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A Sour Relationship between BabA and Lewis b

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Helicobacter pylori **survives in the hostile acidic environment of the stomach through extensive adaptation. In this issue of *Cell Host & Microbe*, Bugaytsova et al. (2017) report an acid-responsive, reversible adherence of *H. pylori* BabA to the gastric mucosa, the strength of which is tuned by dynamic BabA adaptation.**

Adherence of a bacterial pathogen to host cells is a key initial event for successful colonization and subsequent disease development. Typically, bacterial adhesion is mediated through a specific interaction between the bacterial outer membrane protein, called adhesin, and an oligosaccharide (glycan) or protein expressed on the surface of host cells that serves as a cognate adhesin receptor (Moonens and Remaut, 2016). Multiple, distinct adhesin-receptor interactions are often required to achieve the strong bacterium-host cell binding required to elicit bacterial pathogenic actions.

H. pylori, a Gram-negative bacterium that is estimated to infect over half of the planet's population, is a major etiologic agent of atrophic gastritis and peptic ulcer. Notably, chronic infection with *H. pylori* is the strongest risk factor for the development of gastric cancer, which is the third leading cause of cancer-related deaths worldwide (Hatakeyama, 2014). To survive the highly acidic environment of the stomach, in which almost all bacteria are instantly killed, *H. pylori* has acquired unique equipment. For instance, *H. pylori* senses the pH gradient and swims in the direction of less acidity. *H. pylori* also produces the enzyme urease, which generates ammonia to neutralize acid in close proximity, thereby providing more hospitable conditions. Adhesion of *H. pylori* to the surface of gastric epithelial cells is mediated through a number of adhesins, including BabA, SabA, OipA, HopZ, and AlpA/B (Backert et al., 2011). These adhesins may cooperatively contribute to the establishment of tight *H. pylori* binding to the stomach mucosa, which is crucial for long-term bacterial colonization because it prevents clearance from the stomach during mucus turnover. Once stably attached to the gastric epithelial cells, virulent *H. pylori* *cagA*-positive strains deliver the oncogenic bacterial effector protein CagA into the cytoplasm of the host cells via the type IV secretion system (TFSS), a pilus-like bacterial syringe apparatus, to induce gastric mucosal lesions leading to an ulcer or cancer (Hatakeyama, 2014). In the meantime, considering the dynamic spatio-temporal changes of acidity in the stomach, either physiological or pathological, *H. pylori* may also need to develop a system that ensures quick detachment from the gastric epithelial cells so as to escape from deleteriously high acidity.

BabA-dependent adhesion mediates high-affinity binding of *H. pylori* to gastric epithelial cells by exploiting the Lewis b (Le^b) blood-group antigen as a specific receptor (Ilver et al., 1998). In a new study, Bugaytsova et al. (2017) examined the effect of acidity on BabA-mediated adhesion and investigated the role of acidity in terms of BabA microevolution, or gradual adaptation, during chronic *H. pylori* infection in the stomach. They first found that binding of *H. pylori* to Le^b is highly acid-sensitive, showing marked reduction with a shift of pH from 6 to 2 (Figure 1). The Le^b binding was, however, reversible and fully restored by an increase in pH. Although the acid-sensitive binding is a general property of *H. pylori*, there exist tremendous quantitative differences in acid sensitivity among distinct *H. pylori* isolates, suggesting that differential bacterial adaptations occur in individual host stomachs. Along this line of thinking, the authors also investigated whether regional gastric physiology could select *H. pylori* descendants with different acid sensitivities from the same ancestral *H. pylori*. As expected, *H. pylori* isolates

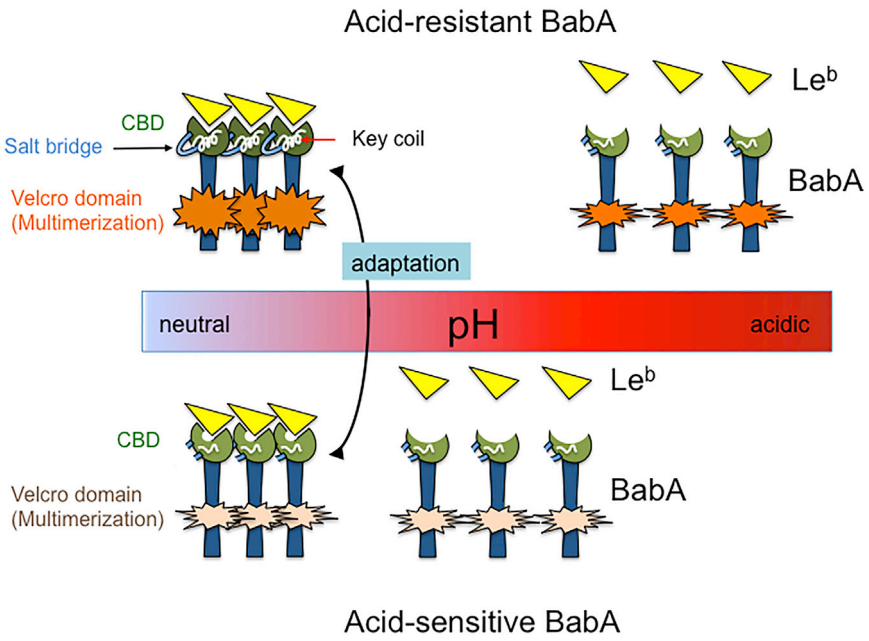

Figure 1. Acid-Sensitive, Reversible Interaction between BabA and Lewis b
The adhesion function of *H. pylori* BabA is highly sensitive to gastric acid; BabA dissociates from Lewis b (Le^b) at lower pH values, but this is reversed by pH increase. There are variations in pH sensitivity between strains, and these differences are associated with intragastric regions (such as corpus and antrum) and mucosal changes during chronic infection with *H. pylori* and disease progression. The variations are due to amino-acid polymorphisms that are promoted by pH-directed microevolution and clustered into the carbohydrate binding domain (CBD), which directly affects Le^b binding affinity, and the Velcro Domain, which robustly stabilizes the binding through multivalent avidity effects. The Key-coil (residues 199–202) in the CBD determines the Le^b binding affinity in a manner that is dependent on the formation of the salt bridge, which is disrupted by high acidity. *H. pylori* is released from the gastric epithelial cells to the lumen by detaching in the low pH environment, allowing the bacterium to move back into the less acidic mucosal lining.

from the upper, more acidic corpus of a patient suffering from reflux dyspepsia were more acid-resistant than those from the lower, less acidic antrum of the same patient.

Since BabA is known to be an extremely polymorphic protein (Nell et al., 2014), the difference in acid sensitivity is most likely due to amino acid alterations in BabA during microevolution or adaptation. Indeed, comparison of BabA sequences in the corpus isolates and antrum isolates revealed polymorphisms at two amino acid positions: Leu199/Glu428 in the antrum isolates and Pro199/Gly428 in the corpus isolates. Of these, position 199, located in the carbohydrate binding domain (CBD), serves as the "Key-position" and is critically involved in determining both acid sensitivity and Le^b binding affinity. The crystal structure showed that this Key-position in the acid-resistant BabA constitutes a short α-helix, denoted the "Key-coil" (residues 199–202), which is clamped by the salt bridge between Asp198 and Arg207 at higher pH (Figure 1). When pH decreases, the salt bridge is disrupted, and subsequent relaxation of the Key-coil enforces dissociation of BabA from Le^b. In the acid-sensitive BabA, the Key-coil is already relaxed because of the Leu-to-Pro substitution at the Key-position. Position 428, located in Helix-9 of BabA, comprises the "Velcro Domain," which together with Helix-1 and Helix-10 is responsible for BabA multimerization (most likely as a trimer). This multimerization, which again increases the Le^b binding strength of BabA through avidity effects, is also impaired by high acidity (Figure 1).

Following identification of these critical residues that determine the acid sensitivity of BabA, the authors sought to relate BabA adaptation and geographic disease patterns among human populations. In Peru, *H. pylori* infection is associated with corpus atrophy, hypochlorhydria, and increased gastric cancer risk. As expected, the majority of Peruvian *H. pylori* strains possess acid-sensitive BabA. In India, where *H. pylori* infection is associated with hyperchlorhydria and duodenal ulcer, it was assumed that a more acid-resistant *H. pylori* BabA might be adaptively selected. Contrary to expectation, however, the Indian strains exhibit high acid sensitivity. The authors argue that this may be due to the endemic circulation in India of potentially lethal intestinal pathogens such as *Vibrio cholerae*, which could be killed by the highly acidic environment of the stomach. Bugaytsova et al. (2017) also investigated BabA evolution during disease progression through analysis of *H. pylori* isolated from a long-term-infected rhesus macaque and a patient who developed gastric cancer. In both cases, chronic *H. pylori* infection leading to gastric cancer (Correa, 1992) gave rise to the generation of acid-sensitive BabA variants containing substitutions clustered in the CBD and/or the Velcro Domain.

From the *H. pylori* standpoint, acquisition of such a pH-dependent, reciprocal attachment-detachment system should be a great advantage for long-term colonization in the stomach. Indeed, its importance is supported by the extensive microevolution of BabA, which should obviously refine the detachable system. On the other hand, the role of BabA microevolution in disease development is less clear, and the possibility remains that the observed BabA variation is simply a consequence of bacterial adaptation to the acid environment and has little active role in the development of diseases such as cancer. In this regard, BabA-mediated adhesion has been shown to potentiate TFSS-dependent CagA delivery into host cells (Ishijima et al., 2011). Evaluation of the impact of BabA adaptation on CagA delivery might provide a clue relevant to this question. Also, there are a number of adhesins other than BabA; these include the recently identified HopQ, which exploits the CEACAM family of proteins as receptors (Javaheri et al., 2016; Königer et al., 2016). It would therefore be important to know the relative contribution of each of those *H. pylori* adhesins in *H. pylori* adherence to the stomach mucosa.

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