagA+ genotypes; "triple-positive" strains.

Subsequently in 2001, Prinz and colleagues [15] explored the role of BabA in gastric inflammation by comparative genotyping of the isolated Hp strains and in situ histopathologic damages. The prevalence of babA2+ Hp strains was found to be 38%, and significantly associated with the activity of gastritis. Furthermore, babA2+ type I (cagA+/vacAs1) Hp strains were more frequent in subjects with severe granulocyte infiltration, atrophic gastritis and and/or intestinal metaplasia. Rad *et al.* [16] confirmed this finding in 2002 and further demonstrated the induction of *in vivo* and *in vitro* expression of pro-inflammatory cytokines, in particular IL-8 in association with babA2+ Hp strains.

Accordingly, a Chinese study with ~80% prevalence of babA2+ Hp strains presented results, which supported those of the Western studies and found a significant association

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between these strains and Hp-induced histopathological changes of the stomach [17].

In contrast, similar investigations on Japanese clinical strains, the majority of which are cagA (96.1%) and babA2 (84.9%) -positive, failed to demonstrate any significant association with the clinical outcomes [18]. Further review of similar genotyping studies, which has been carried out across the globe, will be later reviewed to avoid disruption of this crafty tale.

Performing SDS-digested freeze-fracture replica labeling by Petersson *et al.* [19], later revealed a vast distribution of BabA adhesin on the cell surface of Hp. Hp BabA and Lewis antigen profiling by Thoreson *et al.* [20], in duodenal ulcer patients vs. asymptomatic subjects, demonstrated that Hp strains isolated from DU patients express higher levels of cell surface BabA protein associated with the host Lewis b and x expression, whereas asymptomatic subjects were more likely to be Lewis nontypeable.

Another corner stone, in the gastric epithelial colonization and adhesion arena, was established in 2002 by Mahdavi *et al.* [21], who discovered that a sialylated form of Lewis x antigen is expressed by epithelial cells during Hp infection, which coincides with chronic inflammation in humans and rhesus monkeys. By ligand-receptor retagging method, they also discovered that under such circumstances Hp expresses a sialic acid-binding adhesin; namely SabA, which binds to the sialylated Lewis x antigen. The roles of Lewis b and x were further clarified in a Taiwanese study [22], which used immunohisto-chemistry to demonstrate an association between bacterial colonization and Leb expression, in the absence of which, it was correlated with Lex expression on human gastric epithelial cells.

Previous studies, which nominated BabA as a vaccine candidate, prompted Bai *et al.* [23] to produce the recombinant BabA and demonstrate activation of antigen-specific humoral and cellular immune responses in Hp-infected subjects. Their investigations also recognized rBabA capable of blocking Hp binding to gastric epithelial cells *in vitro*.

It is often reported that following development of Hp-associated gastric histopathology, including atrophy and intestinal metaplasia, the rate of Hp colonization declines. Interestingly, Van de Bovenkamp *et al.* [24] used immunofleurescence to exhibit the co-localization of Muc5AC and Leb on the surface of gastric metaplastic surfaces of the esophagus and duodenum, in addition to normal gastric epithelium. Their findings, in addition to identifying Muc5AC as the carrier of Lewis b antigen and a receptor for Hp colonization, help explain the reduction of Hp colonization in intestinal metaplastic surfaces, which have lost their gastric mucins [25].

Lindén *et al.* [26] studied Hp infection in Rhesus monekeys, whose gastric mucins resemble those of humans. Their investigations identified three modes of Hp adhesion to gastric epithelial cells, which are mediated by Hp BabA, SabA, and ionic charge to Leb, Sialylated Lex and other sialylated structures (at acidic pH), respectively.

Another breakthrough was made by Solnick *et al.* [27] in 2004, who also used the Rhesus monkey infection model to unveil the dynamic changes occurring in BabA genomic structure during the course of chronic Hp infection.

These investigators found that babA gene undergoes antigenic, as well as, phase variations, which consequently modulates its binding to gastric epithelial cells, leading to a successful chronic infection. Antigenic variations of BabA was further supported via studies performed by Hennig *et al.* [28], who used phage display single chain recombinant antibody against recombinant BabA to find mid region variations in amino acid composition of the ~75 kDa BabA protein. Phase variations were further pronounced for SabA expression, which seems to be under strict regulation of variable levels of gastric acid [29].

Another determining factor in the success rate of Hp infection was discovered by Björkholm *et al.* [30] who used transgenic mice to study Hp transmission. They found that mice, deficient in gastric parietal cells, which over-express sialylated Lewis x (Hp SabA receptor), are far more susceptible to Hp transmission, implying that the low acidity in the stomach of children and adults with atrophic gastritis may potentiate Hp transmission in humans [31]. Another piece of evidence supporting the role of SabA in gastric inflammation was provided by Unemo *et al.* [32], who discovered that binding of SabA to its sialylated receptor is required for their nonopsonic activation (oxidative burst) of human neutrophils. Furthermore, deletion of Hp-NapA augments the role of SabA in induction of oxidative burst.

In 2004, Lindén *et al.* [33] explored the very delicate subject of pH-dependent selective binding of Hp to different epithelial receptors (i.e. mucins and Lewis antigens). On the one hand, there is a gradient of pH rising from the lumen of the stomach towards the surface of epithelial cells. On the other hand the gastric mucosal surface is constituted of secreted and membrane bound mucins. These investigators found that at acidic pH of the lumen, there are several bacterial ligands which adhere to the host mucins (Muc5AC, Muc6, etc.). But at the neutral pH of the epithelial cell surface, the adhesion is limited to BabA-Leb interaction. Their findings provide evidence for conditional and selective binding of Hp to secreted and membrane-bound receptors, which circumvents the mucosal barrier throughout the course of infection.

The selective binding of Hp BabA to blood group antigens was also elegantly demonstrated by Aspholm-Hurtig *et al.* [34] who demonstrated a 1500 fold enhanced binding of babA to blood group O typed (specialists) individuals as compared to unselective binding of Hp strains to other blood group antigen (generalists).

The homologous recombination of the silent babA gene into the babB locus, resulting in the chimeric form of babB/A being responsible for the transformation of Leb non-binding strains of Hp into those capable of binding, was beautifully demonstrated by Bäckström and colleagues [35]. These investigators used the panning method with Leb-magnetic beads to unveil metastable transition of non-binding strains into binding strains and thereby selective adhesion to Leb, allegedly orchestrated by the gastric microenvironment.

Shortly after, Sheu *et al.* [36] found that SabA-mediated Hp binding can be substituted for that of BabA in subjects lacking Lewis b antigen. This phenomenon was found directly associated with the bacterial density.

Higher Lex and lower Leb expression in intestinal metaplasia and gastric carcinoma, demonstrated by Lee *et al.* [37] provides evidence not only for antigenic variation of Hp, but also the host undergoing histopathologic changes.

Assessing the strength of Leb binding, Fujimoto *et al.* [38] found an inverse association between the strength of binding and gastric mucosal histopathologic damages. This may implicate loose (detachable) binding as an adaptation tool used by the bacterium for persistence, pathogensis as well as transmission. Supporting evidence was additionally provided by Niehues *et al.* [39], who demonstrated complete loss of BabA expression, as a result of gene truncation, following six months of experimental Hp infection in Mongolian gerbils. Interestingly, however, unlike the effect of BabA expression and binding on gastric histopathologic damages, no impact was found on the rate of Hp colonization.

The four modes of Hp adhesion to mucins, presented by Linden *et al.* [40] identified BabA binding to Leb/Muc5AC as the constitutive mode of adhesion and SabA binding, conditional to low acidic conditions particularly in gastritis patients. Accordingly, Azevedo *et al.* [41] demonstrated that BabA adhesion to Lewis b is more pronounced in subjects with secretor phenotype, in whom the Hp-induced gastric mucosal damages are intensified. Subsequently, Walz *et al.* [42] used a two dimensional bacterial overlay system to further identify independent binding of BabA and SabA to Muc7 and gp340 and their mutual binding to Muc5B.

On the other hand, Linden *et al.* [43] carefully demonstrated the roles of membrane-bound and shed forms of Muc1 in inhibiting Hp colonization by creating steric hindrance and a detachable decoy, respectively. Hence, bringing forth the idea of inhibition of Hp binding by synthetic decoys by Younson *et al.* [44]. These investigators used a BabA-specific human domain antibody and Lewis antigens to successfully inhibit Hp binding to gastric epithelium.

Previous evidence of loss of BabA expression [27] in the rhesus macaques infection model, prompted Styer and colleagues [46] to investigate infection with various strains of Hp and evaluate BabA genotypic and phenotypic variations. These investigators found that *in vivo* loss of BabA expression occurs as a result of a number of variations including mutations leading to stop codons, replacement of BabA with BabB, and amino acid substitutions, all of which can affect blood group antigen binding.

In addition to selective binding of adhesins due to antigenic and phase variations, Nishioka and colleagues [47] were able to measure the mechanical strength of BabA and SabA binding and further prove a stronger level of BabA and SabA binding in Hp strains infecting Japanese cancer patients as compared to controls. These findings may provide additional insight into the pathogenesis of cancer causing Hp strains.

As anticipated, the adhesion of Hp to gastric epithelial cells, specifically via BabA-Leb moieties, was later found essential for the intracellular injection of CagA and its downstream effects including secretion of proinflammatory cytokines and precancerous markers such as IL-8 and MUC2, respectively [48, 49].

Detailed understanding of Hp adhesion, can not only aid pertinent vaccine research, but can also be used in designing eradication regimens. Accordingly, investigators have used bio-engineered surfaces as chelating biomaterials for rummaging and removal of Hp from the gastric epithelial surfaces [50, 51]. In addition to engineered materials, the natural anti-adhesive properties of some food ingredients have also attracted the attention of preventive medicine [52-55].

The collective roles of the Hp adhesins and their interplay with the gastric receptors are beautifully illustrated in a review by Moore and colleagues [45], in which they discuss the risks and benefits of adhesion to this long-lived mucosal pathogen.

In brief, HP uses an array of moieties to adhere to gastric epithelial surfaces, establish stable adaptive colonization and avoid host clearance. The artful nature of these adhesins, in particular the blood group antigen binding proteins, namely BabA and SabA, partly illustrates the ingenious adaptation of this microorganism to the human stomach, creating the paradigm of its identity as a normal constituent of the gastric flora vs. a highly pathogenic carcinogen. Moreover, the nature of the counteracting host responses plays well into the formulation of a wide range of clinical outcomes. Detailed understanding of this complex interplay can help design careful preventive, as well as, therapeutic strategies.

CONFLICT OF INTEREST

No potential conflicts of interest were disclosed.

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