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MiniReview

Helicobacter pylori, T cells and cytokines: the "dangerous liaisons"

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Abstract

Helicobacter pylori infection is the major cause of gastroduodenal pathologies, but only a minority of infected patients develop chronic and life threatening diseases, as peptic ulcer, gastric cancer, B-cell lymphoma, or autoimmune gastritis. The type of host immune response against *H. pylori* is crucial for the outcome of the infection. A predominant *H. pylori*-specific Th1 response, characterized by high IFN-γ, TNF-α, and IL-12 production associates with peptic ulcer, whereas combined secretion of both Th1 and Th2 cytokines are present in uncomplicated gastritis. Gastric T cells from MALT lymphoma exhibit abnormal help for autologous B-cell proliferation and reduced perforin- and Fas–Fas ligand-mediated killing of B cells. In *H. pylori*-infected patients with autoimmune gastritis cytolytic T cells infiltrating the gastric mucosa cross-recognize different epitopes of *H. pylori* proteins and H^+K^+ ATPase autoantigen. These data suggest that peptic ulcer can be regarded as a Th1-driven immunopathological response to some *H. pylori* antigens, whereas deregulated and exhaustive *H. pylori*-induced T cell-dependent B-cell activation can support the onset of low-grade B-cell lymphoma. Alternatively, *H. pylori* infection may lead in some individuals to gastric autoimmunity via molecular mimicry.

Keywords: Mucosal immunity; Th1–Th2 response; Cytokines; *Helicobacter pylori*; Chronic gastritis; Peptic ulcer; Gastric cancer; Gastric lymphoma; Autoimmunity

1. Introduction

Helicobacter pylori infects almost half of the population worldwide and represents the major cause of gastroduodenal pathologies, such as duodenal and gastric ulcer, gastric cancer, B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), and autoimmune gastritis [1–4]. Antigen-specific T-cell responses are essential for defence against the pathogens. T helper cells (Th) are a key part of the adaptive immune response and can express polarized patterns of cytokine secretion (type-1 or Th1 and type-2 or Th2) and different effector functions [5,6]. Th1 cells produce IFN-γ, TNF-β, and IL-2, elicit macrophage activation, whereas Th2 cells produce IL-4, IL-5, and IL-13, that act as growth/differentiation factors for B cells, and inhibit several macrophage functions [7]. Most T cells, named as Th0, do not express a polarized Th1 or Th2 profile and represent a heterogeneous population of cells secreting different combinations of Th1 and Th2 cytokines. Both environmental and genetic factors influence the Th1 or Th2 differentiation mainly by determining the 'leader cytokine' in the microenvironment of the responding T cells. IL-12, IL-18 and IFNs favour Th1 development, whereas IL-4 is a powerful stimulus for Th2 [7]. In most infectious diseases, the type of specific immunity elicited is of crucial importance for protection, but, under certain circumstances, an inappropriate response can even

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contribute to the induction of immunopathology [8,9]. Both the virulence properties of *H. pylori* strains and host factors strongly influence the clinical outcome of the infection. This article will focus on mucosal T-cell and cytokine responses in *H. pylori* infection occurring in peptic ulcer, gastric low-grade B-cell lymphoma (MALToma), atherosclerosis, and autoimmune gastritis.

2. Th1 polarization in peptic ulcer

Helicobacter pylori infection of the gastric antrum represents the primary cause of gastroduodenal diseases, but the reason why only a limited number (10–20%) of patients with *H. pylori*-induced gastritis undergo complications of the infection still remains unclear. *H. pylori* itself can induce mucosal injury, and some mechanisms of gastric damage may be related to the pathogenic products of *H. pylori* [10,11].

In peptic ulcer RT-PCR analysis of antral biopsies showed IL-12, IFN-γ, and TNF-α, but not IL-4, mRNA expression, whereas both IFN-γ and IL-4 mRNA signals were found in non-ulcer gastritis [12–14]. Using serial histological sections, a significant correlation was demonstrated between disease severity and the *in situ* secretion of IFN-γ and TNF-α [15]. The antigen specificity and effector functions of the Th cells resident in the antral mucosa of patients with or without peptic ulcer were extensively investigated [12–16]. Among the *H. pylori*-reactive Th clones derived from peptic ulcer patients, half of them were specific for Cytotoxin-associated protein (CagA), whereas about one fourth of *H. pylori*-reactive clones from non-ulcer gastritis patients recognized the *H. pylori* urease. These data suggest that CagA is the immunodominant antigen of *H. pylori*-specific T-cell responses in the stomach of peptic ulcer patients. The reasons for this are not yet fully elucidated. CagA is injected into APC and epithelial cells by the molecular syringe assembled by products of the *cag* pathogenicity island, and this phenomenon might account for the preferential presentation and the high immunogenicity of this protein [17]. Vacuolating cytotoxin (VacA) is unable to evoke a strong immune response in animals, unless administered with adjuvants [10,17]. VacA inhibits the intracellular pathway of macrophage antigen presentation and two independent signalling pathways of T-cell activation with consequent lower stimulation of antigen-specific T-cell response [18,19].

CagA can be expressed on bacterial surface and therefore it can preferentially evoke Th1 responses by inducing IL-12 secretion by activated macrophages. In peptic ulcer patients indeed, upon stimulation with the specific *H. pylori* antigen, the great majority of *H. pylori*-specific clones, and particularly those specific for CagA, showed a polarized Th1 profile, with high production of IFN-γ but not of IL-4. In contrast, in uncomplicated gastritis, more than a half of *H. pylori*-specific Th clones derived from gastric antrum showed a Th0 profile whereas polarized Th1 were one third only [16].

Increased levels of IL-18 and IL-17, other Th1-inducers, have been found in the gastric mucosa of *H. pylori*-infected patients [20,21]. A preferential activation of Th1 responses has been reported in different animal models, such as mice, beagle dogs, and monkeys experimentally infected with *H. pylori* or *H. felis* [22–24].

A number of independent studies agree that Th1 polarization of *H. pylori*-specific T-cell response is associated with more severe disease [12,15,25–28]. Predominant activation of Th1 cells with production of IFN-γ and TNF-α, in the absence of Th2 cytokines can increase gastrin secretion and pepsinogen release [29,30].

The concept that gastric polarized Th1 response against *H. pylori* contributes to the pathogenesis of peptic ulcer is indirectly supported by different observations showing that inhibition of Th1 or activation of Th2 responses result in reduction of dyspeptic symptoms. The results obtained so far suggest that gastric T-cell responses to *H. pylori* antigens characterized by a mixed Th1–Th2 cytokine profile are associated with lower rate of ulcer complication and that Th2 cytokines, particularly IL-4 and IL-10, are important in balancing and quenching some detrimental effects of polarized Th1 responses. In patients undergoing strong Th1 immunosuppression, such as renal transplanted patients, in spite of a high prevalence of *H. pylori* colonization, peptic ulcer and active inflammatory lesions were virtually absent [31]. In pregnancy, a preferential Th2 response does occur and makes the mother "tolerant" to her offspring by inhibiting Th1 responses [32]. During pregnancy, patients suffering of peptic ulcer significantly reduce their dyspeptic symptoms and tend to undergo remission for the time of pregnancy [33]. Considering that some local IL-4 production may result in protection from ulcer, we proposed that the "African enigma" (i.e. discrepancy between high rate of *H. pylori* infection and low prevalence of peptic ulcer) [34] could be related to the acquired cytokine response of African people living in endemic areas of helminth infections, known to elicit strong and persistent Th2-dominated responses [35].

In mice, T-cell dependent immune responses are needed for protection against *H. pylori* whereas antibody response is not strictly required for protective immunity [36]. However, if the T-cell response induced against *H. pylori* is not fully appropriate and balanced, it may even result in damage to the host, as demonstrated in different animal models [22,24,37]. Transferring T cells derived from *H. pylori*-infected patients into SCID mice has proven to induce gastric ulcer in those mice, demonstrating that host immunity is

involved in the development of peptic ulcers [38]. In *H. felis*-infected mice, neutralization of IFN-γ significantly reduced the severity of gastritis, strongly supporting the concept that preferential long-lasting activation of a Th1-type response contributes to development and maintenance of gastric pathology. The magnitude of *H. felis*-induced inflammation in IL-4-deficient mice was higher than in their wild-type counterparts. Moreover, infection with *H. felis* induced minimal inflammation in BALB/c mice, whose genetic background is prone to high IL-4 production in response to different antigens [22]. The results of these studies provide further evidence that unlimited Th1 response is associated with gastric inflammation and disease, whereas a mixed Th1/Th2 response is able to reduce the pro-inflammatory Th1 response [22]. Fox et al. [39], confirming our hypothetical explanation for the ''African enigma'', demonstrated that co-infection of mice with *H. felis* and *H. polygyrus*, a murine helminth parasite, resulted in less severe gastric inflammation and related epithelial injury than infection with *H. felis* alone. As expected, co-infected mice showed increased production of Th2 and lower production of Th1 cytokines [39]. On other hand, the usefulness for protection against *H. pylori* infection of IL-12 driven Th1 responses has been clearly shown in IL-12, IFN-γ or IL-4 deficient mice [40]. Therefore, we can assume that a never-ending Th1-driven inflammation would result in immunopathology whereas a polarized Th2 response would not even be beneficial for the host because it would not guarantee protection. Only an efficient *H. pylori*-specific Th1 response appropriately tuned by Th2 cells would lead to protection.

3. *Helicobacter pylori*-specific Th cells promote B-cell proliferation in low-grade gastric B-cell lymphoma

Helicobacter pylori-related low-grade gastric MALT lymphoma represents the first described neoplasia susceptible to regression following antibiotic therapy resulting in *H. pylori* eradication [41]. A prerequisite for lymphomagenesis is the development of secondary inflammatory MALT induced by *H. pylori*. Tumor cells of low-grade gastric MALT lymphoma (MALToma) are memory B cells still responsive to differentiation signals, such as CD40 costimulation and cytokines produced by antigen-stimulated Th cells, and dependent for their growth on the stimulation by *H. pylori*-specific helper T cells [42,43]. In early phases, this tumor is sensitive to withdrawal of *H. pylori*-induced T-cell help, providing an explanation for both the tumor tendency to remain localized to its primary site and its regression after *H. pylori* eradication. Detailed analysis of the antigen-induced B-cell help exerted by *H. pylori*-reactive gastric T-cell clones contributed new information on the mechanisms possibly associated with the onset of low-grade gastric MALToma. It is of note that the majority of *H. pylori*-reactive Th clones derived from low-grade MALT lymphomas proliferated to *H. pylori* crude extract only, but not to CagA, VacA, or urease suggesting that some still undefined but important antigens of *H. pylori* are involved in driving T-cell activation and related B-cell proliferation in low-grade gastric lymphoma [44]. In vitro stimulation with *H. pylori* induced *H. pylori*-specific Th clones derived from gastric MALToma to express powerful help for B-cell activation and proliferation. In contrast in chronic gastritis patients without MALToma the helper function to B cells exerted by *H. pylori* antigen-stimulated gastric T-cell clones was negatively regulated by the concomitant cytolytic killing of B cells [44]. Gastric T-cell clones from MALToma were unable to down-modulate their antigen-induced help for B-cell proliferation and none of these clones was able to express perforin-mediated cytotoxicity against autologous B cells. Moreover, the majority of Th clones from uncomplicated chronic gastritis induced Fas–Fas ligand-mediated apoptosis in target cells, whereas only a small fraction of *H. pylori*-specific gastric clones from MALToma were able to induce apoptosis in target cells, including autologous B cells [44]. Both defective perforin-mediated cytotoxicity and poor ability to induce Fas–Fas ligand-mediated apoptosis were restricted to MALToma-infiltrating T cells, since *H. pylori*-specific Th cells derived from the peripheral blood of the same patients expressed cytolytic potential and pro-apoptotic activity like that shown by Th cells from chronic gastritis patients [44]. The reason why gastric T cells of MALToma, while delivering powerful help to B cells, are apparently deficient in mechanisms involved in the concomitant control of B-cell growth, still remains unclear. It has been shown that VacA toxin inhibits antigen processing in APC and T-cell activation, but not the exocytosis of perforin-containing granules of NK cells [18,19]. It is possible that, in some *H. pylori*-infected individuals, some yet undefined bacterial components affect the development or the expression in gastric T cells of regulatory cytotoxic mechanisms on B-cell proliferation, allowing exhaustive and imbalanced B-cell help and lymphomagenesis to occur.

4. *Helicobacter pylori* infection, molecular mimicry and autoimmune gastritis

A strong association between *H. pylori* infection and gastric autoimmunity has been highlighted by a number of clinical and epidemiological studies indicating that most of patients with AIG have or have had *H. pylori* infection [4]. *H. pylori*-associated autoimmune gastritis is characterized by an inflammatory infiltrate of the gastric mucosa, including T cells, mac-

rophages and B cells. It mainly affects the corpus and the fundus, and it is accompanied by loss of gastric parietal and zymogenic cells. We have recently characterized at molecular level the gastric T-cell mediated responses to *H. pylori* and to the H^+,K^+-ATPase autoantigen in a series of *H. pylori*-infected patients with gastric autoimmunity [45].

Among gastric Th clones, a number proliferated to *H. pylori*, but not to the *H. pylori* proteins CagA, VacA, hsp, urease nor to H^+,K^+-ATPase. Some other Th clones proliferated to H^+,K^+-ATPase and not to *H. pylori* (autoreactive), and a third group of clones was found that proliferated to both *H. pylori* and H^+,K^+-ATPase (cross-reactive) [45]. All the Th clones able to proliferate to H^+,K^+-ATPase were studied for their ability to respond to the 261 overlapping 15-mer peptides covering the amino acid sequence of α and β chain of the human H^+,K^+-ATPase. In the series of cross-reactive Th clones 11 recognized their epitope in the α chain and two clones in the β chain. In the subgroup of autoreactive Th clones 6 recognized their epitope in the α chain and 9 in the β chain of the proton pump. Therefore, some "shared" H^+,K^+-ATPase epitopes, mainly in the α chain, are cross-reactive with epitopes of *H. pylori* antigens, whereas others can be considered as "private" epitopes of H^+,K^+-ATPase. A cross-reactive *H. pylori* peptide could be found for each of the 10 H^+,K^+-ATPase/*H. pylori* cross-reactive gastric Th clones [45]. Overall, that study led to the identification of nine different *H. pylori* proteins (such as lipopolysaccharide biosynthesis protein, histidine kinase, porphobilinogen deaminase, dimethyl-adenosine transferase, glucose-inhibited division protein A, VirB4 homolog, phosphoglucosamine mutase, acetate kinase, penicillin-binding protein-2) each harbouring a T-cell peptide suitable for cross-reaction with T-cell epitopes of gastric H^+,K^+-ATPase α chain [45]. Interestingly, none of the bacterial epitopes recognized by cross-reactive Th clones belong to the known *H. pylori* immunodominant antigens, such as CagA, VacA and urease, which are major targets of gastric T-cell responses in *H. pylori* infected patients with peptic ulcer [12]. Two possibilities can be considered: these peptides are implicated in cross-reactivity because of their structural properties or alternatively a physiological relevance implicating these particular nine proteins can be postulated. All the cross-reactive and autoreactive H^+,K^+-ATPase-specific Th clones after activation were able to induce cell death via either Fas–Fas ligand-mediated apoptosis or perforin-mediated cytotoxicity against target cells [45]. This ability to induce apoptosis in T cells might give a selective advantage that can promote survival and persistence of bacteria, allowing *H. pylori* to escape the host immune response. On the other hand, the relevance of cross-reactive and autoreactive cytolytic Th effector cells in the genesis of AIG is consistent with data in the mouse model that Fas-related death is required for the development of full-blown destructive autoimmune gastritis [46]. Based on these results, it is tempting to speculate that in the "gastric autoimmune inflammatory *scenario*" in which cross-reactive and autoreactive Th clones are activated, parietal cells might become target of the pro-apoptotic and cytotoxic activity of cross-reactive and autoreactive gastric Th cells. The end point of this process would be gastric corpus atrophy and hypochlorydria.

5. Lack of *H. pylori*-specific Th cells in the atherosclerotic plaques of *H. pylori*-infected patients

A pathogenetic role in atherosclerosis has been suggested for chronic bacterial infections, such as *H. pylori* or *Chlamydia pneumoniae*, leaving still open the question of how the infectious agents might contribute to the formation of plaques [47]. The role of cell-mediated immunity and the functional status of pathogen-specific effector T cells within atherosclerotic lesions remain poorly characterized. We assessed the functional profile of in vivo activated T lymphocytes that infiltrate atherosclerotic plaques to understand whether and how their effector functions may influence the natural history of atherosclerosis [48]. Among patients undergoing carotid endarterectomy, we selected 10 *H. pylori*-infected individuals, five of whom were also seropositive for anti-*C. pneumoniae* antibodies (Cp-pos), and five were seronegative (Cp-neg). Fragments of carotid plaques of all patients were cultured in IL-2-conditioned medium to allow the preferential expansion of in vivo activated T cells resident in the plaques. Single T-cell blasts were then cloned and studied. In all patients, the majority of plaque-derived Th clones produced IFN-γ and TNF-α, but not IL4, and were able to provide help for tissue factor production by autologous monocytes. We studied the proliferative response to *H. pylori* and *C. pneumoniae* antigens of all the 421 plaque-derived Th clones. We could not find any T-cell reactivity against *H. pylori* antigens in spite all patients harbored that pathogen and *H. pylori*-specific T cells in their stomach [48]. In contrast, 22% of the 206 $CD4^+$ T-cell clones generated from the five Cp-pos patients were specific for *C. pneumoniae* antigens. No *C. pneumoniae*-specific Th cell was found in the plaques neither from the five Cp-neg patients nor in the stomach of Cp-pos patients. Therefore, in *H. pylori*-infected patients *H. pylori*-specific T cells infiltrate the gastric antrum but not the atherosclerotic plaques whereas *C. pneumoniae*-specific T-cells selectively colonized the atherosclerotic plaques, but not other site of inflammation, such as gastric antrum [48]. The results obtained so far suggest that atherosclerosis can result from an inappropriate Th1-driven immunopathological response, part

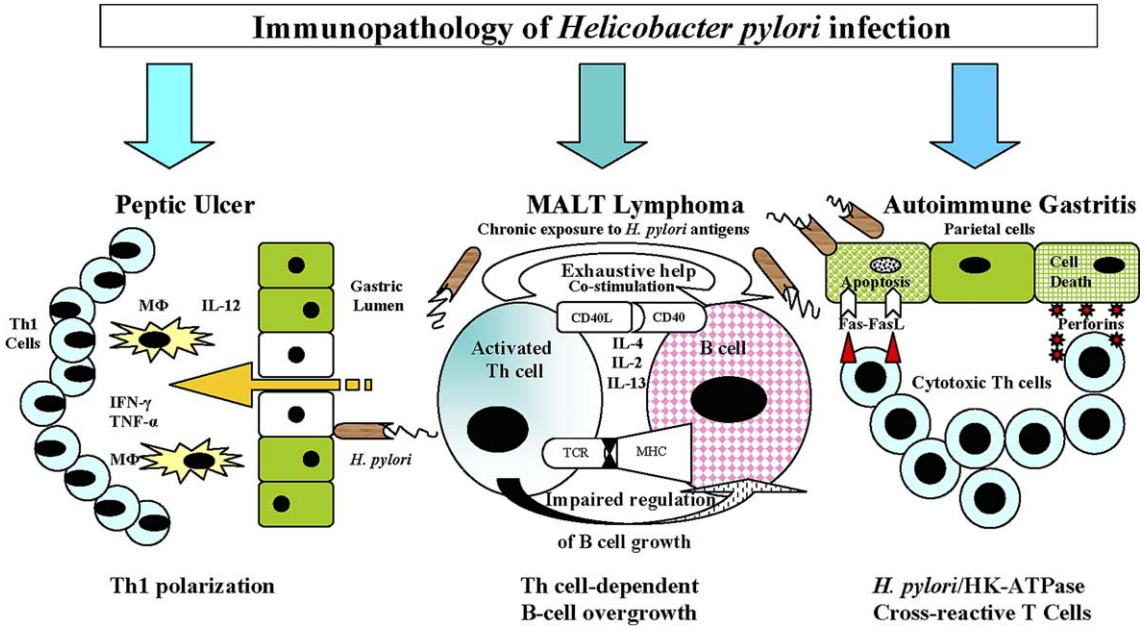

Fig. 1. T-cell mediated immunopathology in peptic ulcer, gastric MALT B-cell lymphoma and autoimmune gastritis. T cells are essential for defence against infection, but inappropriate Th responses can be even harmful for the host. Long-lasting secretion of IFN-γ, TNF-α, IL-12 and other Th1 cytokines may lead to peptic ulcer by inducing functional alterations of gastric cells, and consequent gastric hyperacidity. In a minority of infected patients, gastric *H. pylori*-specific Th cells show deficient cytotoxic control (both perforin and Fas–Fas-ligand mediated) of B-cell growth. Such a defect, the production of cytokines with B-cell growth factor activity and the chronic delivery of costimulatory signals by Th cells, together with chronic exposure to *H. pylori* antigens would result in overgrowth of B cells, thus facilitating the neoplastic B-cell transformation and the onset of gastric low-grade MALT B-cell lymphoma. In susceptible individuals *H. pylori* induces autoimmune gastritis via the expansion of *H. pylori*-specific T cells that cross-react with H^+,K^+-ATPase epitopes. The activation of *H. pylori*-H^+,K^+-ATPase cross-reactive T cells would result in destruction of gastric mucosa, via Fas-ligand (FasL)-induced apoptosis and perforin-mediated cytotoxycity.

of which due to *C. pneumoniae*, but not to *H. pylori* antigens.

6. Conclusions

Helicobacter pylori is able to induce antigen-specific T-cell responses at the gastric site of infection. The effector functions of gastric *H. pylori*-specific T cells are different between patients with peptic ulcer and those with non-ulcer chronic gastritis, MALT lymphoma or autoimmune gastritis (Fig. 1). In some patients, due to genetic and environmental factors not yet fully elucidated, the fine tuning of protective immunity by Th2 and other regulatory T cells may be inadequate, and *H. pylori* drive a long lasting polarized Th1 response which contributes to worsening of the disease, and eventually leads to peptic ulcer. In a small number of infected patients, the host response to *H. pylori* allows the development of specific T cells which express an imbalanced induction of B-cell growth and drive exhaustive B-cell proliferation, making easier the chance of neoplastic transformation, and the onset of low-grade gastric MALT lymphoma. In genetically susceptible individuals, *H. pylori* infection would trigger the activation at gastric level of cross-reactive cytotoxic, and pro-apoptotic T cells leading to the gastric autoimmunity via molecular mimicry.

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