Reasons for the persisting nature of the infection; an update

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H. pylori-induced gastric inflammation does not cause symptoms in most infected persons but is associated with an increased risk for development of duodenal ulcer disease, gastric ulcer disease, gastric adenocarcinoma and gastric lymphoma. Colonization of the stomach elicits humoral and cellular immune responses, which in most cases do not result in bacterial clearance. The pathogen can persist in the human stomach for decades or for an entire lifetime.

To persist in the stomach, *H. pylori* must overcome the acidic environment, gastric peristalsis, antimicrobial factors (digestive enzymes, lactoferrin, and defensins), gastric mucus, and epithelial cell turnover. The gastric epithelial layer constitutes a physical barrier that prevents entry of bacteria into the gastric mucosa. Interactions of *H. pylori* with the epithelium result in the recruitment of neutrophils, macrophages, mast cells, dendritic cells, and lymphocytes in gastric tissue and inflammation. *H. pylori* was also shown to invade to some extent gastric epithelial cells, which together with monocytes, macrophages, and dendritic cells may play a role in antigen presentation and the induction of the adaptive immune response. Severe gastric mucosal inflammation associated with Th1 immune response was shown to be in reciprocal relationship to colonization density; it has been hypothesized that permanent and intensive inflammation could lead to *H. pylori*

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eradication. However, some inflammation may be essential for chronic colonization due to the improvement of the nutritional environment for bacterial cells.

H. pylori was shown to possess multiple means of immune suppression or avoidance consisting of mechanisms to evade the innate as well as adaptive host immune response. Some of these mechanisms are given below:

- Urease contributes to acid resistance of *H. pylori*.
- Flagella permit bacterial motility, which allows bacterial penetration of the mucus layer.
- Most bacteria (~90%) are free living in the mucus layer, which is the permanent reservoir of *H. pylori*. But also bacteria which may invade gastric epithelial cells can be important for persistence under unfavorable conditions such as gastric acid, antibiotics, or the host inflammatory response.
- Adherence to gastric epithelial cells was shown to be inhibited by urease in vitro, which may hinder the interaction between the pathogen and the host thus affecting the extent of inflammation.
- Contact between *H. pylori* and phagocytes probably occurs infrequently unless there are disruptions in the gastric epithelial barrier. *H. pylori* can resist phagocytosis by neutrophils, monocytes, and macrophages (Cag PAI, urease) as well as intracellular killing in macrophages.
- Due to the production of catalase and superoxide dismutase (protection against ROI), but also arginase (inhibits NO production), *H. pylori* can blunt the toxic effects of extracellular products of phagocytes.
- Toll-like receptors (TLRs) on host cells recognize microbial components (PAMPs); TLR4 normally recognizes LPS and TLR5 flagellin resulting in the induction of an initial pro-inflammatory response and priming of the adaptive immune response. However, TLR5 on gastric epithelial cells does not recognize *H. pylori* flagellin and also H. pylori LPS is only a weak agonist for TLR4. TLR2, which is expressed on infiltrating phagocytes and bias toward Th2 immune response, recognizes intact *H. pylori* and may induce immunosuppression.
- Naturally occurring H. pylori-specific regulatory T cells (CD4+CD25+) were shown to play a role in suppressing the immune response to *H. pylori* in the gastric mucosa.
- Arginase and an uncharacterized low-molecular-weight protein of *H. pylori* have been reported to inhibit activation-induced proliferation of T cells, which may also result to immunosuppression.

Furthermore, the marked genetic diversity of *H. pylori* may be of crucial importance. Thus, antigenic or phase variation (gene switch on and off) of the adhesin BabA may contribute to *H. pylori* persistence by altering adhesion to gastric epithelial cells depending on the degree of inflammation and nutrient levels. Phase variation of SabA has also been proposed. Phase variable is also the Lewis antigen expression in *H. pylori*. LPS decorated

with Lewis antigens binds to DC-SIGN on gastric dendritic cells and blocks the development of a Th1 response. Another good example of genetic diversity is the CagA protein. During intimate contact, type I strains secrete by the type IV system CagA into the host cell, which then becomes tyrosine phosphorylated and interrupts host signal transduction and induces a rearrangement of the actin cytoskeleton. The extent of these changes depend on the number of tyrosine phosphorylation motifs in the CagA protein, which arise from intragenomic recombination between direct DNA repeats in the 3´portion of *cagA* and may vary within a strain. VacA activity may also vary between different isolates of the same strain. VacA has been reported to play a role in the inhibition of activation-induced proliferation of T cells, which may result to immunosuppression. This statement, however, has been discussed controversially in recent literature.

In an effort to explain the interplay of different factors in inflammation, thus resulting in persistent infection, the following model has been proposed: Under high inflammation conditions occurring during *H. pylori* infection, especially infection with CagA/VacA/BabA+ (triple positive) strains, sialyl-Lex (S-Lex) is upregulated and serves as a receptor for the *H. pylori* SabA adhesin. This additional adhesin-receptor interaction between S-Lex and SabA is thought to mediate a more intimate interaction and thus facilitate closer attachment of *H. pylori* to the epithelium. Translocation of CagA into host epithelial cells leads to breakdown of tight junctions between gastric epithelial cells and a leaky epithelium. Nutrients transit into the gastric mucous and *H. pylori* virulence factors, such as arginase and VacA, enter into the submucosa. This results in inhibition of IL-2 production and T cell proliferation, which might otherwise lead to *H. pylori* eradication. Regulatory T cells - derived from Th-0 cells under the influence of IL-10 – further dampen the immune response by blocking both CD4+ and CD8+ effector T cell functions. Finally, low inflammation conditions arise in response to high inflammation. Thus, inflammation is probably best thought of as a continuum that may differ between anatomic regions of the stomach and may cycle from one extreme to another. Since *vacAs1*, *cagA*, and *babA* are often co-expressed though genetically unlinked, they likely serve a common function that results in their selection, which may be the regulation of the inflammatory response.

Growth factors may also contribute to the persistent nature of the infection with *H. pylori*. They have been associated with gastric carcinogenesis; however, induction of growth factors in atrophic gastritis and gastric cancer disease by *H. pylori* is very unlikely, because the microorganism is barely present in these conditions. On the other hand, there is only sparse information about the role of growth factors during chronic active gastritis.

EGF-receptor related growth factors like EGF, TGFα, HB-EGF and amphiregulin are produced by gastric epithelial cells and play pivotal roles in gastrointestinal physiology and pathophysiology such as tissue repair and ulcer healing. Recently, *H. pylori* urease was shown to induce HB-EGF upregulation via activation of p44/p42 MAP kinases in gastric epithelial cells (not published data). Also, dendritic cells were shown to release

large amounts of TGF-β1 in response to urease on intact bacteria. TGF-β1, which in the stomach is produced by parietal and neck cells but not by epithelial cells, has a special role in gastrointestinal mucosal healing as it stimulates fibroblasts, induces cell migration, angiogenesis, and enhances cellular matrix production. Furthermore, TGF-β1 downregulates the tissue damaging Th1 response amongst others through the induction of CD4+CD25high regulatory T cells. Thus, due to the induction of growth factors, *H. pylori* and the urease may influence the reconstitution of the gastric epithelial barrier, which hinders the interaction of the pathogen with the host and may contribute to persistence of the infection. In this context, I would like to speculate that urease production may be subject to regulation depending for example on the pH, which decreases in case of thinning of the mucus layer due to ulcer formation.

In conclusion, *H. pylori* has evolved several mechanisms by which the innate and adaptive arms of the immune system are tightly regulated; continuous diversification and selection of the fittest bacteria in each microniche within the gastric environment may be crucial for persistence. Some inflammation may improve the nutritional environment for the bacterium. The adequate degree of gastritis may be achieved through continuous cycling between conditions of high and low inflammation especially in infections with type I strains. Induction of growth factors may also be of importance and their role in chronic gastritis should be further investigated. Understanding *H. pylori* and the biology of persistent infection may not only suggest strategies for treatment and prevention but even lead to more sophisticated approaches to shift the host-pathogen interaction more toward commensalism.