THE STORY SO FAR: HELICOBACTER PYLORI AND GASTRIC AUTOIMMUNITY

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The gastric mucosal pathogen Helicobacter pylori induces autoantibodies directed against the gastric proton pump H⁺,K⁺-ATPase in 20–30% of infected patients. The presence of these autoantibodies is associated with severity of gastritis, increased atrophy, and apoptosis in the corpus mucosa, and patients with these autoantibodies infected with H. pylori display histopathological and clinical features that are similar to those of autoimmune gastritis (AIG). This review will focus on the T helper cell responses, cytokines, and adhesion molecules involved in corpus mucosal atrophy in chronic H. pylori gastritis and in AIG, and the role of H. pylori in the onset of AIG.

Keywords: Helicobacter pylori, antiparietal cell autoantibodies, H⁺,K⁺-ATPase, autoimmune gastritis, Th1 cells, cytokines, Fas, apoptosis

INTRODUCTION

Helicobacter pylori is a gram-negative human gastric pathogen that causes persistent infection in half of the world’s population. H. pylori infection leads to chronic gastric inflammation and peptic ulcer disease, and it is associated with mucosa-associated lymphoid tissue (MALT) lymphoma and with loss of gastric glands in the antrum and corpus, which is referred to as atrophy. Atrophy is considered...
a precursor of gastric adenocarcinoma, the second most frequent cause of cancer-related death, and there is strong evidence that *H. pylori* infection increases the risk of gastric cancer [1]. In a recent prospective study of 1526 Japanese subjects, gastric cancer developed in 2.9% of 1246 *H. pylori*-infected patients over 7.8 years, whereas gastric cancer was not observed in 280 noninfected control subjects, nor in a subgroup of 253 individuals that received *H. pylori* eradication therapy early during follow-up [2].

The trigger of atrophy and mechanisms involved in its development are still poorly understood. Although *H. pylori* is not invasive and usually resides in the antrum, glands located deep in the mucosa of the antrum and corpus disappear. Experimentally infected mice develop atrophy in the corpus, while the colonization takes place mainly in the antrum [3]. Accumulating data on humans suggest that gastric corpus atrophy is caused by an *H. pylori*-driven autoimmune process.

In this review, we describe the difference between antigastric antibody responses upon *H. pylori* infection in animals and in humans, and discuss the histomorphological and functional features of the gastric mucosa that are associated with the presence of gastric autoantibodies in *H. pylori*-associated autoimmunity. Secondly, the pathogenesis of *H. pylori*-associated atrophic gastritis is reviewed and compared with the pathogenesis of classical autoimmune gastritis and pernicious anemia (AIG/PA), which is discussed by D’Elios and colleagues elsewhere in this issue. Based on the striking similarities between AIG/PA and *H. pylori*-gastritis accompanied by corpus atrophy and autoantibodies, it seems plausible to consider an initiating role of *H. pylori* in gastric autoimmunity. In the third part of this review, models that may explain the role of *H. pylori* in gastric autoimmune responses are discussed.

**H. pylori infection induces autoantibodies to gastric mucosal antigens**

*H. pylori* induces autoantibodies reactive with gastric mucosal antigens in approximately half of the infected individuals (range 49–64%) [4–8]. Immunohistochemistry on healthy, noninfected human gastric tissue incubated with serum from *H. pylori*-infected patients, reveals two different binding sites for such autoantibodies [6,7]: one on the luminal membranes of the foveolar epithelial cells in the antrum and corpus mucosa, and the other on the canalicular membranes of parietal cells in the gastric corpus mucosa (Figure 1). Parietal cells in the corpus secrete gastric acid, and their apical
FIGURE 1 Helicobacter pylori—infected patient serum reacts with a section from the glandular region of the corpus of an uninfected person. The in situ binding sites of antigastric autoantibodies induced by H. pylori infection are shown in both panels. A and B (a) (Immunohistochemistry, original magnification 40×) Antiluminal antibodies bind to the luminal membranes (arrows) of the foveolar epithelial cells in the antrum as well as the corpus (shown here). (b) (Immunohistochemistry, original magnification 100×) Anticanalicular antibodies bind to parietal cell canaliculi (black structures, arrows) containing the predominant canalicular antigen, i.e., gastric H⁺, K⁺-ATPase. Presence of anticanalicular antibodies is associated with H. pylori atrophic corpus gastritis (see text).
secretory canaliculi are rich in H\(^+\),K\(^+\)-ATPase, the gastric proton pump. The gastric H\(^+\),K\(^+\)-ATPase has been identified as the single major autoantigen in chronic *H. pylori* gastritis with corpus atrophy [9].

In mice, *H. pylori* infection induces autoantibodies through mimicry with Lewis antigens present on the gastric proton pump (reviewed in Appelmelk et al. [10]). *H. pylori* expresses in its lipopolysaccharide (LPS) Lewis blood group (Le), antigens that are similar to those expressed on human cells, including gastric epithelial cells [11,12]. Mice, that were experimentally infected with *H. pylori* developed antibodies to *H. pylori* LPS, H\(^+\),K\(^+\)-ATPase and Lewis x (Le\(^x\)) and Le\(^y\). In humans, Le\(^x\) and Le\(^y\) are expressed on gastric mucin, whereas Le\(^y\) is expressed on the \(\beta\)-subunit of gastric H\(^+\),K\(^+\)-ATPase. The murine gastric H\(^+\),K\(^+\)-ATPase \(\beta\)-subunit contains Le\(^x\), and Le\(^y\), or both, and serum of *H. pylori*–infected mice has been shown to cross-react with the human gastric mucosa. These murine cross-reactive antibodies can be removed by preincubation of the serum with *H. pylori* cells [11,12], and therefore they are the result of molecular mimicry between *H. pylori* and its host. Human sera, however, also react with recombinant H\(^+\),K\(^+\)-ATPase that lacks Lewis antigens [9], and their reactivity to gastric parietal cells cannot be removed by preincubation of the serum with *H. pylori* cells [13]. In humans, anti-H\(^+\),K\(^+\)-ATPase autoantibodies associated with *H. pylori* infection are directed against protein epitopes, and their formation does not involve Lewis mimicry.

Ferrets are naturally colonized with *Helicobacter mustelae* and develop diseases similar to those that are associated with *H. pylori* infection in humans, including gastritis and ulcer disease [14,15], gastric adenocarcinoma [16], and MALT lymphoma [17]. Like *H. pylori*, *H. mustelae* expresses in its LPS antigenic structures that are also present on host epithelial cells, in this case blood group A [18]. However, as in humans natural infection of ferrets with *H. mustelae* induces autoantibodies that react with ferret parietal cells, and these antibodies cannot be removed with *H. mustelae* cells or red blood cells expressing blood group A [19]. Thus, *H. mustelae*–induced gastric autoantibodies in ferrets are not due to molecular mimicry and may arise via similar mechanisms that lead to gastric autoantibody production in humans. These findings clearly show the difference in immune response seen with natural infection models, compared to the response that occurs in animals after experimental infection or immunization, and indicate that the naturally *H. mustelae*–infected ferret may be a suitable model to investigate the pathogenic mechanisms underlying *H. pylori*–associated corpus atrophy in humans. The target of antiparietal cell autoantibodies in *H. mustelae*–infected
ferrets is likely the gastric $\text{H}^+\text{K}^+$-ATPase, which is also the target of antiparietal cell autoantibodies in *H. pylori*-infected humans.

**HISTOLOGICAL AND CLINICAL FEATURES ASSOCIATED WITH ANTICANALICULAR AUTOANTIBODIES IN *H. PYLORI* GASTRITIS**

Both antiluminal and anticanalicular antibodies are significantly associated with *H. pylori* infection. However, only the presence of anticanalicular antibodies is significantly correlated with morphological features and functional state of the gastric mucosa and clinical parameters in *H. pylori*-induced gastritis [7] (Table I). Severity of gastritis in the corpus mucosa of *H. pylori*-infected patients is positively correlated with the presence of anticanalicular autoantibodies, and anticanalicular autoantibodies also correlate with atrophy and increased apoptosis in the gastric corpus mucosa [5–7]. This suggests that *H. pylori*-associated corpus atrophy may result from an auto-

**TABLE I** Similarities between Classical AIG and *H. pylori*-Associated Corpus Atrophic Gastritis

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<td>Gastric $\text{H}^+\text{K}^+$-ATPase is the autoantigen recognized by circulating PCA [9,39].</td>
<td>Circulating antibodies against $\text{H}^+\text{K}^+$-ATPase in <em>H. pylori</em> gastritis are suggestive of the presence of $\text{H}^+\text{K}^+$-ATPase-specific T helper cells, such as in AIG.</td>
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**Cellular immune responses**

- Increased B/T cell influx around glands and into the epithelium [9,39].
- Putative antigen presentation by gastric epithelium; increased levels of MHC class II [46,83,84] and B7.1 and B7.2 molecules on gastric epithelial cells [84,85].
- Increased expression of MAdCAM-1 on gastric endothelium$^a$ [54,59,88] in association with homing of $\alpha 4\beta 7$ T lymphocytes to the gastric mucosa [54,88].
- Increased Fas expression on parietal cells [53, 56] in EAIG and on gastric epithelial cells$^b$ in *H. pylori* infection [90–92].

**Histological and clinical features**

- Increased apoptosis in the corpus mucosa [6–8].
- Increased body mucosa atrophy [7,9].
- Higher serum gastrin levels [6,7,20].
- Lower pepsinogen I:II ratio [7].
- Lower gastric acid secretion [20,21].
- Decreased incidence of duodenal ulcer [7].

$^a$In *H. felis*-infected mice. In humans, MAdCAM-1 is equally expressed on the gastric epithelium of *H. pylori*-infected and noninfected individuals [54].

$^b$Data regarding Fas expression on parietal cells, compared with other epithelial cells, during *H. pylori* infection are absent.
immune attack against the gastric glands, leading to an increased rate of cell death.

\( \text{H}^+,\text{K}^+\text{-ATPase} \) is the major target of anticanalicular autoantibodies, and patients with autoreactivity against the \( \alpha \)- or \( \beta \)-subunit of \( \text{H}^+,\text{K}^+\text{-ATPase} \) show the highest prevalence of corpus atrophy [9]. In addition, several clinical features of \( \text{H. pylori} \)-associated antigastric autoimmunity are also common to glandular atrophy in classical AIG/PA. \( \text{H. pylori} \)-infected patients with anticanalicular autoantibodies have significantly higher fasting serum gastrin levels and lower pepsinogen I to II ratios, which is a sensitive marker for corpus mucosa atrophy, as compared to patients without anticanalicular autoantibodies [7,20]. The presence of anticanalicular autoantibodies also correlates with a decreased gastric acid output in both \( \text{H. pylori} \)-infected patients with nonulcer dyspepsia [20] and those with duodenal ulcer [21].

Based on the similar histopathological and clinical characteristics of \( \text{H. pylori} \)-associated atrophic corpus gastritis with anticanalicular antibodies and classical AIG/PA, it is hypothesized that \( \text{H. pylori} \) is a causative agent for the development of autoimmune gastritis [10,22]. This concept is supported by the observations that antigastric autoantibodies in some patients—but not all—decrease after cure of infection [23], and that histologically defined preclinical stages of autoimmune gastritis can be successfully treated by \( \text{H. pylori} \) eradication [24–26]. However, conflicting data regarding the beneficial effects of eradication therapy have been reported. Eradication of \( \text{H. pylori} \) in individuals with atrophic body gastritis had no effect on body atrophy and intestinal metaplasia, but cure of infection was associated with increased gastric acid secretion [27,28] and with a reduction of hypergastrinemia [28]. In a recent study, \( \text{H. pylori} \) eradication in infected patients with corpus atrophy did restore both histomorphology and function of the corpus mucosa, but in only 20% of the cases [29].

Initially, a negative association between \( \text{H. pylori} \) and pernicious anemia was reported, and it was concluded that \( \text{H. pylori} \) is uniquely associated with chronic, nonspecific gastritis, and that the pathological process in pernicious anemia protects against infection with \( \text{H. pylori} \) [30]. In contrast, an association between \( \text{H. pylori} \) infection and gastric autoimmunity is supported by a number of later studies that indicate that a substantial portion of patients with autoimmune gastritis have or have had \( \text{H. pylori} \) infection [31–33]. The apparent controversial reports regarding the prevalence of \( \text{H. pylori} \) infection in AIG/PA, and in less strictly defined atrophic body gastritis, are largely based on the methods used for detection of infection, i.e.,
histology versus serology. Although actual colonization could only be detected in 10–14% of PA patients and in 33% of individuals with atrophic body gastritis [31,34,35], antibodies to *H. pylori* were shown in 51–83% of patients with PA and in 53–86% of atrophic body gastritis patients [31,32,35,36]. Furthermore, in a group of 150 patients with atrophic body gastritis, 23% were positive for *H. pylori* in the corpus mucosa, both in histology and serology. In this subpopulation of atrophic body gastritis patients, the presence of PA, as well as the grade of corpus atrophy, were lower than in patients that were only positive in serology, whereas the group of patients that were negative for *H. pylori* in both serology and histology had the highest prevalence of PA and corpus mucosal atrophy [36]. Thereby, the group of serologically and histologically *H. pylori*-positive patients represents an intermediate stage between atrophic body gastritis and full blown AIG, suggesting that *H. pylori* infection can induce gastric autoimmune disease and that a majority of patients with atrophic body gastritis had *H. pylori* gastritis before the bacteria were cleared by the development of atrophy. This supports the hypothesis that in at least a subpopulation of AIG/PA, e.g., patients with a certain genetic background, *H. pylori* may be or have been involved in the etiology of the disease [10,35].

Interestingly, such a proposed association between *H. pylori* and gastric autoimmunity seems to be absent in type 1 diabetes patients [37]. Type 1 diabetes mellitus results from autoimmune destruction of pancreatic β-cells, and in 15–20% of type 1 diabetic patients parietal cell antibodies are also present, which is associated with manifestations of gastric autoimmunity [38]. Except, in these patients the presence of H⁺,K⁺-ATPase antibodies, serum gastrin levels, and acid secretion parameters do not differ between *H. pylori*-positive and *H. pylori*-negative individuals. However, upon division of patients into groups based on their level of circulating parietal cell antibodies, it was suggested that low titers (between 1/20 and 1/40) of PCA reflect *H. pylori* infection, whereas higher PCA titers appear to be indicative of gastric autoimmune disease. In addition, in type 1 diabetics, *H. pylori* infection or parietal cell antibodies are associated with different HLA-DQ haplotypes, i.e., HLA-DQA1*0501-B1*0201 or HLA-DQA1*0501-B1*0301, respectively [37]. Together, these observations suggest that *H. pylori* gastritis and autoimmune gastritis may be separate entities in type 1 diabetes patients. Longitudinal and post-*H. pylori* eradication studies are needed to assess the role of *H. pylori* in gastric autoimmune responses in type 1 diabetes patients or to clarify whether type 1 diabetes mellitus predisposes to gastric autoimmunity independent of *H. pylori* infection.
SIMILAR PATHOGENIC MECHANISMS IN H. PYLORI–ASSOCIATED ATROPHIC CORPUS GASTRITIS AND CLASSICAL AUTOIMMUNE GASTRITIS

Striking similarities between corporal glandular autoimmunity associated with H. pylori and the gastric mucosal damage observed in classical AIG suggest that the development of these diseases involves similar pathogenic mechanisms and may even share the same trigger, i.e., H. pylori.

Human Autoimmune Gastritis and Pernicious Anemia

AIG is characterized by a chronic inflammatory infiltrate in the gastric mucosa accompanied by loss of gastric parietal cells and zymogenic cells; it affects the fundus and the corpus of the stomach but spares the antrum, and may eventually proceed to PA. PA is considered to be the most common cause of vitamin B12 deficiency in Western populations [39]. In AIG, autoantibodies to gastric parietal cells are present in the circulation, and clinical characteristics of patients with AIG are hyperplasia of gastrin-producing cells, resulting in high serum gastrin concentration, decreased acid secretion, and decreased pepsinogen I:II ratio [39]. As mentioned above, this clinical spectrum is also significantly correlated with the presence of anticanalicular autoantibodies in H. pylori infection [7,20].

In addition, H. pylori has been suggested as a causative agent in the development of adult vitamin B12 deficiency. H. pylori was detected in 57% of patients with vitamin B12 deficiency, and eradication of infection improved anemia and serum vitamin B12 levels in a subgroup (40%) of the infected patients [40]. These findings further support the possibility that H. pylori plays a role in the development of gastric autoimmunity, i.e., AIG/PA.

T Cells, H⁺,K⁺-ATPase, and Cytokines in AIG/EAIG

Current knowledge of the pathogenesis of human AIG is derived largely from studies of experimental autoimmune gastritis (EAIG) mouse models, reviewed in Alderuccio et al. [41]. Like AIG, EAIG is characterized by a chronic inflammatory infiltrate that extends into the gastric mucosa with loss of acid-secreting parietal cells and zymogenic cells, followed by appearance of circulating autoantibodies directed against the α- and β-subunits of H⁺,K⁺-ATPase [42,43]. Again, these features are similar to those seen in H. pylori–infected patients with corpus atrophy.
In EAIG and AIG, the gastric inflammatory infiltrate contains both CD4\(^+\) and CD8\(^+\) T cells, macrophages, and B cells [44], and the histopathological lesions in mouse models are similar to those observed in humans with chronic AIG [45,46]. EAIG is mediated by H\(^+\),K\(^+\)-ATPase-specific CD4\(^+\) T cells [47], and T cell epitopes in EAIG have been identified [48–50]. Also, human AIG is mediated by autoreactive CD4\(^+\) T cells that are specific for H\(^+\),K\(^+\)-ATPase [51], and recently it has been shown that a significant number (36\%) of H\(^+\),K\(^+\)-ATPase peptide epitopes recognized by human gastric T cell clones are relevant in EAIG [52]. Autoreactive T cells in human AIG and murine EAIG are predominantly of the T helper 1 phenotype, secreting high levels of IFN-\(\gamma\) and TNF-\(\alpha\) in the absence of IL-4, and express cytotoxic functions [51,53,54], as do \(H. pylori\)–specific CD4\(^+\) T cells derived from the gastric mucosa of infected patients [55].

**Destruction of Parietal Cells in AIG/PA and EAIG**

Accumulating evidence points to the Fas (CD95)-Fas ligand (FasL/CD95L) pathway as a major effector mechanism in the mucosal damage observed in AIG. An H\(^+\),K\(^+\)-ATPase-specific T cell clone from an EAIG mouse has been reported to express FasL upon activation and to induce Fas-FasL-mediated apoptosis of epitope-loaded target cells in an antigen-dependent way [53]. Likewise, gastric mucosal H\(^+\),K\(^+\)-ATPase-specific T cell clones derived from AIG patients exert their cytotoxic effects via Fas/FasL-induced apoptosis and are capable of perforin-mediated lysis of target cells [51]. A definite requirement for Fas in the development of murine EAIG was recently demonstrated by the failure of lpr/lpr mice, deficient in Fas expression, to develop destructive gastritis and autoantibodies upon neonatal thymectomy [56]. In the same study, Fas expression was colocalized with gastric parietal cells in EAIG mice, whereas nontymectomized, nongastritic mice did not express Fas in their gastric mucosa. This indicates upregulated Fas expression on parietal cells in EAIG and may partially explain the selective destruction of parietal cells observed in murine and human AIG. Recently it has been shown, again in mice, that dendritic cells (DC) constitutively acquire H\(^+\),K\(^+\)-ATPase from the gastric mucosa, after which they migrate to the draining lymph node and present the autoantigen to T cells [57]. This process is markedly increased upon induction of murine EAIG and suggests a major role for DC as antigen-presenting cells in T cell activation during murine and human AIG. Increased expression of Major Histocompatibility Complex (MHC) class II and costimulatory molecule B7.1 on DC from EAIG mice compared to normal animals, further supports this view [57]. Furthermore, the
observations of increased MHC class II expression on gastric epithelial cells [46] suggest that gastric mucosal cells are also capable of antigen presentation to T cells, a view that is supported by the functional expression of antigen-processing cathepsins by human gastric epithelial cells [58]. In addition, expression of MAdCAM-1, the endothelial counter receptor for integrin α4β7, on the mucosal endothelium is increased in murine EAIG [54,59], and plays a role in selective extravasation (“homing”) of α4β7-integrin positive, autoreactive CD4+ Th1 cells to lesions in the gastric mucosa in EAIG [54].

The above-mentioned observations are in line with the model for destruction of parietal cells in murine EAIG and human AIG/PA, as originally proposed by Toh et al. [44]: DC in the gastric mucosa become activated, capture and process gastric H⁺,K⁺-ATPase that may be released during normal turnover of parietal cells, and migrate to a draining lymph node. DC present H⁺,K⁺-ATPase-peptides to naive, potentially pathogenic H⁺,K⁺-ATPase-specific CD4+ T cells, which become activated, proliferate, and acquire adhesion molecules that mediate their homing to the gastric mucosa. Subsequently, inflammatory cells comprising other T cells, either CD4+ or CD8+, monocytes, and B cells are recruited through release of chemokines and cytokines by the H⁺,K⁺-ATPase-specific CD4+ T cells [44]. In the gastric corpus mucosa, CD4+ H⁺,K⁺-ATPase-specific T cells directly mediate the loss of parietal cells in EAIG/AIG by Fas-FasL-mediated induction of apoptosis of parietal cells that express Fas, and they have MHC II/ H⁺,K⁺-ATPase complexes on their surface, by H⁺,K⁺-ATPase-specific T cells expressing Fas ligand [44]. In human AIG, Human Leukocyte Antigen (HLA)-DR is aberrantly expressed on glandular epithelium in the vicinity of T cell infiltrates [45], indicating that similar mechanisms may be responsible for parietal cell loss.

**Gastric T Cell and Cytokine Responses in *H. pylori* Infection**

*H. pylori* infection leads to a lymphocytic influx, similar to the one observed in AIG, and *H. pylori*-specific cellular immune responses have been studied in human and animal models for several years. Many different animal models, such as mice, ferrets, dogs, and cats, have been used for studying helicobacter infection, and particularly *Helicobacter felis*-infected mice provided a useful model resembling gastric pathological changes in human *H. pylori* infection. *H. felis* infection of B and T cell-deficient (RAG-1-/-) mice and T cell-deficient (TCRβδ-/-) mice [60] does not result in gastric pathology despite high levels of colonization, whereas infection of B cell-deficient (μMT) mice results in severe gastric alterations, identical to those seen in
immunocompetent mice [60]. These results demonstrate that immune-mediated gastric damage that is seen after *Helicobacter* infection requires cellular immune responses and is mediated by T cells, not by B cells or their secreted antibodies.

The outcome of *H. pylori* infection is dependent on both bacterial strain and host factors [61,62], and in particular the host cytokine response is considered an important determinant in the onset of gastritis and the development of disease. Data regarding early stages in *H. pylori* infection are scarce, but experimental infection of mice and nonhuman primates revealed that inflammatory responses to acute *H. pylori* infection are of the Th1 phenotype [63,64]. Also, in humans infected with *H. pylori* gastric mucosal lymphocytes have a predominant Th1 phenotype [65,66], which is associated with pathology [67,68]. However, in individuals with asymptomatic chronic *H. pylori* gastritis, the majority—up to 64%—of the gastric mucosal T cells are of the Th0 phenotype, i.e., able to secrete both IFN-γ and IL-4 [55,68].

In vivo neutralization of IFN-γ reveals the existence of Th2 responses in *H. felis*—immunized challenged C57BL/6 mice [63]. In addition, in BALB/c mice oral vaccination with recombinant urease induces a Th2 response and cures *H. felis* infection [69]. These observations suggest that a shift to a Th2 response would be required for protection from *H. pylori* infection. However, vaccination with *H. pylori* antigen in the presence of either ALOH or Freund’s complete adjuvant, which induces IL-5-secreting or IFN-γ-secreting antigen-specific T cells, respectively, both confer protection from *H. pylori* infection [70]. Furthermore, recent vaccination studies in mice show that protection against *H. pylori* does not require IL-4 [71]; instead it is dependent on IL-12 and is mediated by Th1 cells [72,73]. Together, these observations indicate that Th1 and Th2 cytokines are both involved in the adaptive immune response against *H. pylori*, and that protection from disease may require the ability of the host to mount a balanced Th1/Th2 response upon infection.

It has been recognized that the BALB/c and C57BL/6 inbred mouse strains profoundly differ in susceptibility and outcome of *H. pylori* infection [3,61,74]. BALB/c mice, which have a genetic tendency to favor Th2 responses, are much more resistant to infection and *H. pylori*—induced gastrointestinal pathology when compared to Th1 prone C57BL/6 mice. With regard to the observations that Th1 and Th2 are both involved in protection from *H. pylori* infection, a recent study of Panthel and coworkers [75] may be of special interest. In this study, the influence of the host genetic background on the role of Th1/Th2 responses during helicobacter infection, was assessed by using IL-4 and IL-12 knockout mutants of BALB/c and C57BL/6J
mice. It was demonstrated that IL-4 and IL-12—cytokines marking a Th2 or a Th1 response, respectively—play opposing roles in *H. pylori* colonization of the BALB/c and C57BL/6J mouse strains. Disruption of the IL-12 gene in BALB/c mice, thereby enhancing the pre-existing Th2 background of these mice, results in strong colonization by *H. pylori* compared to BALB/c wild-type mice. In striking contrast, the same mutation in C57BL/6J mice, making these mice more Th2 skewed than C57BL/6J wild-type mice, results in animals that can hardly be colonized at all. Similar, but less strong, effects were seen after disruption of IL-4 in BALB/c and C57BL/6J backgrounds, respectively. Except for the C57BL/6J IL-12 knockout mice, disruption of IL-4 or IL-12 in both mouse strains does not affect the response of the mice to vaccination, compared to the cognate wild-type animals [75]. These findings further confirm the importance of host factors on outcome of *H. pylori* infection, and they may provide a basis for further studies to elucidate the determinants that are associated with susceptibility for colonization and subsequent development of *H. pylori*–induced pathology.

Like H⁺,K⁺-ATPase-specific T cell clones [51], *H. pylori*–specific gastric T cell clones produce high levels of TNF-α and IFN-γ upon antigenic stimulation [55,76]. In a recent study, a highly significant in situ correlation was shown between TNF-α and IFN-γ production and grade of gastritis, *H. pylori* colonization density, epithelial cell apoptosis, and Fas/FasL-expression [76].

In conclusion, both Th1 and Th2 cytokines are involved in protection from *H. pylori* infection, but a predominant Th1 response is associated with disease, whereas the ability of the host to mount a combined Th1/Th2 response is associated with protection from *H. pylori*–induced pathology.

**CHANGES IN THE GASTRIC EPITHELIUM IN *H. PYLORI*–ASSOCIATED GASTRIC AUTOACTIVITY**

The autoantigen recognized by *H. pylori*–induced antigastic autoantibodies is the gastric proton pump H⁺,K⁺-ATPase [9]. Gastric H⁺,K⁺-ATPase is also the major autoantigen recognized by autoantibodies in AIG/PA [77–80], and is the target for autoreactive T cells that mediate the destruction of glandular epithelium in murine and human AIG [48,51,81]. Furthermore, *H. pylori* gastritis patients with anticanaliculic autoantibodies develop gastric pathology and symptoms similar to those seen in AIG/PA patients [7,20]. These observations suggest that a similar autoimmune response, involving parietal cell autoantigens may be responsible for corpus atrophy in *H. pylori*
gastritis. Several findings suggest a role for autoantigen-specific destruction of the gastric glandular epithelium by CD4⁺ T cells in *H. pylori* infection with gastric corpus atrophy, similar to the destruction of glands seen in AIG/PA.

Sustained predominance of the acute Th1 cytokine profile is thought to play a prominent role in the chronicity of *H. pylori*–induced gastric inflammation. In vivo neutralization of IFN-γ in *H. felis*–infected mice dramatically reduces the severity of gastric inflammation, further supporting the contribution of Th1 cell-mediated immune responses in disease pathogenesis [63]. IFN-γ also plays a key role in the onset of murine EAIG, and induction of this disease can also be abrogated by neutralizing this Th1 cytokine in vivo [82].

Like in EAIG/AIG, gastric epithelial cells may function as antigen-presenting cells in the *H. pylori*–infected gastric mucosa. *H. pylori* infection leads to de novo expression of MHC class II [83,84] and costimulatory molecules B7.1 and B7.2 [84,85] on gastric epithelium. Increase in MHC class II expression correlates with an increased gastric mucosal influx of CD4⁺ T cells. Furthermore, IFN-γ–induced expression of B7.2 on epithelial cell lines increases after cognate interaction of surface MHC molecules [85]. In addition, human gastric epithelial cells are capable of antigen processing. Gastric epithelial cell lines, as well as epithelial cells isolated from gastric biopsies, functionally express several cathepsins that are capable of processing both *H. pylori* and dietary antigens, as well as degrading the class II MHC-associated invariant chain [58], which is required to allow peptide-binding by MHC class II molecules [86]. Together, these observations indicate that gastric epithelial cells may play a role in antigen presentation and subsequent activation of gastric intraepithelial CD4⁺ T cells. Both bacterial antigens and autoantigens that are released during cell turnover, such as gastric H⁺,K⁺-ATPase, could be presented to gastric T cells. Increased expression of ICAM-1 on gastric epithelial cells is found in *H. pylori*–infected patients [84] and may play a role in adhesion of T cells to the epithelial cells during antigen presentation.

Similar to EAIG mice, mice infected with *H. pylori* express increased levels of MAdCAM-1 in their lamina propria and submucosa, as compared to noninfected control animals. Most of the lamina propria infiltrating CD4⁺ lymphocytes in infected animals coexpress β7-integrin and are localized in the vicinity of MAdCAM-1 rich areas 6 months after infection [87]. However, when measured 2 weeks after, *H. felis* infection does not induce α4β7hi T lymphocytes in mice, whereas oral immunization with *H. felis* sonicate does [88]. MAdCAM-1 and α4β7-integrin are involved in the homing of CD4⁺
T cells to the gastric mucosa and protection against *H. felis* infection in mice [88], but their roles in human *H. pylori* infection remain to be elucidated. MAdCAM-1 was found to be equally expressed on the gastric epithelium of *H. pylori*-infected and noninfected individuals [89].

**Destruction of Glandular Epithelium in *H. pylori* Gastritis with Corpus Mucosa Atrophy**

Several studies have shown the involvement of Fas/FasL signaling in apoptosis of epithelial cells in *H. pylori* infection [90–92]. Fas receptor and FasL are expressed on foveolar and glandular epithelial cells in the antrum and corpus [84,92]. Whereas FasL is constitutively expressed [84], Fas expression on epithelial cells is increased during *H. pylori* infection [92]. Activated Fasl⁺ T cells can lyse Fas-expressing antigen-presenting cells in an antigen-dependent way (direct lysis), as well as nearby Fas⁺ cells in an antigen-independent way (bystander lysis) [93]. As compared to Th2 cells, Th1 cells express higher levels of Fasl [94], and Th1 cells have been reported to contribute to apoptosis of gastric epithelial cells by Fas/FasL interaction [92]. The expression of Fas on gastric epithelial (cell line) cells is increased by *H. pylori* and by the Th1 cytokines IFN-γ and TNF-α, either alone or in any combination, and by IL-1β [95]. Gastric epithelial cell lines expressing Fas can be killed by T cells that express Fasl, and antibodies that block Fas/Fasl interaction inhibit this cytotoxicity [92]. These findings are in line with the above-mentioned in situ correlation between TNF-α and IFN-γ secretion and apoptosis in *H. pylori*-associated gastritis [76]. Thus, during *H. pylori* infection Fas⁺ gastric parietal cell may be killed upon presentation of autoantigen, e.g., H⁺,K⁺-ATPase, to autoantigen-specific CD4⁺ T cells expressing Fasl. Gastric parietal cells might also be killed via bystander lysis by circulating activated Fasl⁺ CD4⁺ T cells specific for other antigens, including *H. pylori*.

In addition to elevated Fas expression on gastric epithelium, *H. pylori* is also able to induce Fas expression and Fas/FasL-mediated apoptosis in T cells. This process is dependent on the presence of the cag pathogenicity island (PAI) in the infecting *H. pylori* strain, and it has been proposed that induction of apoptosis in T cells enhances the survival of *H. pylori* and contributes to persistence of infection [96].

Fas/Fasl signaling has been shown to be involved in *H. pylori*-associated apoptosis in several studies [90–92]. Recently the regulatory role of this apoptotic pathway has been addressed in a murine *H. pylori* infection model [97]. Mucosal atrophic changes, including mucus cell hyperplasia and parietal cell loss, are detected more
frequently in the corpus regions of *H. pylori*–infected C57BL/6 gld (FasL-deficient) mice compared to infected C57BL/6 wild-type mice, despite comparable levels of bacterial colonization and gastritis [97]. In addition, apoptotic cells are virtually absent in the mucosa of *H. pylori*–infected gld mice, whereas increased apoptosis is observed in the gastric mucosa of *H. pylori*–infected C57BL/6 wild-type mice [97]. The authors suggest that dysregulation of Fas/FasL signaling may either promote carcinogenesis, in the case of the absence of Fas-triggered programmed cell death, or ulcerogenesis due to enhanced apoptosis, which would lead to disruption of the gastric epithelial barrier [97]. It is tempting to hypothesize that the observed parietal cell loss in *H. pylori*–infected FasL-deficient mice [97] may be due to Fas-independent destruction, e.g., perforin-mediated lysis, of parietal cell by Th1 cells that have escaped Fas-triggered programmed cell death [98]. However, the observations that splenocytes from neither *H. pylori*–infected nor uninfected gld mice produce detectable levels of IFN-γ, whereas they produce low levels of IL-5 [97], seem to contradict this idea.

In addition to cytokine-induced upregulation of Fas antigen expression and apoptosis mediated by *H. pylori* infection, direct contact with the bacterium induces both apoptosis through cytochrome c release from the mitochondria (“the mitochondrial pathway”) and antiapoptotic signals via and NFκB in human gastric cancer cell lines [99]. However, the significance of induction of apoptosis in parietal cells by direct contact with *H. pylori* may be questioned, since *H. pylori* usually resides in the human antrum [1]. When inoculated in mice, *H. pylori* colonizes gastric niches devoid of parietal cells [100]. This restriction of bacterial tropism is not seen in *H. pylori*–infected transgenic mice that lack parietal cells [100].

Excessive expression of Bcl-2, a 26 kDa protein that usually counteracts apoptotic effects of another protein involved in apoptosis, i.e., Bax, is found in AIG and *H. pylori*–associated atrophic gastritis, but not in *H. pylori* antral gastritis without atrophy [101]. Similarities in increased Fas and FasL expression, and in excess expression of Bcl-2, between AIG/PA and *H. pylori*–associated atrophic corpus gastritis, may indicate similar pathogenic pathways in both diseases.

**Models for the Pathogenesis of *H. pylori*–Associated Antigastric Autoimmunity**

Despite the strikingly similar pathophysiological changes of the gastric corpus mucosa in AIG/PA and in *H. pylori*–associated atrophic gastritis, that suggest an initiating role for *H. pylori* in both these
gastric autoimmune disorders, there is often a negative association between current *H. pylori* infection and AIG/PA. Studies on the association between AIG/PA and *H. pylori* infection indicate that patients with PA are less often infected with *H. pylori* than age-matched controls [102]. However, as indicated before, a majority of patients with PA show serological evidence of previous *H. pylori* infection [32,35], while actual infection with *H. pylori*, as shown by histology, is detected in only a minority of PA patients [34,35]. *H. pylori* infection may have been present before the development of pernicious anemia and may be cleared during the period of transition from normal antral and corpus mucosa to preatrophic corpus mucosa and established corporal gastric atrophy. This course of infection is supported by observations from a long-term follow-up study, in which a subgroup of *H. pylori*-infected patients initially had gastritis of the antrum that later progressed to severe atrophy of the corpus [103]. This process was often accompanied by normalization of the antral mucosa, disappearance of *H. pylori*, and appearance of parietal cell antibodies. These data strongly support a causative role of *H. pylori* in at least a subpopulation of patients suffering from gastric autoimmunity.

*H. pylori*-associated corpus mucosal atrophy, may develop via the following processes (visualized in Figures 2a–2c). In the noninflamed gastric mucosa, only a few gastric periglandular lymphocytes are present. Infection with *H. pylori* leads to an inflammatory influx of T and B lymphocytes and macrophages. Subsequently, epithelial cells acquire properties that are required for antigen presentation (described above) under the influence of the predominant Th1 cytokine milieu resulting directly from *H. pylori* infection [64,66]. Epithelial cells may then present gastric *H*⁺,*K*⁺-ATPase to CD4⁺ *H*⁺,*K*⁺-ATPase-specific Th1 cells that have escaped negative selection in the thymus, which may result in killing of Fas⁺ parietal cells (Figure 2a), and to autoreactive T cells that provide help for B cell stimulation and autoantibody production. Activated Th1 cells expressing FasL could kill Fas⁺ parietal cells by either antigen-dependent Fas–FasL interaction or by Fas-mediated bystander lysis, resulting in destruction of glands (atrophy). The abundance of *H*⁺,*K*⁺-ATPase in parietal cells, together with the lack of expression of the *H*⁺,*K*⁺-ATPase β-subunit in the thymus [104,105], at least in mice, might favor presentation of *H*⁺,*K*⁺-ATPase over presentation of other autoantigens that are present in the gastric mucosa. During the course of the chronic antigastric cell-mediated inflammatory response, epitope spreading to other autoantigens such as intrinsic factor and pepsinogen may occur. These antigens are targets of autoantibodies in full-blown AIG/PA [39,106]. Loss of *H. pylori* and normalization of the antrum
FIGURE 2 Autoimmune destruction of parietal cells during *H. pylori* infection may involve several mechanisms (for details see text). (a) *H. pylori* infection leads to increase in local levels of Th1 cytokines, resulting in both breakdown of...
may parallel increasing corpus atrophy. In the final stage, the autoimmune T cell responses that were initially triggered by local inflammatory factors resulting from \textit{H. pylori} infection do not require the presence of bacteria anymore but are maintained by the predominant Th1 response and cytokine milieu, and they are indistinguishable from the gastric inflammatory responses seen in AIG/PA (Figure 2a). This model is supported by the observation in mice that local expression of GM-CSF, a proinflammatory cytokine, is sufficient to break tolerance and initiate gastric autoimmunity mediated by H\textsuperscript{+},K\textsuperscript{+}-ATPase specific CD4\textsuperscript{+} T cells [107].

Alternatively, or parallel to antigen presentation by gastric epithelial cells, H\textsuperscript{+},K\textsuperscript{+}-ATPase may also be presented by DCs. DCs have been shown to constitutively acquire H\textsuperscript{+},K\textsuperscript{+}-ATPase from the gastric mucosa, after which they migrate to the draining lymph node and present the autoantigen to T cells [57].

In addition to autoantigen (i.e., H\textsuperscript{+},K\textsuperscript{+}-ATPase)-dependent Fas-mediated lysis, epithelial/parietal cells may be killed by bystander effect of FasL\textsuperscript{+} gastric T cells that are \textit{H. pylori}–specific [92,93]. Presentation of bacterial antigens by gastric epithelial cells and professional APCs, such as macrophages and DCs, may result in activation of \textit{H. pylori}–specific T cells that kill the antigen-presenting epithelial cells by \textit{H. pylori}–antigen-dependent (i.e., direct) mechanisms, e.g., perforin-mediated lysis. Nearby Fas\textsuperscript{+} parietal cells may be subsequently killed by antigen-independent bystander lysis (Figure 2b).

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self-tolerance and survival of negative selection by autoreactive (e.g., H\textsuperscript{+}, K\textsuperscript{+}-ATPase-specific) T cells. Increased antigen-presentation function of epithelial cells, including parietal cells, and elevated levels of Fas expression on parietal cells as compared to other epithelial cells, may result in selective destruction of parietal cells by H\textsuperscript{+},K\textsuperscript{+}-ATPase-specific autoreactive T cells, via antigen-dependent Fas/FasL-mediated apoptosis. (b) \textit{H. pylori} infection induces activation and proliferation of \textit{H. pylori}–specific T cells that directly target epithelial cells presenting \textit{H. pylori} antigens by antigen-dependent mechanisms, like perforin-mediated lysis. Nearby Fas\textsuperscript{+} parietal cells may be destroyed via “bystander” apoptosis by \textit{H. pylori}–specific T cells that express FasL. The selective disappearance of parietal and zymogenic cells may be due to disruption of mucosal developmental pathways during gastric autoimmunity (see text). (c) The population of \textit{H. pylori}–specific T cells, induced by infection, may contain a subpopulation of T cells that cross-react with peptide epitopes of H\textsuperscript{+},K\textsuperscript{+}-ATPase. \textit{H. pylori}/H\textsuperscript{+},K\textsuperscript{+}-ATPase cross-reactive T cells could mediate destruction of both nonparietal epithelial cells and parietal cells via antigen-dependent, perforin-mediated lysis, and may also target Fas\textsuperscript{+} parietal cells by “bystander” apoptosis. (d) Legend to (a)–(c).
FIGURE 2. Continued.
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FIGURE 2. Continued.
The increased expression of Fas on parietal cells compared with other cells in the gastric epithelium may explain the selective destruction of parietal cells in (E)AIG and the *H. pylori*–associated corpus atrophy models described above. However, zymogenic cells also disappear during these diseases. It has been proposed that in EAIG the normal developmental pathways of the gastric mucosa are disrupted, resulting in the accumulation of mucous neck cells and immature stem cells (hyperplasia), that do not differentiate to end-stage cells. This may explain the depletion of zymogenic cells, although they are not directly targeted by the immune system [108].

A third model of how *H. pylori* infection may mediate autoimmune destruction of the gastric corpus mucosa, and finally result in AIG/PA, PA, involves molecular mimicry at the level of T cell epitopes (Figure 2c). The detection of anti-H+,K+-ATPase antibodies in the circulation of *H. pylori*–infected patients is suggestive of the presence of T helper cells specific for the same autoantigen. It has been proposed that sequence homology between *H. pylori* polypeptides and H+, K+-ATPase may underlie the induction of autoreactive antibodies and T cells by *H. pylori* [109]. In such a setting, infection induces activation and expansion of *H. pylori*–specific T cells that recognize not only their bacterial peptide epitope but also a peptide derived from H+,K+-ATPase. Upon activation, these cross-reactive T cells may directly kill antigen-presenting gastric epithelial cells that present the appropriate peptide (i.e., derived from *H. pylori* or H+,K+-ATPase), and indirectly induce apoptosis in Fas+ parietal cells. Such events may provide an additional explanation for the selective destruction of parietal cells, because H+,K+-ATPase is exclusively expressed in parietal cells, and also Fas expression seems to be predominantly upregulated in parietal cells during gastric autoimmunity as compared to other epithelial cells.

This model, in which molecular mimicry forms the basis of the pathogenesis of autoimmune gastric atrophy, is strongly supported by the recent discovery of in vivo–activated cross-reactive autoreactive T cells in patients with both AIG and concurrent *H. pylori* infection [110]. In addition to CD4+ T cell clones reactive to *H. pylori* lysate, and CD4+ T cell clones that recognized H+,K+-ATPase, these patients harbor gastric Th1 cells that recognize *H. pylori* antigens as well as H+,K+-ATPase. The different submolecular specificities of such gastric T cells have been characterized, and cross-reactive epitopes from nine *H. pylori* proteins have been identified. Of note, recognition of the cross-reactive peptides is dependent on a particular HLA-DR haplotype, and none of the identified cross-reactive proteins belong to the known immunodominant antigens of *H. pylori*. Instead they belong to products of *H. pylori* household genes, and include histidine
kinase, acetate kinase, and penicillin-binding protein as well as a LPS biosynthesis protein. Recognition of these \textit{H. pylori} cross-reactive peptides leads to functional activation of cross-reactive T cell clones and primes mechanisms that are associated with gastric pathology in AIG \cite{51,110}.

The novel data provided by our laboratories fit into the following model for the role of \textit{H. pylori} in the development of gastric corpus mucosal atrophy and subsequently chronic AIG: \textit{H. pylori}-induced chronic inflammation may result in breakdown of tolerance for self-antigens, including \(H^+,K^+\)-ATPase, in genetically predisposed individuals, leading to escape from negative selection of self-reactive/cross-reactive T cells, i.e., both \(H^+,K^+\)-ATPase-specific and \textit{H. pylori}/\(H^+,K^+\)-ATPase cross reactive. These potentially autoreactive T cells become activated and expand due to constitutive presentation of \(H^+,K^+\)-ATPase by professional APC, such as DCs and macrophages. In addition, in individuals expressing certain but as yet unidentified HLA haplotypes, appropriate presentation of \textit{H. pylori} antigens may result in expansion and activation of \textit{H. pylori}/\(H^+,K^+\)-ATPase cross-reactive, autoreactive T cells. As a result from continuous inflammation, epitope spreading to other autoantigen epitopes of \(H^+,K^+\)-ATPase (that are not mimicked by bacterial peptides), may occur, and the presence of \textit{H. pylori} antigens to maintain the population of autoreactive T cells is not further required. With ongoing corpus atrophy and increase in gastric pH due to disappearance of parietal cells, \textit{H. pylori} may be deprived from its preferred niche and be eventually lost. After this step, the gastric mucosal functions and clinical characteristics of an individual with \textit{H. pylori}-triggered atrophic corpus gastritis will resemble classical AIG.

In conclusion, we have discussed the striking similarities between \textit{H. pylori}-induced gastric autoimmunity and classical AIG/PA with respect to both humoral and cell-mediated immune responses. Although there are still many questions regarding the exact role of \textit{H. pylori} in gastric autoimmunity and the pathogenic mechanism(s) involved in the development of gastric corpus atrophy, there is increasing evidence that supports the idea that in some hosts \textit{H. pylori} may initiate AIG via molecular mimicry.

**REFERENCES**


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