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Helicobacter pylori and autoimmune diseases

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Abstract

Helicobacter pylori (*H. pylori*) is a widely prevalent microbe, with between 50 and 80% of the population infected worldwide. Clinically, infection with *H. pylori* is commonly associated with peptic ulcer disease, but many of those infected remain asymptomatic. *H. pylori* has evolved a number of means to affect the host immune response and has been implicated in many diseases mitigated by immune dysregulation, such as immune thrombocytopenic purpura (ITP), atrophic gastritis, and mucosa associated lymphoid tissue (MALT) lymphoma. Autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and Sjogren's syndrome, are the result of a dysregulated host immune system which targets otherwise healthy tissues. The exact etiology of autoimmune diseases is unclear, but it has long been suggested that exposure to certain environmental agents, such as viral and bacterial infection or chemical exposures, in genetically susceptible individuals may be the catalyst for the initiation of autoimmune processes. Because of its prevalence and ability to affect human immune function, many researchers have hypothesized that *H. pylori* might contribute to the development of autoimmune diseases. In this article, we review the available literature regarding the role of chronic *H. pylori* infection in various autoimmune disease states.

Keywords

autoimmunity; etiology; infection; lymphoma

Introduction

Helicobacter pylori is a widely prevalent, Gram-negative bacterium which typically infects the gastric mucosa. Since its initial discovery as a human pathogen in 1983, *H. pylori* has been implicated in numerous diseases. Effective diagnostic modalities and treatment strategies are currently available and have proven to be efficacious for the detection and eradication of *H. pylori* infections. Because of its ability to elicit a chronic immune response in the host, studies have suggested a possible role for *H. pylori* in the development of autoimmune diseases. The purpose of this article was to review the role of *H. pylori* in the pathogenesis of various autoimmune diseases.

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Author contributions

Drs. Hasni and Illei conceived of this project. Drs. Hasni and Ippolito wrote and revised the manuscript. Dr. Illei aided in the revision process and offered guidance on content.

Background and epidemiology

Helicobacter pylori is a Gram-negative, flagellated bacterium which was first isolated in 1983 by Warren and Marshal (Marshall and Warren, 1984). It is widely prevalent, with approximately 50% of the Western world and over 80% of those living in developing countries infected with the bacterium (McColl, 2010). Disease prevalence positively correlates with increasing age and poor socioeconomic status, but varies widely by geography and the specific patient population studied (Brown, 2000; Bruce and Maaroos, 2008; Azevedo *et al*, 2009).

Initial infection typically occurs during childhood after oral ingestion and the bacterium persists for the life of the host unless treated (Blaser, 1997; Everhart, 2000). Spontaneous remission in childhood is relatively common, but is usually associated with the use of antibiotics to treat unrelated illnesses (Tindberg *et al*, 1999). Otherwise, spontaneous eradication of *H. pylori* occurs only very rarely (Xia and Talley, 1997). Person to person transmission via contact with infected secretions is the most likely means of transmission. Other recent studies suggest that, especially in developing countries, the available water supply may be another source of transmission (Goodman *et al*, 1996; Parsonnet *et al*, 1999; Brown, 2000). There does not appear to be a predilection for either gender, but a number of other risk factors, including smoking, population density, and hygiene practices, make infection more likely (Brown, 2000).

Clinically, *H. pylori* have been associated with a number of diseases including peptic ulcer disease, gastric cancer, and mucosa associated lymphoid tissue (MALT) lymphoma. But, despite the high prevalence of infection, *H. pylori* produce symptoms in only a minority of patients (Kuipers *et al*, 1993; Malaty *et al*, 2002). Currently, routine screening is not recommended, but any individual with confirmed gastric or duodenal ulcers, or MALT lymphoma, should be tested (Chey and Wong, 2007; Malfertheiner *et al*, 2007). The urea breath test, serologic tests for anti- *H. pylori* antibodies, and the stool antigen test are all reliable, non-invasive diagnostic methods (Suerbaum and Michetti, 2002). However, any patient with symptoms suggestive of malignancy should undergo endoscopy with antral biopsy (Howden and Hunt, 1998). A urease test should be performed on the biopsy specimen to confirm the presence of *H. pylori* (Suerbaum and Michetti, 2002). Culture and sensitivity is typically not necessary unless there has been a treatment failure (Bazzoli, 2001). Effective treatments are readily available and consist of antibiotics and either a proton pump inhibitor or an H2 receptor antagonist for 7–14 days. The stool antigen test should be used to confirm eradication 8 weeks post-therapy (Suerbaum and Michetti, 2002). Treatment results in complete eradication of the organism in about 80% of patients and reinfection rates after treatment in developed countries are quite low (Suerbaum and Michetti, 2002).

Immunological response to *H. pylori* infection

To survive in human hosts, *H. pylori* must be capable of tolerating the harsh, acidic environment of the stomach while evading removal by host immune mechanisms. To this end, *H. pylori* has evolved numerous survival mechanisms.

Several unique characteristics help *H. pylori* persist in such a harsh environment. It is able to persist in the gastric mucosa, in no small part, because of its ability to produce urease. This enzyme converts urea into carbon dioxide and ammonia, and enables *H. pylori* to overcome the acidic gastric environment of the stomach (Suerbaum and Michetti, 2002). This enzyme also serves to alter the viscosity of the gastric mucous, thus promoting bacterial motility (McGee and Mobley, 1999). Other physical attributes, such as the spiral shape and multiple flagella, also help *H. pylori* to persist in gastric mucosa and survive removal by gastric peristalsis (Peek *et al*, 2010).

In addition to surviving in an acidic environment, *H. pylori* must be able to evade the hosts' immune response. *H. pylori* must first circumvent the innate immune response. To this end, the bacterium is capable of modifying the antigens present on the cell wall; such as the bacterial endotoxin lipopolysaccharide (LPS), and flagella, rendering both potential antigens relatively anergic (Suerbaum and Michetti, 2002; Peek *et al*, 2010).

Helicobacter pylori possesses numerous virulence factors that aid in successful colonization of the host. After ingestion, the majority of the bacterial load remains confined to the mucosal gel layer, but approximately 20% of bacteria bind to gastric epithelial cells via by multiple adhesion proteins (Peek *et al*, 2010). The *H. pylori* genome encodes a number of bacterial outer membrane proteins, collectively known as Helicobacter outer membrane porin (Hop) proteins, which facilitate binding to gastric epithelial cells. Examples of these proteins include blood group antigen-binding adhesion A (BabA), Outer inflammatory protein A (OipA), and sialic acid-binding adhesin (SabA) (Hessey *et al*, 1990; Guruge *et al*, 1998; Suerbaum and Michetti, 2002). Some of these adhesins, such as BabA and OipA, are capable of inducing proinflammatory cytokines (Robinson *et al*, 2007). In addition, BabA may be associated with disease manifestations such as duodenal ulcers and gastric cancer (Guruge *et al*, 1998).

In addition to the adhesins, the *H. pylori* genome encodes a number of virulence factors. Many of these genes are located on the cytotoxin-associated gene pathogenicity island (*cag* PaI). Patients infected with bacteria that posses the *cag* PaI are more likely to develop peptic ulcers or gastric cancer (Robinson *et al*, 2007; Peek *et al*, 2010). Two of the primary products encoded by the *cag* PaI are the type IV secretion system (T4SS) and the CagA protein. The T4SS serves as a means to allow translocation of microbial proteins, such as CagA, into the host epithelial cells (Asahi *et al*, 2000; Odenbreit *et al*, 2000; Stein *et al*, 2000). CagA enters the cell, and after phosphorylation, acts as a host cell growth factor and induces pro-inflammatory cytokines, such as IL-8(Suerbaum and Michetti, 2002; Robinson *et al*, 2007; Peek *et al*, 2010).

Another interesting virulence factor is the vacuolating cytotoxin, VacA. This exotoxin creates gated membrane channels in epithelial cells and can also interact with mitochondrial membrane and induce apoptosis (Peek *et al*, 2010).

Infection with *H. pylori* elicits a number of host immune responses that are typically triggered by pathogen binding and chronic inflammation (Suerbaum and Michetti, 2002). Pathogen binding to class II major-histocompatibility-complex (MHC) on the surface of gastric epithelial cells can induce apoptosis (Fan *et al*, 2000). As noted above, translocation of CagA into the gastric epithelial cells leads to higher levels of proinflammatory cytokines such as TNF-α, IL-6, IL-10, and most importantly, IL-8 (Klausz *et al*, 2004; Kim *et al*, 2006). The VacA protein interacts with macrophages, B-and T- lymphocytes. VacA causes reduced IL-2 production with resultant suppression of IL-2-mediated T-lymphocyte proliferation (Sundrud *et al*, 2004).

Helicobacter pylori infection results in a primarily Th1 T-cell response, resulting in the production of IL-2 and interferon gamma (Harris *et al*, 2000). The interaction between *H. pylori* and B-lymphocytes results in uncontrolled growth and proliferation of predominantly CD5+ B-cells (Wotherspoon *et al*, 1991). These cells produce polyreactive and auto-reactive IgM and IgG3 antibodies (Wotherspoon *et al*, 1991). Subsequent studies showed that chronic infection with *H. pylori* and resultant exposure to urease results in stimulation and increased survival of this subset of B lymphocytes (Yamanishi *et al*, 2006). The antibodies produced do not result in clearance of the pathogen and may result in the production of auto-reactive antibodies, such as anti-H/K-ATPase antibodies (Amedei *et al*, 2003). These autoantibodies have been implicated in the development of gastric atrophy.

The persistent, complex interplay between pathogen and host immunity may contribute to immune dysregulation and subsequent development of autoimmunity in susceptible patients.

Autoimmune diseases and *H. pylori* infection

Autoimmune diseases are characterized by dysregulation of the immune system resulting in a loss of tolerance to self-antigen. The exact etiology for the majority of these diseases is unknown; however, a complex combination of host and environmental factors are believed to play a pivotal role.

Numerous pathogens have been implicated as possible environmental agents contributing to the development of autoimmune disease in susceptible individuals (Bach, 2005; Getts and Miller, 2010). Polyclonal lymphocyte activation, molecular antigen mimicry, epitope spreading, bystander activation, and activation by a super-antigen, have all been proposed as possible mechanistic links between the development of autoimmunity and exposure to infectious agents. Discussion of these mechanisms has been previously detailed in the medical literature (Getts and Miller, 2010). In their review of the role of infectious agents in autoimmunity, Getts *et al* suggested that autoimmune disease is triggered by these mechanisms working ‘simultaneously and/or sequentially’ (Getts and Miller, 2010). Evidence for the role of infectious agents in diseases such as rheumatic fever and Guillain-Barre syndrome is convincing (Bach, 2005). However, evidence for the involvement of infectious agents in other autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) remains controversial.

Chronic infection with *H. pylori* serves as a source of persistent antigenic stimulation and underlies the pathogens’ ability to induce a systemic inflammatory response (Jackson *et al*, 2009). The prolonged interaction between the bacterium and host immune mechanisms makes *H. pylori* a plausible infectious agent for triggering autoimmunity. Molecular mimicry of *H. pylori* antigens was found to activate cross-reactive T cells which may lead to autoimmune gastritis (Amedei *et al*, 2003). Autoantibodies, such as IgM rheumatoid factor, anti-single stranded DNA antibody and anti-phosphotidyl choline antibodies, were demonstrated to be produced by B cells after their activation by *H. pylori* components, particularly urease (Yamanishi *et al*, 2006). A role of microbial heat shock proteins (HSP) in the pathogenesis of autoimmune diseases has been postulated because of the high level of sequence homology with human HSP. A possible role of HSP 60 produced by *H. pylori* in pathogenesis of Sjögren’s syndrome is proposed (Aragona *et al*, 1999). Eradication of *H. pylori* infection in patients with immune thrombocytopenic purpura (ITP) has been shown to be effective in improving platelet counts in 50% of cases (Kuwana and Ikeda, 2006). There is conflicting and controversial data regarding association of *H. pylori* infection with other autoimmune diseases. In some instances, such as inflammatory bowel disease, the evidence suggests a protective effect from *H. pylori* infection (Vare *et al*, 2001).

H. pylori infection and Sjögren’s syndrome

Sjögren’s syndrome is a chronic, inflammatory, autoimmune disease characterized by lymphoid cell infiltration and destruction of exocrine glands, specifically lacrimal and salivary glands. As *H. pylori* infection is acquired by ingestion of the organism, during its transit in the oral cavity it interacts with saliva. In fact, the oral cavity may be an extra-gastroduodenal reservoir for the bacterium (Dowsett and Kowolik, 2003). Prevalence of H. pylori in the oral cavity is reported anywhere from 0% to 100% in various studies (Song *et* *al*, 2000). Bürgers *et al* showed that *H. pylori* are present in the oral cavity without concurrent stomach colonization or serum anti-*H. pylori* antibodies (Burgers *et al*, 2008).

As previously mentioned, adhesins such as BabA and SabA help the pathogen bind to the gastric mucosa (Hessey *et al*, 1990). These particular adhesins can also bind to human salivary glycoproteins such as, MUC5B (MG1) and MUC7 (MG2) and salivary agglutinin (gp-340) (Prakobphol *et al*, 2005; Walz *et al*, 2009). These salivary glycoproteins are involved in host defense by providing a protective barrier. They are also involved in innate immunity indicating a possible mechanism by which the interaction of *H. pylori* with saliva may activate the innate immune system (Prakobphol *et al*, 2005).

To explore a possible link between *H. pylori* infection and Sjögren's syndrome, several groups looked at presence of *H. pylori* and its related antibodies in these patients. A possible causal relation between *H. pylori* infection and the production of a 62-kDa HSP protein was investigated by Aragona *et al* (Aragona *et al*, 1999). Of the 34 patients with primary Sjögren's syndrome, 27(79.4%) and 30(88.2%) had antibodies against *H. pylori* and its HSP60, respectively. The prevalence was significantly higher ($P < 0.0001$) when compared with patients with other autoimmune diseases (antibodies against *H. pylori* 18.2%; against HSP60 27.3%) and healthy controls (antibodies against *H. pylori* 48.8%; against HSP60 37.2%). Similarly, Showji *et al* demonstrated high titers of anti-*H. pylori* antibodies in sera of patients with Sjögren's syndrome when compared with patients with other connective tissue diseases (CTDs) and age-matched controls (Showji *et al*, 1996). By contrast, a much larger study of 164 primary Sjögren's syndrome patients from Sweden did not show a higher *H. pylori* seroprevalence rates as compared with controls (Theander *et al*, 2001). Furthermore, *H. pylori* seropositivity was not associated with the presence of autoantibodies or abnormal focus scores, a measure of inflammation, on lip biopsy (Theander *et al*, 2001).

Another study by El Miedany *et al* compared 36 patients with primary Sjögren's syndrome to 31 patients with secondary Sjögren's syndrome and determined the prevalence of *H. pylori* infection to be 80.6% and 71%, respectively (El Miedany *et al*, 2005). When compared with patients with CTDs without sicca symptoms and healthy controls, this was statistically significant ($P < 0.01$). There was no significant association found between *H. pylori* positivity and presence of autoantibodies in primary or secondary Sjögren's syndrome patients. A higher prevalence of *H. pylori* antibodies was found in patients with longer duration of disease (100% in patients with Sjögren's syndrome for >5 years). Moreover, a significant positive correlation with C-reactive protein, but not erythrocyte sedimentation rate, was found.

The results of these studies are conflicting. Some data suggests that patients with Sjögren's syndrome have a higher prevalence of infection. However, in a much larger study of a homogenous population (with an overall low incidence of *H. pylori*) no such association was found.

Mucosa-associated lymphoid tissue lymphomas are a group of low grade lymphomas which arise in tissue normally devoid of lymphoid tissue such as the stomach, lungs, salivary, and lacrimal glands. These tissues accumulate lymphoid tissue on chronic antigenic stimulation such as chronic infections and autoimmune diseases. A higher incidence of MALT lymphoma has been reported in patients with chronic *H. pylori* infection as well as in those with Sjögren's syndrome. The majority of patients (70–90%) with gastric lymphoma have *H. pylori* in the gastric mucosa and the eradication of *H. pylori* in early stages of disease results in regression in 80% of cases (Parsonnet *et al*, 1994). Similarly patients with Sjögren's syndrome have a much higher incidence of developing lymphoma and most of these lymphomas are MALT type (Royer *et al*, 1997).

Development of gastric MALT lymphoma in patients with *H. pylori* infection is considered to be secondary to chronic antigenic stimulation of the immune system by the pathogen. It has been postulated that a similar mechanism maybe responsible for the development of extra-gastric lymphoma as well. The regression of parotid MALT lymphoma after the eradication of *H. pylori* in Sjögren's syndrome patients has been reported by some groups (Suchy and Wolf, 2000; Iwai *et al*, 2009).

Although Sjögren's syndrome and *H. pylori* infection are risk factors for developing MALT lymphoma, it is not yet clear if there is a causal association. Thus far, there is no evidence that the coexistence of Sjögren's syndrome and *H. pylori* infection would play an additive role and lead to a much higher incidence of MALT lymphoma.

H. pylori and rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder primarily characterized by a symmetric destructive polyarthritis affecting small, medium, and large joints. A number of genetic and environmental factors, including smoking, contribute to disease onset and severity (Scott *et al*, 2010). In addition, a number of viral and bacterial pathogens such as, Epstein-Barr virus (EBV), parvovirus B19, Hepatitis C virus, *Proteus mirabilis*, and *Mycobacterium tuberculosis*, may have a role in disease pathogenesis as well (Pordeus *et al*, 2008).

The association of *H. pylori* infection in the pathogenesis of RA is controversial. On one hand, *in vitro* studies suggest a role for the bacterium in the development of autoimmunity. Yamanishi *et al* found that B cells chronically stimulated with urease produced by *H. pylori* had the potential to generate autoantibodies, including IgM rheumatoid factor (Yamanishi *et al*, 2006). But, despite the results of *in vitro* experiments, the clinical correlation between *H. pylori* infection and RA has been less convincing. Although RA patients have an increased risk of developing peptic ulcer disease (PUD), it is not clear that this is directly related to an increased prevalence of *H. pylori* infection (Janssen *et al*, 1992). Certainly, the abundant use of NSAIDS (non-steroidal anti-inflammatory drugs) in the RA patient population contributes a significant amount of risk for PUD as well (Tanaka *et al*, 2005). In fact, studies have shown that not only do RA patients have a lower prevalence of *H. pylori* infection compared with patients with other CTDs, but the prevalence of infection was nearly identical to that of healthy controls (Showji *et al*, 1996; Tanaka *et al*, 2005; Meron *et al*, 2010). Although, a few small studies suggested some clinical improvement in RA symptoms after eradication of *H. pylori*, (Seriolo *et al*, 2001; Zentilin *et al*, 2002) many other studies have been unable to corroborate these findings (Ishikawa *et al*, 2002; Matsukawa *et al*, 2005). One study found that eradication of *H. pylori* in patients with RA did not affect the C-reactive protein, a marker of inflammation typically elevated in RA patients (Steen *et al*, 2009). Overall, the data regarding the association of *H. pylori* infection with the onset or severity of RA remains unclear.

H. pylori and systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multisystem inflammatory autoimmune disorder of unknown etiology. The clinical manifestations of SLE are myriad and can affect essentially any organ system. The serologic hallmark of lupus is the production of autoantibodies, including anti-nuclear antibodies (ANA) and anti-double stranded DNA antibodies (anti-dsDNA). A number of infectious agents, such as cytomegalovirus, parvovirus B19, and EBV, have been implicated in the pathogenesis of SLE (Pordeus *et al*, 2008; Poole *et al*, 2009).

Unlike the other infectious agents implicated in SLE, a rather unusual relationship exists between *H. pylori* and lupus. Similar to their findings in RA, Yamanishi *et al* found that urease was indeed capable of inducing SLE-related autoantibodies in mice, namely anti-ssDNA (Yamanishi *et al*, 2006). Showji *et al* demonstrated that not only did SLE patients have lower anti-*H. pylori* serum antibody titers compared with patients with other CTDs, but the levels seen in SLE patients were also identical to those seen in controls (Showji *et al*, 1996). Despite evidence demonstrating *H. pylori*-related proteins can induce anti-ssDNA antibodies in mice, it seems that infection with *H. pylori* may actually have a protective effect on the development of lupus. Sawalha *et al* compared the prevalence of *H. pylori* seropositivity in 466 SLE patients to matched controls and, not surprisingly, found that SLE patients were less likely to be seropositive (Sawalha *et al*, 2004). After subgroup analysis, it was noted that African-American females seropositive for *H. pylori* tended to develop SLE at an older age compared with *H. pylori* negative SLE patients. The authors suggest that exposure to *H. pylori* may offer some protective benefit against developing SLE in this specific population. Although intriguing, a satisfactory mechanism to explain this relationship remains elusive.

H. pylori and immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is the autoimmune destruction of platelets resulting in low platelet counts and mucocutaneous bleeding (Cines and Blanchette, 2002). ITP may occur without an identifiable cause (idiopathic/primary) or secondary to an underlying condition such as malignancy, infection, medications, thyroid disease, SLE, or anti-phospholipid antibody syndrome.

Previous studies suggest a more convincing role for *H. pylori* in the development of ITP compared with other CTDs. In terms of initiating an autoimmune response, the *H. pylori* Cag protein may provide antigenic stimulus for the production of antiplatelet antibodies (Pordeus *et al*, 2008). Similar to the findings in both RA and SLE, Liebman showed that the prevalence of *H. pylori* infection in patients with ITP was similar to controls matched for age and geographical location (Liebman, 2007). However, in stark contrast to the findings in RA and SLE, a number of studies have demonstrated improvement in platelet counts after *H. pylori* eradication (Emilia *et al*, 2001; Stasi *et al*, 2005; Suzuki *et al*, 2005). These findings help to substantiate the relationship between the pathogen and autoimmunity in ITP.

Conclusion

The prevalence of *H. pylori* and its unique ability to chronically infect its human hosts has led researchers to explore the relationship between infection and the development of other disease entities. Some associations, such as its role in gastric carcinoma, MALT lymphoma, and ITP are strong. Although *H. pylori* can induce inflammation and activate host immunity, the evidence suggesting a role in the development of autoimmune diseases is conflicting and inconclusive. Further study of the immunological response to infectious agents, including *H. pylori*, and their role in the pathogenesis of autoimmune diseases are warranted.

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