HELICOBACTER PYLORI AND AUTOIMMUNE DISEASES

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INTRODUCTION

Autoimmune diseases vary significantly in their clinical presentations, but share same pathophysiological mechanism resulting from a loss of self-tolerance. Despite significant advances in our understanding and management of autoimmune diseases, factors leading to this loss of self-tolerance are still poorly understood.

Studies in twins with autoimmune diseases show a much higher concordance rate in identical twins compared with nonidentical twins, indicative of a clear genetic component. However, the concordance rate is not 100% and the majority of identical twins with autoimmune diseases have a nonaffected twin [1]. In a recent review monozygotic twin concordance rate was reported to be as low as 4.2 for systemic sclerosis [2].

This suggests a second environmental factor triggering immune dysregulation in these genetically susceptible hosts leading to autoimmune diseases. Among the various possible environmental triggers, studies looking at the role of various infectious agents have been most promising [3]. Microbial organisms are considered to be likely triggers of autoimmunity because of their ubiquitous presence in the environment and their interaction with the immune system. There are several proposed mechanisms by which microbial organisms can lead to loss of self-tolerance; such asmolecular-mimicry, when shared amino acid sequences between microbial antigens and host proteins leads to a more generalized triggering of immune response against both the host proteins and microbial antigens [4].

Other proposed mechanisms leading to triggering of autoimmunity include polyclonal activation, epitope spread, bystander activation and superantigens [5]. Of the various bacteria and viruses proposed as agents triggering autoimmunity, *Helicobacter pylori* (*H. pylori*) is one of the most widely studied. This is because of attributes unique to *H. pylori* such as prolonged survival in host environment, worldwide prevalence, and its complex interactions with the host immune system. In this review, we will look at the interactions between *H. pylori*and the immune system in general and the role of *H. pylori* in individual autoimmune diseases.

HELICOBACTER PYLORI AND THE IMMUNE SYSTEM

H. pylori is a curved gram-negative bacillus first identified from gastric mucosa by Marshall and Warren [6]. Most commonly *H. pylori* colonize the gastric mucosa in early childhood and can persist throughout life, if no antibiotic therapy is given [7]. Its worldwide prevalence is variable, with highest prevalence in areas with overcrowding

and poor sanitation [8]. Presence of *H. pylori* in gastric mucosa has been associated with various gastrointestinal ailments, including peptic ulcers, noncardia gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma [7].

Phylogeographic studies support the presence of helicobacter in our early east African ancestors more than 58 000 years ago [9]. *H. pylori* have managed to persist in its only confirmed hosts (humans) since then, living in the normally inhospitable acidic environment of the stomach. *H. pylori* have acquired several unique attributes helping it escape clearance through the normal immune mechanisms. This prolonged coexistence of *H. pylori* in humans raises the possibility of a rather symbiotic relationship; in which its persistence may at least in part be beneficial to humans. Inverse association between the presence of *H. pylori* and gastroesophageal reflux disease, asthma and allergic disorders have been reported [7]. Epidemiological data suggest an increase in asthma and autoimmune diseases in populations wherein *H. pylori*infection is aggressively treated and being eradicated.

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The innate immune system provides the first line of defense against invading microorganisms. This defense mechanism is based on recognition of microbial pathogen-associated molecular patterns (PAMP) through various pattern recognition receptors (PRR) present on the cells of the innate immune system. *H. pylori* recognition by PRR such as toll-like receptors (TLR) leads to a net anti-inflammatory effect. For example, as compared to lipopolysaccharide (LPS) from *Escherichia coli*, *H. pylori* LPS is found to be significantly less potent in promoting a proinflammatory response mediated via TLR 4 signaling [10]. Similarly, *H. pylori*flagellin evades recognition by TLR 5 [11].

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H. pylori evades activation of acquired immune system through its bacterial antigens. *H. pylori*vacuolatingcytotoxin (VacA) blocks proliferation of $CD4^+$ helper T-lymphocytes, primarily by interfering with the T-cell receptor/interleukin (IL) 2 signaling pathway [12]. In experiments, when bone marrow derived dendritic cells were exposed to *H. pylori*, they failed to produce pro-inflammatory cytokines. In addition, *H. pylori*leads to a preferential priming of naïve T-cells into the anti-inflammatory regulatory T-cell (T-regs) [13].

High antibody titers against *H. pylori*are usually present in infected individuals. But unlike other antimicrobial antibodies, anti-*H. pylori* antibodies (especially immunoglobulin (Ig)A antibodies) promote the presence of bacteria [14]. Studies in mouse models showed that B-lymphocyte activation by helicobacter species leads to an increase in the number of IL-10 (an anti-inflammatory cytokine) producing T-regs [15].

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Evidence presented above indicates an overall downregulation of the host immune

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Conversely, there is some recent data suggestive of a protective effect of *H. pylori* against auto-immune and allergic diseases. A recent meta-analysis suggested a protective role of *H. pylori* in inflammatory bowel disease [19]. An inverse relationship between *H. pylori* infection and allergic conditions is also reported. Rate of asthma was found to be lower in children who were *H. pylori*positive when compared with those who were *H. pylori* negative [20]. In a Japanese cohort an inverse association of *H. pylori* seropositivity and multiple sclerosis (MS) was reported [21]. Based on a review of literature recently, we concluded that in most auto-immune diseases the role of *H. pylori* remains inconclusive [22].

AIM OF THE WORK

The etiology of most autoimmune diseases remains elusive. Prevailing evidence suggests an environmental trigger in a genetically susceptible individual. *Helicobacter pylori* (*H. pylori*) have managed to survive in a hostile environment in its host for long period and have evaded eradication by immune system. Its chronic interaction with the immune system and the ubiquitous presence worldwide makes *H. pylori*an ideal candidate to study as a trigger of autoimmune phenomena. In this review, we would present data regarding the interplay between *H. pylori* and various components of the immune system and its association with various autoimmune diseases.

Helicobacter pylori and immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune disease resulting from antibodies against platelet glycoproteins. Several microbial agents causing chronic infections such as HIV, Hepatitis C virus and *H. pylori* have been shown to be associated with ITP.

In their recent review, Stasi *et al*. [23] reported worldwide prevalence of *H. pylori* in ITP patients from 25 studies. The result from these studies revealed an overall prevalence of 62.3%. However, when matched with age and geographic area prevalence rate of *H. pylori* infection in most of these studies were similar to the healthy population.

Several studies have attempted to explain the underlying pathogenic mechanism of *H. pylori* induced ITP. Most prevailing hypothesis suggest molecular mimicry between one of the *H. pylori* antigens and platelet glycoproteins causing production of cross-reacting autoantibodies [24]. A detailed discussion of *H. pylori*induced pathogenesis of ITP is beyond the scope of this review.

Eradication of *H. pylori* in patients with ITP leads to sustained increase in their platelet counts. A little over 50% of patients are expected to show an improvement in their platelet counts after eradication of *H. pylori* [25]. This response rate correlates with the prevalence of *H. pylori* in the population being treated, with higher response rates reported from Japan and much lower rates in studies from United States.

Even though there is evidence of *H. pylori* infection in the development of ITP, its exact pathogenetic role is largely unknown.

Helicobacter pylori and rheumatoid arthritis

Looking for a microorganism causing rheumatoid arthritis (RA) dates back to the 19th century [26]. In a cohort of 187 samples from RA patients, 80.4% were found to be seropositive for *H. pylori*; however this was not significantly different from the control population, reflective of an overall increased prevalence [27]. A study of 1815 Japanese RA patients, 49.3% were reported to have *H. pylori*antibodies, which was lower compared with the healthy Japanese individuals [28].

However, another study from Japan looking at the prevalence of *H. pylori* infection in RA patients reported a much higher percentage (61.4%) [29]. Prevalence of *H. pylori* in the study of a European population with RA was reported to be 48%, which is similar to

healthy individuals in the Western countries [30].

However, in the same study RA patients with *H. pylori* seropositivity showed a trend towards more severe disease and its eradication led to a significant improvement in RA related clinical outcomes [30]. Hence, the role of *H. pylori* infection in causing RA is not clear; but its presence in patients with RA might result in a more severe phenotype.

Helicobacter pylori and systemic lupus erythematosus

A recent review looked at the role of various infectious agents including *H. pylori* in the development of SLE; concluding an overall negative association with *H. pylori* [31]. Studies done on mice revealed that *H. pylori* urease exposure can lead to production of antiss-DNA antibodies [32]. In a study of 466 patients with SLE matched with 466 controls, SLE patients were less frequently seropositive (36.5%) for *H. pylori* as compared to healthy controls (42.9%) $P = 0.045$ [33]. This negative association was even stronger for African–American female SLE patients as compared to controls (38.1 versus 60.2%; $P = 0.0009$).

In another study patients with SLE were found to have lower titers of anti-*H. pylori* antibodies when compared to patients with other autoimmune diseases [34]. These studies had several limitations but all of them are indicative of a negative association between SLE and *H. pylori* infection. This raises an interesting question: could *H. pylori* infected individuals be protected against development of SLE?

Helicobacter pylori and sjögren's syndrome

Some earlier studies suggested a possible association between *H. pylori* and Sjögren's syndrome [34]. One of the studies suggested a possible link between antibodies produced against heat shock protein (HSP 60) of *H. pylori* and development of Sjögren's syndrome [35].

However subsequent studies failed to show any association between *H. pylori* seropositivity and presence of Sjögren's syndrome. In a study of 164 Swedish patients with Sjögren's syndrome, *H. pylori* seroprevelance (45%) was similar to the controls [36]. In addition there was no association found between *H. pylori*status and abnormal levels of autoantibodies or abnormal lip biopsy in these patients. In a separate cohort of 54 patients with Sjögren's syndrome, seroprevelance of *H. pylori* was 57% as opposed to 62% in the controls [37]. Authors also concluded that eradication of *H. pylori* was not associated with improvement of dyspeptic symptoms in patients with Sjögren's syndrome.

Helicobacter pylori and polymyositis and dermatomyositis

Limited data is available on any role of *H. pylori* and polymyositis (PM)/dermatomyositis (DM). Review of the available literature revealed no significant difference in frequency of *H. pylori* in patients with PM/DM compared with the controls [35,38].

Helicobacter pylori and systemic sclerosis

Several environmental factors including microbial organisms have long been debated as possible triggers for systemic sclerosis.

In a study of 12 European scleroderma patients, five (42%) were found to be positive for *H. pylori* infection [39]. In a much larger cohort of 124 Japanese patents with systemic sclerosis, seroprevelance of *H. pylori* was reported at 55.6%, much higher than the healthy controls [40]. Yet another study found no difference in *H. pylori* infection rates between patients with systemic sclerosis and the controls [41]. However, most of these patients in the study were infected with a more virulent (CagA) strain of *H. pylori* as compared to infected controls.

Several studies looked at association between specific manifestations of scleroderma and presence of *H. pylori* infection. In a Japanese study 64 patients with scleroderma underwent endoscopy to assess reflux esophagitis. Being infected with *H. pylori* was shown to be protective against development of reflux esophagitis in patients with scleroderma [42]. There are conflicting reports of association between *H. pylori* and Raynaud's phenomena as reported in a recent review [43].

Helicobacter pylori and vasculitis

In their search for a microbial agent causing Behcet's disease several investigators have looked at the seroprevelance of *H. pylori* in Behcet's disease patients. Variable rates of *H. pylori* positivity are reported in patients with Behcet's disease from 85% (higher than controls) to 73.3%(lower than controls) [44,45].

Several published case reports suggested an association of *H. pylori*infection with Henoch-Schönlein purpura; with resolution of symptoms coinciding with the eradication of *H. pylori* infection [46].

In a study looking at serological evidence of various infectious agents in patients with Granulomatosis with polyangitis (Wegner's Granulomatosis), *H. pylori*IgG antibodies were reported to be more common in patients as compared to controls [47].

Hence, there is some evidence of an association of *H. pylori* infection with various

vasuilitides but further research is needed to infer any causality.

Helicobacter pylori and fibromyalgia

Etiology and pathogenesis of fibromyalgia (FMG) remains controversial. Studies focusing on association of several viral and bacterial microorganisms and FMG have been published, but literature regarding role of *H. pylori* is rather limited. A recent study explored association of FMG with *H. pylori*seropositivity in 65 patients and compared it with 41-year old and gender-matched controls [48].

Prevalence of IgG anti-*H. pylori*antibodies was significantly higher in FMG patients (30.8%) as compared to controls (17.1%). However, among these patients, there was no difference in clinical manifestations of FMG between *H. pylori* seropositive versus seronegative individuals. Another study of 28 female FMG patients reported similar rates of *H. pylori*seropositivity in patients and controls [49].

CONCLUSION

H. pylori infection is very common and widespread. It has survived in its host (humans) for at least last 58 000 years. *H.*

pylori have extensive interactions with immune system resulting in its downregulation. Its role as a causative agent of autoimmune diseases in genetically susceptible host has been extensively studied.

Studies looking at the presence of *H. pylori* in various autoimmune diseases found mixed results with some even suggesting a protective role. However, mechanistic studies establishing causality are lacking. Further research looking at the possible role of *H. pylori* in autoimmune diseases is needed.

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AIM OF THE WORK

The etiology of most autoimmune diseases remains elusive. Prevailing evidence suggests an environmental trigger in a genetically susceptible individual. *Helicobacter pylori* (*H. pylori*) have managed to survive in a hostile environment in its host for long period and have evaded eradication by

immune system. Its chronic interaction with the immune system and the ubiquitous presence worldwide makes *H. pylori*an ideal candidate to study as a trigger of autoimmune phenomena. In this review, we would present data regarding the interplay between *H. pylori* and various components of the immune system and its association with various autoimmune diseases.

Helicobacter pylori and immune thrombocytopenic purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune disease resulting from antibodies against platelet glycoproteins. Several microbial agents causing chronic infections such as HIV, Hepatitis C virus and *H. pylori* have been shown to be associated with ITP.

In their recent review, Stasi *et al*. [23] reported worldwide prevalence of *H. pylori* in ITP patients from 25 studies. The result from these studies revealed an overall prevalence of 62.3%. However, when matched with age and geographic area prevalence rate of *H. pylori* infection in most of these studies were similar to the healthy population.

Several studies have attempted to explain the underlying pathogenic mechanism of *H. pylori* induced ITP. Most prevailing hypothesis suggest molecular mimicry between one of the *H. pylori* antigens and platelet glycoproteins causing production of cross-reacting autoantibodies [24]. A detailed discussion of *H. pylori*induced pathogenesis of ITP is beyond the scope of this review.

Eradication of *H. pylori* in patients with ITP leads to sustained increase in their platelet counts. A little over 50% of patients are expected to show an improvement in their platelet counts after eradication of *H. pylori* [25]. This response rate correlates with the prevalence of *H. pylori* in the population being treated, with higher response rates reported from Japan and much lower rates in studies from United States.

Even though there is evidence of *H. pylori* infection in the development of ITP, its exact pathogenetic role is largely unknown.

Helicobacter pylori and rheumatoid arthritis

Looking for a microorganism causing rheumatoid arthritis (RA) dates back to the 19th century [26]. In a cohort of 187 samples from RA patients, 80.4% were found to be seropositive for *H. pylori*; however this was not significantly different from the control population, reflective of an overall increased prevalence [27]. A study of 1815 Japanese RA patients, 49.3% were reported to have *H. pylori*antibodies, which was lower compared with the healthy Japanese individuals [28].

However, another study from Japan looking at the prevalence of *H. pylori* infection in RA patients reported a much higher percentage (61.4%) [29]. Prevalence of *H. pylori* in the study of a European population with RA was reported to be 48%, which is similar to healthy individuals in the Western countries [30].

However, in the same study RA patients with *H. pylori* seropositivity showed a trend towards more severe disease and its eradication led to a significant improvement in RA related clinical outcomes [30]. Hence, the role of *H. pylori* infection in causing RA is not clear; but its presence in patients with RA might result in a more severe phenotype.

Helicobacter pylori and systemic lupus erythematosus

A recent review looked at the role of various infectious agents including *H. pylori* in the development of SLE; concluding an overall negative association with *H. pylori* [31]. Studies done on mice revealed that *H. pylori* urease exposure can lead to production of antiss-DNA antibodies [32]. In a study of 466 patients with SLE matched with 466 controls, SLE patients were less frequently seropositive (36.5%) for *H. pylori* as compared to healthy controls (42.9%) $P = 0.045$ [33]. This negative association was even stronger for African–American female SLE patients as compared to controls (38.1 versus 60.2%; $P = 0.0009$).

In another study patients with SLE were found to have lower titers of anti-*H. pylori* antibodies when compared to patients with other autoimmune diseases [34]. These studies had several limitations but all of them are indicative of a negative association between SLE and *H. pylori* infection. This raises an interesting question: could *H. pylori* infected individuals be protected against development of SLE?

cohort of 54 patients with Sjögren's syndrome, seroprevelance of *H. pylori* was 57% as opposed to 62% in the controls [37]. Authors also concluded that eradication of *H. pylori* was not associated with improvement of dyspeptic symptoms in patients with Sjögren's syndrome.

Helicobacter pylori and sjögren's syndrome

Some earlier studies suggested a possible association between *H. pylori* and Sjögren's syndrome [34]. One of the studies suggested a possible link between antibodies produced against heat shock protein (HSP 60) of *H. pylori* and development of Sjögren's syndrome [35].

However subsequent studies failed to show any association between *H. pylori* seropositivity and presence of Sjögren's syndrome. In a study of 164 Swedish patients with Sjögren's syndrome, *H. pylori* seroprevelance (45%) was similar to the controls [36]. In addition there was no association found between *H. pylori*status and abnormal levels of autoantibodies or abnormal lip biopsy in these patients. In a separate

Helicobacter pylori and polymyositis and dermatomyositis

Limited data is available on any role of *H. pylori* and polymyositis (PM)/dermatomyositis (DM). Review of the available literature revealed no significant difference in frequency of *H. pylori* in patients with PM/DM compared with the controls [35,38].

between patients with systemic sclerosis and the controls [41]. However, most of these patients in the study were infected with a more virulent (CagA) strain of *H. pylori* as compared to infected controls.

Several studies looked at association between specific manifestations of scleroderma and presence of *H. pylori* infection. In a Japanese study 64 patients with scleroderma underwent endoscopy to assess reflux esophagitis. Being infected with *H. pylori* was shown to be protective against development of reflux esophagitis in patients with scleroderma [42]. There are conflicting reports of association between *H. pylori* and Raynaud's phenomena as reported in a recent review [43].

Helicobacter pylori and systemic sclerosis

Several environmental factors including microbial organisms have long been debated as possible triggers for systemic sclerosis.

In a study of 12 European scleroderma patients, five (42%) were found to be positive for *H. pylori* infection [39]. In a much larger cohort of 124 Japanese patents with systemic sclerosis, seroprevelance of *H. pylori* was reported at 55.6%, much higher than the healthy controls [40]. Yet another study found no difference in *H. pylori* infection rates

Helicobacter pylori and vasculitis

In their search for a microbial agent causing Behcet's disease several investigators have looked at the seroprevelance of *H. pylori* in Behcet's disease patients. Variable rates of *H. pylori* positivity are reported in patients with Behcet's disease from 85% (higher than controls) to 73.3%(lower than controls) [44,45].

Several published case reports suggested an association of *H. pylori*infection with Henoch-Schönlein purpura; with resolution of symptoms coinciding with the eradication of *H. pylori* infection [46].

In a study looking at serological evidence of various infectious agents in patients with Granulomatosis with polyangitis (Wegner's Granulomatosis), *H. pylori*IgG antibodies were reported to be more common in patients as compared to controls [47].

Hence, there is some evidence of an association of *H. pylori* infection with various vasuilitides but further research is needed to infer any causality.

Helicobacter pylori and fibromyalgia

Etiology and pathogenesis of fibromyalgia (FMG) remains controversial. Studies focusing on association of several viral and bacterial microorganisms and FMG have been published, but literature regarding role of *H. pylori* is rather limited. A recent study explored association of FMG with *H. pylori*seropositivity in 65 patients and compared it with 41-year old and gender-matched controls [48].

Prevalence of IgG anti-*H. pylori*antibodies was significantly higher in FMG patients (30.8%) as compared to controls (17.1%). However, among these patients, there was no difference in clinical manifestations of FMG between *H. pylori* seropositive versus seronegative individuals. Another study of 28 female FMG patients reported similar rates of *H. pylori*seropositivity in patients and controls [49].

mixed results with some even suggesting a protective role. However, mechanistic studies establishing causality are lacking. Further research looking at the possible role of *H. pylori* in autoimmune diseases is needed.

CONCLUSION

H. pylori infection is very common and widespread. It has survived in its host (humans) for at least last 58 000 years. *H. pylori* have extensive interactions with immune system resulting in its downregulation. Its role as a causative agent of autoimmune diseases in genetically susceptible host has been extensively studied.

Studies looking at the presence of *H. pylori* in various autoimmune diseases found

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