World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i36.12839

World J Gastroenterol 2014 September 28; 20(36): 12839-12846
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

Role of *Helicobacter pylori* infection in autoimmune systemic rheumatic diseases

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Received: October 15, 2013 Revised: June 11, 2014
Accepted: July 22, 2014
Published online: September 28, 2014

Abstract

The relationship between infection and autoimmunity has been increasingly defined over the last 20 years. The systemic rheumatic 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. *Helicobacter pylori* (*H. pylori*) is one of the most widely studied infectious agents proposed as agents triggering autoimmune response. The persistent presence of *H. pylori* in the gastric mucosa results in chronic immune system activation with ongoing cytokine signaling, infiltration of gastric mucosa by neutrophils, macrophages, lymphocytes, as well as production of antibodies and effector T-cells. Various mechanisms have been proposed in an attempt to explain the extra-intestinal manifestations of *H. pylori* infections. These include: molecular mimicry, endothelial cell damage, superantigens and microchimerism. I performed a systematic literature review using the keywords "rheumatoid arthritis", "Sjögren's syndrome", "systemic sclerosis", "systemic lupus erythematosus", "*Helicobacter pylori*" and "pathogenesis". A systematic literature search was carried out in MEDLINE; EMBASE; Cochrane Library and ACR/EULAR meeting abstracts. In systemic rheumatic diseases *H. pylori* infection prevalence alone should not be expected to provide sufficient evidence for or against a pathologic role in the disease. In this article I review studies examining the potential involvement of *H. pylori* infection in autoimmune systemic rheumatic diseases. Further studies of the immunological response to *H. pylori* and its role in the pathogenesis of systemic rheumatic diseases are warranted.

Key words: Rheumatoid arthritis; Sjögren's syndrome; Systemic sclerosis; Systemic lupus erythematosus; *Helicobacter pylori*; Pathogenesis

Core tip: The exact etiology of systemic rheumatic diseases is unclear, but it has long been suggested that exposure to certain environmental agents, such as bacterial infection, in genetically predisposed individuals may be the trigger for the initiation of autoimmune processes. Because of its prevalence and ability to affect human immune function, many researchers have hypothesized that *Helicobacter pylori* (*H. pylori*) might contribute to the systemic rheumatic diseases development. I summarize the current state of knowledge about *H. pylori* role in autoimmune systemic rheumatic diseases and the possible mechanisms by which *H. pylori* exposures might induce pathological processes.

Radić M. Role of *Helicobacter pylori* infection in autoimmune systemic rheumatic diseases. *World J Gastroenterol* 2014; 20(36): 12839-12846 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i36/12839.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i36.12839

INTRODUCTION

The relationship between infection and autoimmunity has been intensely investigated over the last 20 years[1]. The systemic rheumatic diseases are characterized by immune system dysregulation which resulting in a loss of tolerance to self-antigen. The accurate etiology for the majority of these diseases is unknown; nevertheless, a complex combination of host and environmental factors are assumed to play a pivotal role. Numerous infectious agents have been implicated as possible environmental agents contributing to the development of systemic rheumatic diseases in predisposed patients. The persistent, complex of interplay between infectious agent and host immunity may cause to immune dysregulation and subsequent development of autoimmunity in predisposed individuals (Figure 1). An extensive body of evidence suggests that there are many potential environmental triggers for systemic rheumatic diseases and that host factors determine the sensitivity of the host to disease in response to these triggers[1]. *Helicobacter pylori* (*H. pylori*) is one of the most commonly studied infectious agents proposed as agents triggering autoimmune response. This is due to the unique attributes of *H. pylori* such as long-term survival in the host environment, worldwide prevalence, and its complex interactions with the host immune system. 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. We performed a systematic literature review using the keywords "rheumatoid arthritis", "Sjögren's syndrome", "systemic sclerosis", "systemic lupus erythematosus", "*Helicobacter pylori*" and "pathogenesis". A systematic literature search was conducted from MEDLINE; EMBASE; Cochrane Library and ACR/EULAR meeting abstracts. In this article, we review the current state of knowledge of *H. pylori* infection as a risk factor in some autoimmune systemic rheumatic diseases and the possible mechanisms by which infectious exposures might induce pathologic processes. The aim of this article was to review the possible role of *H. pylori* in the pathogenesis of various systemic rheumatic diseases.

H. pylori is a widespread, Gram-negative bacterium which usually infects the gastric mucosa. Since its initial detection as a human pathogen in 1983, *H. pylori* has been associated in numerous diseases[2]. The presence of *H. pylori* in gastric mucosa has been implicated with various gastrointestinal ailments, including peptic ulcers, noncardia gastric adenocarcinoma and gastric mucosa associated lymphoid tissue (MALT) lymphoma[2]. *H. pylori* is one of the most common pathogens affecting humans, infecting approximately 50% of the world's population. It is found more frequently in developing countries than in industrialized countries, probably due to poor sanitary conditions[3]. However, despite the high prevalence of infection, *H. pylori* produce a disease in only a minority of patients[4]. In this moment, routine screening is not recommended, but any individual with confirmed gastric or duodenal ulcers, or MALT lymphoma, should be tested[5].

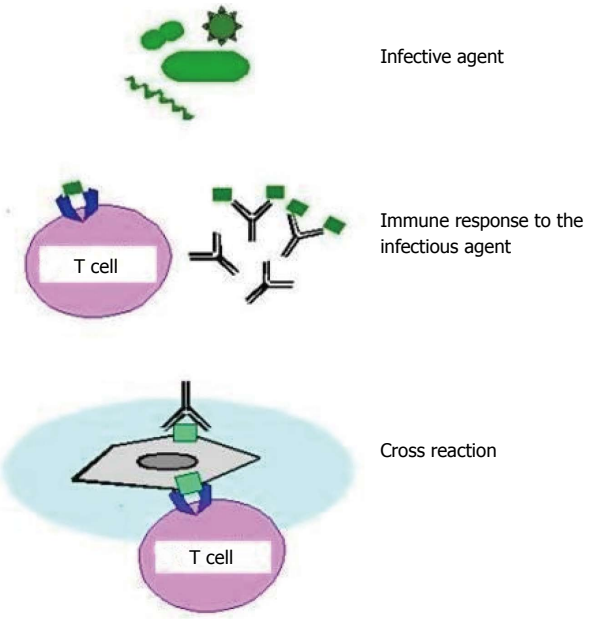

Figure 1 Infection induced autoimmunity.

The outcome of the infection depends on several factors: bacterial virulence, host factors, and environmental factors[6]. Ulceration and carcinogenesis are reciprocally exclusive outcomes of this infection. *H. pylori* infection is a very persistent infection, and in high prevalence regions, repeated infections are common[3,7]. The bacteria have been isolated from saliva, feces and dental plaques of infected patients, which suggest the fecal-oral route as the possible transmission mode[8]. The pathogen is a gram-negative spiral shaped bacterium that has the unique capability to colonize the human gastric mucosa[9]. Some virulence factors such as urease and flagella are present in all strains and are obligatory for the colonization of the gastric mucosa and pathogenetic findings. With its flagella, the bacterium moves through the stomach lumen and pierces into the gastric mucosal layer. The presence of the flagella and their constant mobility is required for persistent gastric colonization[10]. The main bacterial factors associated with pathogenicity inclusive outer membrane proteins, including the vacuolating cytotoxin VacA, and the product CagA. An interaction between bacterial agents such as CagA and host signal transduction pathways appears to be critical for mediating cell transformation, cell proliferation, invasion, apoptosis/antiapoptosis, and angiogenesis[11]. The main pathophysiological event in *H. pylori* infection is initiation and continuation of an inflammatory response. Bacteria or their products induce this inflammatory process and the main mediators of which are cytokines[12,13]. This response is linked to the expression of proinflammatory cytokines, both on the surface epithelium and in macrophages/monocytes[14-17]. Furthermore, another determinant of virulence is the neutrophil-activating protein (*NapA*) gene, a gene that was shown to be induced by contact with the epithelium (iceA1)[5].

Evidence presented above indicates an overall down-

regulation of the host immune response in *H. pylori* infected individuals. However, the persistent presence of *H. pylori* in gastric mucosa has the effect of chronic immune system activation with ongoing cytokine signaling, infiltration of gastric mucosa by neutrophils, macrophages, lymphocytes, as well as production of effectors T-cells and antibodies[18]. Various mechanisms have been suggested in an attempt to explain the extra-intestinal manifestations of *H. pylori* infections. These involves: molecular mimicry, endothelial cell damage, microchimerism and superantigens. Molecular mimicry is a mechanism by which we may explain the pathogenicity of antibodies against bacterial proteins in systemic sclerosis (SSc). It is already known that the immunological response caused by *H. pylori* is an important determinant of the amount of gastric mucosal damage. Therefore the production of large number of various proinflammatory substances, such as cytokines, proteins of the acute phase and eicosanoids, follows gastric colonization by *H. pylori*[19]. Finally, this inflammatory response may lead to the development of cross-reactive antibodies (by molecular mimicry) and antigen-antibody complexes causing the damage to other organs[6]. Superantigens are proteins that are derived exogenously by bacteria or expressed endogenously in the organism[20]. Microbial superantigens may stimulate an immediate T cell while it has been shown that B cell response may bind to microbial superantigens to surface class Ⅱ MHC molecules and become a target of T-helper lymphocytes. The term microchimerism applies to one individual harbouring DNA or cells at a low level that stemming from another individual. Furthermore, $CD4^+$ and $CD8^+$ T cells circulating levels have been found significantly higher in SSc patients than in controls. Furthermore, diffuse SSc patients have significantly more $CD4^+$ microchimeric T cells compared to controls[21]. In individuals with circulating microchimeric T cells, the endothelium represents an allotypic stimulus to those cells. This could mimic the same pathway transplanted T cells follow in graft-*vs*-host disease. Infections by any microorganism may cause the activation of χ/δ T cells (found in significant amount in SSc skin). The encounter of χ/δ T cells with microorganism shift from a Th2 tolerogenic to a Th1 cytotoxic pattern. The χ/δ T cells may meet resident microchimeric cells inducing a cross-reaction against "nonself" cells igniting automatically a graft-versus-host disease-like reaction[22]. Because of these reasons, confounders like co-infections, host factors and differences between *H. pylori* strains should be observed and controlled to understand the possible role of *H. pylori* infection in autoimmune systemic rheumatic diseases.

It has been suggested that *H. pylori* infection induces a phenomenon similar to that seen in the molecular mimicry between host proteins and haemolytic streptococcus group A antigens resulting in both humoral and cell mediated autoimmune reactions and ultimately causing rheumatic fever and rheumatic heart disease[21]. Based on these perceptions, investigators have examined the possible role of *H. pylori* as a pathogenic determinant for idiopathic extra intestinal diseases, in which immune dysregulation is included.

H. PYLORI AND SYSTEMIC SCLEROSIS

The most recent research on the involvement of bacterial infections in the pathogenesis of SSc focuses on *H. pylori* which has been implicated in other vascular diseases[22]. Several studies have investigated an association between *H. pylori* infection and Raynaud's phenomenon, Sjögren syndrome, and SSc. In a group of primary Raynaud's phenomenon patients eradication of *H. pylori* infection was associated with complete disappearance of the episodes of Raynaud's phenomenon in 17% of treated patients and a reduction in symptoms in an additional 72%[23]. Although this study was not double blinded, it is interesting that symptoms of Raynaud's phenomenon did not improve in subgroup of patients in whom eradication of *H. pylori* failed. A more recent trial of similar design reported almost equal results[24]. Furthermore the results of one study identified higher incidence rates of serological evidence of *H. pylori* infection in patients with rheumatologic diseases, including SSc[25]. In contrast to previous findings, three larger studies did not find any difference in *H. pylori* infection rates between patients with SSc with Raynaud's phenomenon compared with healthy controls[26-28]. However, even if it was true that *H. pylori* infection rates do not correlate with SSc, this does not necessarily exclude its involvement in SSc. One clinical study showed that, despite the absence of a difference in *H. pylori* infection rates between SSc patients and controls, 90% of SSc patients were infected with the virulent CagA strain compared with only 37% of the infected controls[29]. Therefore, confounding factors such as differences in *H. pylori* strains, coinfections and immunological and genetic host factors will have to be further identified and controlled in order to understand the possible role of *H. pylori* in Raynaud's phenomenon, SSc, and other vascular phenomena. The association between Raynaud's syndrome and *H. pylori* infection has been attributed to increased levels of cytokines and acute phase reactants, such as C-reactive protein and fibrinogen, causing the vasospasm and platelet aggregation[27,29-31]. Kalabay *et al*[32], who found a high prevalence of *H. pylori* infection in SSc patients (78%) (n = 55), tried to explain the preferential occurrence of *H. pylori* infection in SSc in two ways. First, an increased *H. pylori* infection prevalence might be caused by the disturbed gastrointestinal motility, a clinical phenomenon well known in SSc patients. The second explanation may be that *H. pylori* infection and the immunological mechanisms operative throughout SSc may be interconnected. We recently performed a study aiming to evaluate the possible association between *H. pylori* infection with disease activity, biochemical and serological data[31]. Our preliminary results suggest that *H. pylori* infection is implicated in activity of SSc, especially in skin involvement of this disease. This study may indicate

H. pylori infection as a possible cofactor in the development of SSc. In our following research we have showed that in SSc patients, *H. pylori* infection status, as directly observed by invasive test, is related to disease severity; *H. pylori*-positive patients showed an increased risk to have a severe disease and to be affected by a moderate/severe skin or visceral involvement, compared to *H. pylori*-negative SSc patients[32]. Therefore, *H. pylori* infection status provides us some prognostic information. Clinical trials are still necessary in purpose to define the pathogenesis and confirm the increase in association between *H. pylori* and SSc.

H. PYLORI AND SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a chronic, inflammatory, autoimmune disease characterized by lymphoid cell infiltration and destruction of exocrine glands, specifically salivary and lacrimal glands. To evaluate a possible link between *H. pylori* infection and SS, several groups investigated the presence of *H. pylori* and its related antibodies in these patients. SS patients are more inclined to have *H. pylori* infection in comparison to patients with other connective tissue diseases[33]. In SS patients serum antibody titers to *H. pylori* correlated with a disease activity index, age, disease duration and C-reactive protein levels. Evaluation of *H. pylori* infection status in older SS patients with active disease for a relatively long duration is therefore recommended, especially those who have been suffering from primary SS for more than 3 years[34]. One of the studies suggested a possible connection between antibodies produced against heat shock protein (HSP 60) of *H. pylori* and SS development[25]. Susceptibility to develop an autoimmune reaction after the *H. pylori* infection may be associated to the specific immune background of the host such as that of SS patients. In contrary to previous studies, a much larger study of 164 primary SS patients from Sweden did not prove a higher seroprevalence rates of *H. pylori* as compared with control group[35]. Moreover there was no association found between *H. pylori* status and abnormal autoantibodies levels or abnormal lip biopsy in these patients. In a separate cohort of 54 SS patients, seroprevalence of *H. pylori* was 57% compared to 62% in the control group[36]. Another study compared 36 primary SS patients to 31 patients with secondary SS and determined the *H. pylori* infection prevalence was 80.6% and 71%, respectively[34]. Furthermore, no significant association was found between *H. pylori* positivity and autoantibodies presence in primary or secondary SS patients. Therefore, as previously mentioned a significant positive correlation with C-reactive protein was found in SS patients, but not with erythrocyte sedimentation rate. The results of these studies are contradictory. Some data suggests that SS patients have a higher prevalence of *H. pylori* infection. However, in a larger cohort of a homogenous population (with an overall low *H. pylori* incidence) no such association was found. Finally, there is no real evidence for the definitive confirmation of association of *H. pylori* infection and SS.

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 numerous and can affect the skin, joints, kidneys, brain, and other organs. The serologic hallmark of SLE is the production of autoantibodies, including anti-nuclear antibodies (ANA) and antidouble stranded DNA antibodies (anti-dsDNA). Previous studies conducted on mice have shown that exposure to *H. pylori* urease can lead to production of anti ss-DNA antibodies[37]. One study compared the *H. pylori* seropositivity prevalence in 466 SLE patients with matched controls and found that SLE patients had lower probability to be seropositive (36.5%) for *H. pylori* as compared to healthy control group (42.9%)[38]. After subgroup analysis, it was noted that *H. pylori* seropositive African-American females prone to develop SLE at an older age compared to *H. pylori* negative SLE patients. This study suggests that exposure to *H. pylori* may provide some protection against developing SLE in this specific population. Furthermore, these findings raise an interesting question: could *H. pylori* infected individuals be protected against SLE development? Although this is quite interestingly, an acceptable mechanism to explain this interconnection remains elusive.

H. PYLORI AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune inflammatory disorder primarily characterized by symmetrical erosive arthritis affecting small, medium, and large joints. Several environmental and genetic factors, including smoking, contribute to disease onset and severity[39]. The relationship of *H. pylori* infection in the RA pathogenesis is controversial. *In vitro* studies have found that B cells chronically stimulated with urease produced by *H. pylori* had the potential to produce autoantibodies, including IgM rheumatoid factor[37]. However, regardless the result of in vitro experiments, the clinical correlation between *H. pylori* infection and RA has been less persuasive. RA patients have an increased risk for the development of peptic ulcers but it is not clear is this directly related to an increased *H. pylori* infection prevalence or due to the abundant non-steroidal anti-inflammatory drugs usage[40]. Data regarding the prevalence of *H. pylori* infection in RA patient are contradictory. In a cohort of 187 samples from RA patients, 80.4% were found to be *H. pylori* seropositive; nevertheless there was no significant difference in the control group[41]. In accordance with previous study, large epidemiological study of 1815 RA Japanese patients, 49.3% were reported to have *H. pylori* antibodies and it was lower compared with the healthy Japanese

Table 1 Possible role of *Helicobacter pylori* infection in the autoimmune systemic rheumatic diseases *n* (%)

Disease	Ref.	Study sample	Conclusion
SS	Aragona *et al*[27], 1999	34 patients with primary SS	27 (79.4) and 30 (88.2) had antibodies against *H. pylori* and its HSP60
	Showji *et al*[35], 1996	7 patients with primary SS	High titers of anti-*H. pylori* antibodies in sera of patients with SS compared with patients with other CTDs
	Theander *et al*[37], 2001	164 patients with primary SS	Similar *H. pylori* seroprevalence rates as in control group
	El Miedany *et al*[36], 2005	36 patients with primary SS compared to 31 patients with secondary SS	The prevalence of *H. pylori* infection was 80.6% (primary SS) and 71% (secondary SS)
	Iwai *et al*[49], 2009	case report	The regression of parotid MALT lymphoma after the eradication of *H. pylori* in SS patients
RA	Yamanishi *et al*[39], 2006	6- to 8-wk-old female BALB/c mice	B cells chronically stimulated with urease produced by *H. pylori* had the potential to generate IgM rheumatoid factor
	Meron *et al*[43], 2010	187 serum samples from RA patients	RA patients have a lower prevalence of *H. pylori* infection compared with patients with other CTDs
	Zentilin *et al*[45], 2002	58 consecutive patients with dyspeptic symptoms and variable RA activity	Clinical improvement in RA symptoms after eradication of *H. pylori*
	Matsukawa *et al*[47], 2005	case report	No clinical improvement in RA symptoms after eradication of *H. pylori*
SLE	Yamanishi *et al*[39], 2006	6- to 8-wk-old female BALB/c mice	Urease is capable to induce SLE-related autoantibodies in mice, namely anti-ssDNA
	Showji *et al*[35], 1996	15 SLE patients	SLE patients have lower anti-*H. pylori* serum antibody titers compared with patients with other CTDs
	Sawalha *et al*[40], 2004	466 SLE patients and matched controls	SLE patients were less likely to be seropositive compared to controls
SSc	Aragona *et al*[27], 1999	16 SSc patients	Higher incidence rates of serological evidence of *H. pylori* infection in SSc patients
	Hervé *et al*[30], 2006	40 consecutive SSc patients	No difference in *H. pylori* infection rates between SSc patients with Raynaud's phenomenon compared with healthy controls
	Danese *et al*[31], 2000	124 SSc patients (67 with limited cutaneous SSc, 57 with diffuse cutaneous SSc)	90% of patients with SSc were infected with the virulent CagA strain compared with only 37% of the infected control subjects
	Radić *et al*[33], 2010	42 SSc patients	*H. pylori* infection is implicated in activity of SSc, especially in skin involvement of this disease

SS: Sjögren's syndrome; CTD: Connective tissue diseases; NHL: Non-Hodgkin's lymphoma; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; *H. pylori*: *Helicobacter pylori*; MALT: Mucosa associated lymphoid tissue.

individuals[40]. Nevertheless, another study from the same country searching the *H. pylori* infection prevalence in RA patient cohort reported different results, a much higher percentage (61.4%)[42]. In the study of a European cohort with RA *H. pylori* prevalence was reported to be 48%, which is quite similar to healthy individuals in the Western countries[43]. In fact, previously mentioned studies have shown that the prevalence of *H. pylori* infection in RA patients was almost identical as in healthy controls. Although, several small studies suggested some clinical improvement in RA symptoms after eradication of *H. pylori*[43,44], many other studies have been unable to confirm these findings[42,45]. Therefore, the data for the final confirmation of *H. pylori* infection association with the onset or severity of RA are still missing.

DISCUSSION

If *H. pylori* induces autoimmune disease, how does it do so? There are various mechanisms by which an infecting agent may instigate autoimmunity which includes polyclonal activation, molecular mimicry, epitope spread, superantigens and bystander activation. In any case, it is broad agreement that microbial agents play an important role in the pathogenesis of a large number autoimmune diseases and it is clear that, in genetically predisposed individuals, some environmental factor (especially an infective agent) may induce or aggravate them[46]. Table 1 provides an overview of the main findings regarding the possible part of *H. pylori* infection in the pathogenesis of autoimmune systemic rheumatic diseases.

H. pylori infection causes in a primarily Th1 T-cell response, which leads to the production of IL-2 and interferon gamma[47]. The interact between *H. pylori* and B-lymphocytes develops proliferation and uncontrolled growth of predominantly $CD5^+$ B-cells[48]. These cells assemble auto-reactive and polyreactive IgM and IgG3 antibodies[48]. Subsequent studies showed that chronic *H. pylori* infection and deriving exposure to urease has the effect of stimulation and increased survival of this B lymphocytes subset[37].

Chronic *H. pylori* infection serves as a source of ongoing antigenic stimulation and underlies the pathogens' capability to provoke a systemic inflammatory response[49]. The prolonged interact between the *H. pylori* infection and host immune mechanisms makes this bacterium a probable infectious agent for triggering autoimmunity. The continuous, complex interaction between pathogen

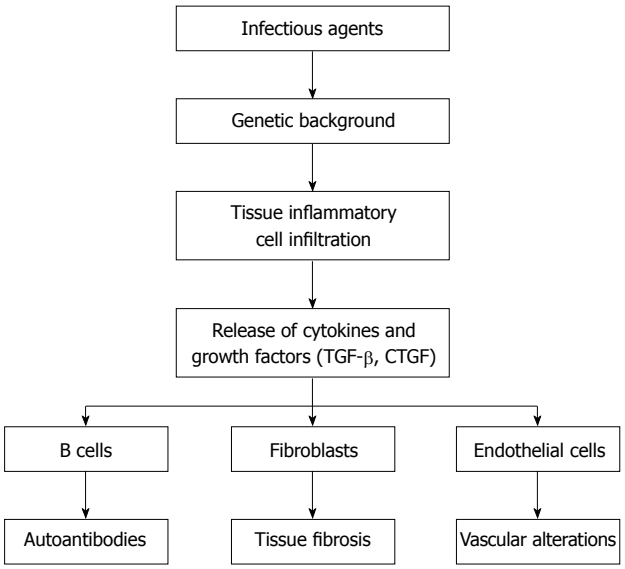

Figure 2 Infection hypothesis of the pathogenesis of systemic sclerosis. CTGF: Connective tissue growth factor; TGF-β: Transforming growth factor-β.

and host immunity may contribute to immune dysregulation and further development of autoimmunity in predisposed individuals.

Several different mechanisms have been suggested in an attempt to explain the extra-intestinal manifestations of *H. pylori* infection. The proposed mechanisms are: atrophic gastritis, enhancement in vascular permeability during the gastric infection, the release of inflammatory mediators, systemic immune response and molecular mimicry. Development of systemic rheumatic disease is unlikely to depend exclusively on an infectious agent. Instead, it likely occurs as a result of interactions between the infectious agent and a cascade of host-specific factors and events. This is not surprising because immune response to infection is highly individual. It is controlled by multiple genes, age, and the route of infection. It may even be different in the same individual from one day to the next owing to a number of factors, including coinfections, stress, and pregnancy. In addition, polymorphisms in genes unrelated to immunity may cause an infectious agent to induce disease through molecular mimicry in one person and not another. The complex network of specialized cells and molecules in the immune system has evolved to defend against pathogens, but inadvertent immune system attacks on "self" result in autoimmune disease. Both genetic regulation of immune cell levels and their relationships with autoimmunity are largely undetermined. A recent study has shown variants at three loci (HLA, IL2RA, and SH2B3/ATXN2) overlap with known autoimmune disease associations[50]. There is also a potential role of gastric epithelial cells in mucosal immunity, not only because they are predominant cell type in mucosa and initial site of host-bacterial interaction, but also as a major contributor to molecules that are thought to be primarily expressed by immune cells so far[51-54].

For example, the most prominent clinical manifestations of systemic sclerosis are caused by the exaggerated accumulation of collagen and other connective tissue components in the affected organs. In Figure 2, it is hypothesised that the infectious agent (*H. pylori*) is the incising factor that acts on a genetically predisposed host and results in the subsequent recruitment and homing of macrophages and T cells to the affected tissues. The inflammatory cells would undergo selective proliferation and expansion, perhaps because of an antigen-driven response, and then release cytokines and growth factors that initiate the process of tissue and vascular fibrosis. Infectious agents cause a profound phenotypic change in various target cells of different lineages (immune cells, fibroblasts, and endothelial and vascular smooth-muscle cells). This phenotypic change could be caused by integration of genetic material (for example, of *H. pylori* origin) within the genetic sequence of the target cells that through unknown mechanisms would induce the expression of specific regulatory genes, altering the function and behaviour of the target cells. These alterations are manifested by increased collagen and extracellular matrix production in fibroblasts, generation of autoantibodies and cellular immune abnormalities in lymphocytes, and severe fibroproliferative and prothrombotic alterations in endothelial cells. The target cell effects cytokines and growth factors, particularly transforming growth factor-β and connective tissue growth factor.

In conclusion, in systemic rheumatic diseases infection prevalence alone should not be expected to provide sufficient evidence for or against a pathologic role in the disease. A competing theory that is also being discussed is that an infection-induced immune response continues after the pathogen has been eradicated. This could explain why patients with confirmed eradication therapy failed to show improvement in short-term observations. Further studies of the immunological response to *H. pylori* and its role in the pathogenesis of systemic rheumatic diseases are warranted. We definitely need some new studies or experimental (animal) models to define exact mechanisms by which a *H. pylori* infection contributes to the systemic rheumatic diseases process because a direct association is still missing.

REFERENCES

1 **Amital H**, Govoni M, Maya R, Meroni PL, Ori B, Shoenfeld Y, Tincani A, Trotta F, Sarzi-Puttini P, Atzeni F. Role of infectious agents in systemic rheumatic diseases. *Clin Exp Rheumatol* 2008; **26**: S27-S32 [PMID: 18570751]

2 **Cover TL**, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; **136**: 1863-1873 [PMID: 19457415 DOI: 10.1053/j.gastro.2009.01.073]

3 **Lehours P**, Yilmaz O. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2007; **12** Suppl 1: 1-3 [PMID: 17727452 DOI: 10.1111/j.1523-5378.2007.00541.x]

4 **Jung JH**, Choi KD, Han S, Jung HY, Do MY, Chang HS, Choe JW, Lee GH, Song HJ, Kim do H, Choi KS, Lee JH, Ahn JY, Kim MY, Bae SE, Kim JH. Seroconversion rates of Helicobacter pylori infection in Korean adults. *Helicobacter* 2013; **18**: 299-308 [PMID: 23521610 DOI: 10.1111/hel.12043]

5 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori

infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499]
6 **Graham DY**. History of Helicobacter pylori, duodenal ulcer, gastric ulcer and gastric cancer. *World J Gastroenterol* 2014; **20**: 5191-5204 [PMID: 24833849 DOI: 10.3748/wjg.v20.i18.5191]
7 **Calvet X**, Ramírez Lázaro MJ, Lehours P, Mégraud F. Diagnosis and epidemiology of Helicobacter pylori infection. *Helicobacter* 2013; **18** Suppl 1: 5-11 [PMID: 24011238 DOI: 10.1111/hel.12071]
8 **Miendje Deyi VY**, Van den Borre C, Fontaine V. Comparative evaluation of 3 selective media for primary isolation of Helicobacter pylori from gastric biopsies under routine conditions. *Diagn Microbiol Infect Dis* 2010; **68**: 474-476 [PMID: 20926220 DOI: 10.1016/j.diagmicrobio.2010.08.009]
9 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023 DOI: 10.1016/S0140-6736(84)91816-6]
10 **Sheu BS**, Yang HB, Yeh YC, Wu JJ. Helicobacter pylori colonization of the human gastric epithelium: a bug's first step is a novel target for us. *J Gastroenterol Hepatol* 2010; **25**: 26-32 [PMID: 20136973 DOI: 10.1111/j.1440-1746.2009.06141.x]
11 **Faria C**, Zakout R, Araújo M. Helicobacter pylori and autoimmune diseases. *Biomed Pharmacother* 2013; **67**: 347-349 [PMID: 23583190 DOI: 10.1016/j.biopha.2011.09.015]
12 **Palli D**, Masala G, Del Giudice G, Plebani M, Basso D, Berti D, Numans ME, Ceroti M, Peeters PH, Bueno de Mesquita HB, Buchner FL, Clavel-Chapelon F, Boutron-Ruault MC, Krogh V, Saieva C, Vineis P, Panico S, Tumino R, Nyrén O, Simán H, Berglund G, Hallmans G, Sanchez MJ, Larrãnaga N, Barricarte A, Navarro C, Quiros JR, Key T, Allen N, Bingham S, Khaw KT, Boeing H, Weikert C, Linseisen J, Nagel G, Overvad K, Thomsen RW, Tjonneland A, Olsen A, Trichoupoulou A, Trichopoulos D, Arvaniti A, Pera G, Kaaks R, Jenab M, Ferrari P, Nesi G, Carneiro F, Riboli E, Gonzalez CA. CagA+ Helicobacter pylori infection and gastric cancer risk in the EPIC-EURGAST study. *Int J Cancer* 2007; **120**: 859-867 [PMID: 17131317 DOI: 10.1002/ijc.22435]
13 **Costa AC**, Figueiredo C, Touati E. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2009; **14** Suppl 1: 15-20 [PMID: 19712163 DOI: 10.1111/j.1523-5378.2009.00702.x]
14 **Raghwan R**. Host cell contact induces fur-dependent expression of virulence factors CagA and VacA in Helicobacter pylori. *Helicobacter* 2014; **19**: 17-25 [PMID: 24020886 DOI: 10.1111/hel.12087]
15 **Chan AO**, Chu KM, Huang C, Lam KF, Leung SY, Sun YW, Ko S, Xia HH, Cho CH, Hui WM, Lam SK, Rashid A. Association between Helicobacter pylori infection and interleukin 1beta polymorphism predispose to CpG island methylation in gastric cancer. *Gut* 2007; **56**: 595-597 [PMID: 17369391 DOI: 10.1136/gut.2006.113258]
16 **García-González MA**, Lanas A, Quintero E, Nicolás D, Parra-Blanco A, Strunk M, Benito R, Angel Simón M, Santolaria S, Sopeña F, Piazuelo E, Jiménez P, Pascual C, Mas E, Irún P, Espinel J, Campo R, Manzano M, Geijo F, Pellisé M, González-Huix F, Nieto M, Espinós J, Titó L, Bujanda L, Zaballa M. Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: a Nationwide Multicenter Study in Spain. *Am J Gastroenterol* 2007; **102**: 1878-1892 [PMID: 17640324]
17 **Obonyo M**, Sabet M, Cole SP, Ebmeyer J, Uematsu S, Akira S, Guiney DG. Deficiencies of myeloid differentiation factor 88, Toll-like receptor 2 (TLR2), or TLR4 produce specific defects in macrophage cytokine secretion induced by Helicobacter pylori. *Infect Immun* 2007; **75**: 2408-2414 [PMID: 17353291 DOI: 10.1128/IAI.01794-06]
18 **Blaser MJ**, Atherton JC. Helicobacter pylori persistence: biology and disease. *J Clin Invest* 2004; **113**: 321-333 [PMID: 14755326 DOI: 10.1172/JCI20925]
19 **Neumann WL**, Coss E, Rugge M, Genta RM. Autoimmune atrophic gastritis--pathogenesis, pathology and management. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 529-541 [PMID: 23774773 DOI: 10.1038/nrgastro.2013.101]
20 **Randone SB**, Guiducci S, Cerinic MM. Systemic sclerosis and infections. *Autoimmun Rev* 2008; **8**: 36-40 [PMID: 18706530 DOI: 10.1016/j.autrev.2008.07.022]
21 **Rak JM**, Pagni PP, Tiev K, Allanore Y, Farge D, Harlé JR, Launay D, Hachulla E, Didelot R, Cabane J, Kahan A, Martin M, Granel B, Roudier J, Lambert NC. Male microchimerism and HLA compatibility in French women with sclerodema: a different profile in limited and diffuse subset. *Rheumatology* (Oxford) 2009; **48**: 363-366 [PMID: 19208687]
22 **Gilliam AC**. Scleroderma. *Curr Dir Autoimmun* 2008; **10**: 258-279 [PMID: 18460891]
23 **Faé KC**, Diefenbach da Silva D, Bilate AM, Tanaka AC, Pomerantzeff PM, Kiss MH, Silva CA, Cunha-Neto E, Kalil J, Guilherme L. PDIA3, HSPA5 and vimentin, proteins identified by 2-DE in the valvular tissue, are the target antigens of peripheral and heart infiltrating T cells from chronic rheumatic heart disease patients. *J Autoimmun* 2008; **31**: 136-141 [PMID: 18541406 DOI: 10.1016/j.jaut.2008.04.023]
24 **Blum A**, Tamir S, Mualem K, Ben-Shushan RS, Keinan-Boker L, Paritsky M. Endothelial dysfunction is reversible in Helicobacter pylori-positive subjects. *Am J Med* 2011; **124**: 1171-1174 [PMID: 22114831 DOI: 10.1016/j.amjmed.2011.08.015]
25 **Gasbarrini A**, Massari I, Serricchio M, Tondi P, De Luca A, Franceschi F, Ojetti V, Dal Lago A, Flore R, Santoliquido A, Gasbarrini G, Pola P. Helicobacter pylori eradication ameliorates primary Raynaud's phenomenon. *Dig Dis Sci* 1998; **43**: 1641-1645 [PMID: 9724144 DOI: 10.1023/A:1018842527111]
26 **Csiki Z**, Gál I, Sebesi J, Szegedi G. [Raynaud syndrome and eradication of Helicobacter pylori]. *Orv Hetil* 2000; **141**: 2827-2829 [PMID: 11202119]
27 **Aragona P**, Magazzù G, Macchia G, Bartolone S, Di Pasquale G, Vitali C, Ferreri G. Presence of antibodies against Helicobacter pylori and its heat-shock protein 60 in the serum of patients with Sjögren's syndrome. *J Rheumatol* 1999; **26**: 1306-1311 [PMID: 10381048]
28 **Savarino V**, Sulli A, Zentilin P, Raffaella Mele M, Cutolo M. No evidence of an association between Helicobacter pylori infection and Raynaud phenomenon. *Scand J Gastroenterol* 2000; **35**: 1251-1254 [PMID: 11199362 DOI: 10.1080/003655200453575]
29 **Sulli A**, Seriolo B, Savarino V, Cutolo M. Lack of correlation between gastric Helicobacter pylori infection and primary or secondary Raynaud's phenomenon in patients with systemic sclerosis. *J Rheumatol* 2000; **27**: 1820-1821 [PMID: 10914880]
30 **Hervé F**, Cailleux N, Benhamou Y, Ducrotté P, Lemeland JF, Denis P, Marie I, Lévesque H. [Helicobacter pylori prevalence in Raynaud's disease]. *Rev Med Interne* 2006; **27**: 736-741 [PMID: 16978744 DOI: 10.1016/j.revmed.2006.07.003]
31 **Danese S**, Zoli A, Cremonini F, Gasbarrini A. High prevalence of Helicobacter pylori type I virulent strains in patients with systemic sclerosis. *J Rheumatol* 2000; **27**: 1568-1569 [PMID: 10852299]
32 **Kalabay L**, Fekete B, Czirják L, Horváth L, Daha MR, Veres A, Fónyad G, Horváth A, Viczián A, Singh M, Hoffer I, Füst G, Romics L, Prohászka Z. Helicobacter pylori infection in connective tissue disorders is associated with high levels of antibodies to mycobacterial hsp65 but not to human hsp60. *Helicobacter* 2002; **7**: 250-256 [PMID: 12165033 DOI: 10.1046/j.1523-5378.2002.00092.x]
33 **Radić M**, Martinović Kaliterna D, Bonacin D, Morović Vergles J, Radić J. Correlation between Helicobacter pylori infection and systemic sclerosis activity. *Rheumatology* (Oxford) 2010; **49**: 1784-1785 [PMID: 20498013 DOI: 10.1093/rheumatology/keq137]
34 **Radić M**, Kaliterna DM, Bonacin D, Vergles JM, Radić J, Fabijanić D, Kovačić V. Is Helicobacter pylori infection a risk factor for disease severity in systemic sclerosis? *Rheumatol Int*

2013; **33**: 2943-2948 [PMID: 23224499 DOI: 10.1007/s00296-012-2585-z]
35 **Showji Y**, Nozawa R, Sato K, Suzuki H. Seroprevalence of Helicobacter pylori infection in patients with connective tissue diseases. *Microbiol Immunol* 1996; **40**: 499-503 [PMID: 8865155 DOI: 10.1111/j.1348-0421.1996.tb01100.x]
36 **El Miedany YM**, Baddour M, Ahmed I, Fahmy H. Sjogren's syndrome: concomitant H. pylori infection and possible correlation with clinical parameters. *Joint Bone Spine* 2005; **72**: 135-141 [PMID: 15797493 DOI: 10.1016/j.jbspin.2004.04.005]
37 **Theander E**, Nilsson I, Manthorpe R, Jacobsson LT, Wadström T. Seroprevalence of Helicobacter pylori in primary Sjögren's syndrome. *Clin Exp Rheumatol* 2001; **19**: 633-638 [PMID: 11791633]
38 **Sorrentino D**, Faller G, DeVita S, Avellini C, Labombarda A, Ferraccioli G, Kahlow-Toussaint S. Helicobacter pylori associated antigastric autoantibodies: role in Sjögren's syndrome gastritis. *Helicobacter* 2004; **9**: 46-53 [PMID: 15156903 DOI: 10.1111/j.1083-4389.2004.00197.x]
39 **Yamanishi S**, Iizumi T, Watanabe E, Shimizu M, Kamiya S, Nagata K, Kumagai Y, Fukunaga Y, Takahashi H. Implications for induction of autoimmunity via activation of B-1 cells by Helicobacter pylori urease. *Infect Immun* 2006; **74**: 248-256 [PMID: 16368978 DOI: 10.1128/IAI.74.1.248-256.2006]
40 **Sawalha AH**, Schmid WR, Binder SR, Bacino DK, Harley JB. Association between systemic lupus erythematosus and Helicobacter pylori seronegativity. *J Rheumatol* 2004; **31**: 1546-1550 [PMID: 15290733]
41 **Scott DL**, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet* 2010; **376**: 1094-1108 [PMID: 20870100 DOI: 10.1016/S0140-6736(10)60826-4]
42 **Tanaka E**, Singh G, Saito A, Syouji A, Yamada T, Urano W, Nakajima A, Taniguchi A, Tomatsu T, Hara M, Saito T, Kamatani N, Yamanaka H. Prevalence of Helicobacter pylori infection and risk of upper gastrointestinal ulcer in patients with rheumatoid arthritis in Japan. *Mod Rheumatol* 2005; **15**: 340-345 [PMID: 17029090 DOI: 10.3109/s10165-005-0419-5]
43 **Meron MK**, Amital H, Shepshelovich D, Barzilai O, Ram M, Anaya JM, Gerli R, Nicola B, Shoenfeld Y. Infectious aspects and the etiopathogenesis of rheumatoid arthritis. *Clin Rev Allergy Immunol* 2010; **38**: 287-291 [PMID: 19575154 DOI: 10.1007/s12016-009-8158-6]
44 **Ishikawa N**, Fuchigami T, Matsumoto T, Kobayashi H, Sakai Y, Tabata H, Takubo N, Yamamoto S, Nakanishi M, Tomioka K, Fujishima M. Helicobacter pylori infection in rheumatoid arthritis: effect of drugs on prevalence and correlation with gastroduodenal lesions. *Rheumatology* (Oxford) 2002; **41**: 72-77 [PMID: 11792883 DOI: 10.1093/rheumatology/41.1.72]
45 **Zentilin P**, Seriolo B, Dulbecco P, Caratto E, Iiritano E, Fasciolo D, Bilardi C, Mansi C, Testa E, Savarino V. Eradication of Helicobacter pylori may reduce disease severity in rheumatoid arthritis. *Aliment Pharmacol Ther* 2002; **16**: 1291-1299 [PMID: 12144579 DOI: 10.1046/j.1365-2036.2002.01284.x]
46 **Seriolo B**, Cutolo M, Zentilin P, Savarino V. Helicobacter pylori infection in rheumatoid arthritis. *J Rheumatol* 2001; **28**: 1195-1196 [PMID: 11361212]
47 **Matsukawa Y**, Asai Y, Kitamura N, Sawada S, Kurosaka H. Exacerbation of rheumatoid arthritis following Helicobacter pylori eradication: disruption of established oral tolerance against heat shock protein? *Med Hypotheses* 2005; **64**: 41-43 [PMID: 15533608 DOI: 10.1016/j.mehy.2004.06.021]
48 **Mora GF**. Systemic sclerosis: environmental factors. *J Rheumatol* 2009; **36**: 2383-2396 [PMID: 19797508 DOI: 10.3899/jrheum.090207]
49 **Iwai H**, Nakamichi N, Nakae K, Konishi M, Inaba M, Hoshino S, Baba S, Amakawa R. Parotid mucosa-associated lymphoid tissue lymphoma regression after Helicobacter pylori eradication. *Laryngoscope* 2009; **119**: 1491-1494 [PMID: 19504556 DOI: 10.1002/lary.20258]
50 **Harris PR**, Smythies LE, Smith PD, Dubois A. Inflammatory cytokine mRNA expression during early and persistent Helicobacter pylori infection in nonhuman primates. *J Infect Dis* 2000; **181**: 783-786 [PMID: 10669377 DOI: 10.1086/315257]
51 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. Helicobacter pylori-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176 [PMID: 1682595 DOI: 10.1016/0140-6736(91)92035-Z]
52 **Jackson L**, Britton J, Lewis SA, McKeever TM, Atherton J, Fullerton D, Fogarty AW. A population-based epidemiologic study of Helicobacter pylori infection and its association with systemic inflammation. *Helicobacter* 2009; **14**: 108-113 [PMID: 19751435 DOI: 10.1111/j.1523-5378.2009.00711.x]
53 **Orrù V**, Steri M, Sole G, Sidore C, Virdis F, Dei M, Lai S, Zoledziewska M, Busonero F, Mulas A, Floris M, Mentzen WI, Urru SA, Olla S, Marongiu M, Piras MG, Lobina M, Maschio A, Pitzalis M, Urru MF, Marcelli M, Cusano R, Deidda F, Serra V, Oppo M, Pilu R, Reinier F, Berutti R, Pireddu L, Zara I, Porcu E, Kwong A, Brennan C, Tarrier B, Lyons R, Kang HM, Uzzau S, Atzeni R, Valentini M, Firinu D, Leoni L, Rotta G, Naitza S, Angius A, Congia M, Whalen MB, Jones CM, Schlessinger D, Abecasis GR, Fiorillo E, Sanna S, Cucca F. Genetic variants regulating immune cell levels in health and disease. *Cell* 2013; **155**: 242-256 [PMID: 24074872 DOI: 10.1016/j.cell.2013.08.041]
54 **Al-Sammak F**, Kalinski T, Weinert S, Link A, Wex T, Malfertheiner P. Gastric epithelial expression of IL-12 cytokine family in Helicobacter pylori infection in human: is it head or tail of the coin? *PLoS One* 2013; **8**: e75192 [PMID: 24069393 DOI: 10.1371/journal.pone.0075192]

P- Reviewer: Day AS, Dumitrascu DL, Firinu D, Tosetti C, Vorobjova T **S- Editor**: Ma YJ **L- Editor**: A **E- Editor**: Wang CH

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ISSN 1007-9327