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MINIREVIEWS

Ins and outs of *Helicobacter pylori* association with autoimmune rheumatic diseases

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Abstract

Helicobacter pylori (*H. pylori*) infection is widely prevalent throughout worldwide. *H. pylori* manage a long-term survival in hostile environment of human stomach leading to peptic ulcer diseases and gastric cancer. But mostly infected person remains asymptomatic. Its chronic interaction with immune system makes *H. pylori* as an attractive candidate for the researchers to study its association with autoimmune diseases. This article presents a review of the literature on the association of *H. pylori* infection in selective autoimmune rheumatic diseases (RD). The authors used MeSH terms "*Helicobacter pylori*" with "rheumatoid arthritis," "systemic lupus erythematosus," or "fibromyalgia" to search PubMed database. All relevant studies identified were included. Despite extensive medical advancement many questions on role of *H. pylori* infection in autoimmune RD still remain unanswered. Further studies are therefore needed to address the role of *H. pylori* in pathogenesis of RD.

Key words: Autoimmunity; Systemic lupus erythematosus; Rheumatoid arthritis; Fibromyalgia; *Helicobacter pylori*

Core tip: *Helicobacter pylori* (*H. pylori*) infection is widely prevalent throughout worldwide. Its chronic interaction with immune system makes *H. pylori* is an attractive candidate for the researchers to study its association with autoimmune disorders. This study presents a review of the literature on the *H. pylori* association with selective autoimmune rheumatic disorders. Despite extensive medical advancement many questions on the association of *H. pylori* infection with autoimmune rheumatic disorders still remain unanswered. More studies are therefore required to address the role of *H. pylori* infection in

pathogenesis of rheumatic diseases.

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INTRODUCTION

Rheumatic diseases (RD) include disorders related to joints and connective tissue. Generally these disorders have an autoimmune origin that is associated with progressive disability, systemic complications and early death. Involvement of musculoskeletal system, central and peripheral nervous systems, and other organs such as blood vessels, bone marrow, eye, heart, kidneys, lungs, skin and salivary glands may occurs in more than 40% of patients with RD over a lifetime of disease[1-3].

Typically initial *Helicobacter pylori* (*H. pylori*) infection is acquired by oral ingestion during the early childhood and *H. pylori* will persist for life in untreated cases[4]. Frequency of *H. pylori* infection is approximately 80% in underdeveloped countries compared to 50% in developed parts of the world, correlating the disease prevalence with poor socioeconomic status[5]. Clinically *H. pylori* infection leads to gastric diseases such as gastric ulcer, mucosa-associated lymphoid tissue lymphoma and gastric cancer[6]. *H. pylori* infection can induce a chronic immune response in the host cells (Figure 1), suggesting a possible role of *H. pylori* in the development of autoimmune disorders[7].

Autoimmune RD are thought to depend upon host genetic susceptibility interaction with environmental factors[8]. Amongst various environmental factors, infections agents plays significant role and have been studied extensively[9]. Infectious agents include bacteria, viruses and parasites. Out of all bacterial species implicated in non-organ specific autoimmune disorders, *H. pylori* have received much attention by researchers[10]. The purpose of this study was to summarize the recent literature on selected RD with autoimmune pathophysiologic mechanisms, which shows positive or negative evidence in relation to *H. pylori*-associated autoimmune rheumatic disorders.

H. PYLORI -INDUCED IMMUNOLOGIC RESPONCE

H. pylori have evolved various survival mechanisms to combat harsh acidic gastric environment and to suppress host immune response. Urease is a key virulence factor of *H. pylori* which is required for bacterial colonization to gastric mucosa; also it is a potent immunogen that elicits a strong immune response[11]. Urease also serves to promote bacterial motility by decreasing gastric mucous viscosity[12]. In order to evade host innate immune response, the bacterium is also capable of altering its own cell wall antigens rendering antigens to relatively non-antigenic[13].

H. pylori Infection induces a number of immune responses in the host cell by bacterial adhesion to cells and leading to chronic inflammation (Figure 1)[11]. Pathogen can bind to class Ⅱ major histocompatibility complex present on the cell membrane of gastric epithelial cells leading to apoptosis[14]. CagA translocate inside the gastric epithelial cells to induce high levels of inflammatory cytokines such as IL-6, IL-8, IL-10 and TNF-α[15]. The VacA protein interacts with lymphocytes resulting in blockage of IL-2-mediated T-lymphocyte proliferation[16].

A study by Jackson *et al*[17] shows elevated C-reactive protein in chronic *H. pylori* infected patients. Few other reports have demonstrated that chronic *H. pylori* infection leads to activation and survival of B lymphocytes to produce rheumatoid factor (IgM), antisingle-stranded DNA (anti-ssDNA) and anti-double-stranded DNA (anti-dsDNA) antibody and antiphosphotadylcholine antibody[18,19]. Instead of clearing *H. pylori*, these antibodies result in the synthesis of anti-H^+/K^+-ATPase antibodies[20]. These auto-reactive autoantibodies have been involved in the progress of atrophic gastritis. Complex and persistent interaction between host immune system and pathogen might cause immune dysregulation and consequent development of autoimmune RD in susceptible patients.

H. PYLORI-ASSOCIATED RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune chronic inflammatory disorder primarily of unknown origin. The arthritis in RA is symmetrical destructive polyarthritis affecting almost all joints of the body[21]. Various environmental and genetic factors may contribute to disease onset and severity[22]. Search for the role of microbial association with RA dates back to 19th century[23], and several viral and bacterial pathogens such as hepatitis C virus, parvovirus B19, Epstein-Barr virus (EBV), Proteus mirabilis, and Mycobacterium tuberculosis may have a role in its pathogenesis[24]. However the role of *H. pylori* infection in the pathogenesis of RA is controversial.

A cohort study on RA patients showed 80.4% to be seropositive for *H. pylori*. However, this was not significantly different from the control group[25]. A study from Japan by Tanaka *et al*[26] reported 49.3% of RA patients to have *H. pylori* antibodies, which was lesser compared with the healthy population. Another Japanese study reported a much higher prevalence (61.4%) of *H. pylori* infection in RA patients[27]. A study by Zentilin *et al*[28] showed severity of RA in *H. pylori* seropositive patients and suggested improvement in clinical symptoms after *H. pylori* eradication.

A direct role of *H. pylori* infection in RA pathogenesis seems controversial. Besides studies given above, few *in vitro* studies also suggest association of *H. pylori*

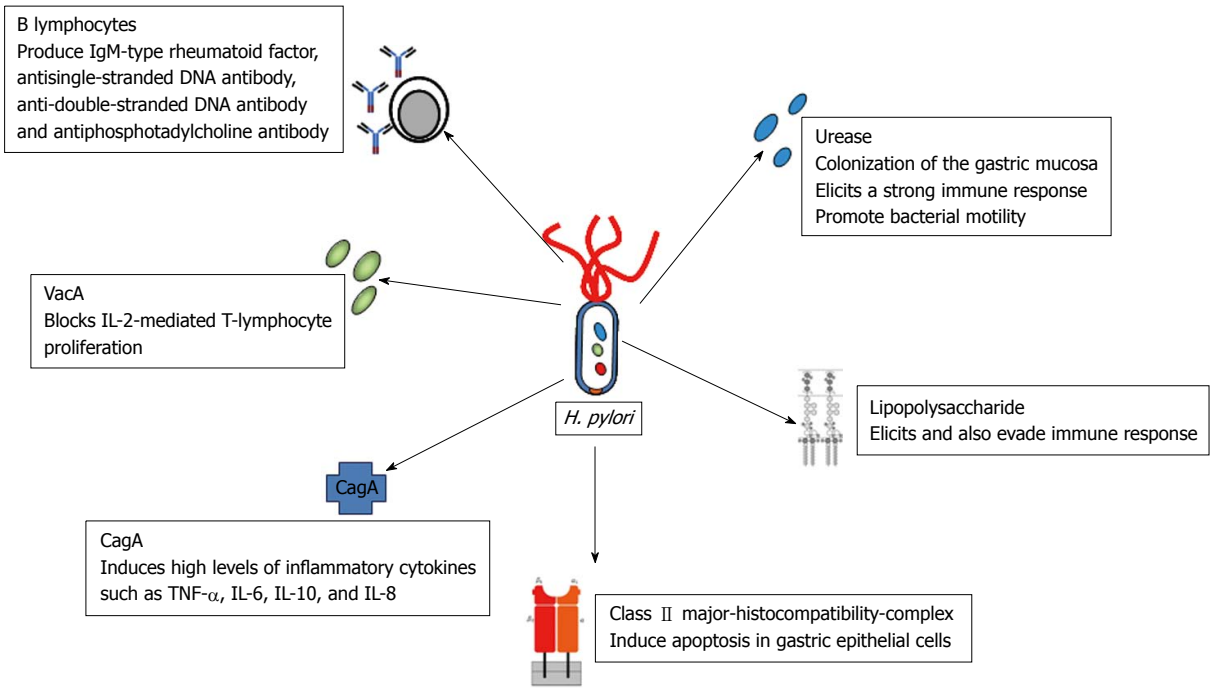

Figure 1 ***Helicobacter pylori*** **mediated immunologic responses.** IL: Interleukin; TNF: Tumor necrosis factor; *H. pylori*: *Helicobacter pylori*; DNA: Deoxyribonucleic acid.

in development of autoimmunity in RA patients. Like Yamanishi *et al*[18] found chronic stimulation of B cells due to urease produced by *H. pylori*. This ultimately leads to the generation of rheumatoid factor. But, on the other hand, the clinical evidence for association between RA and *H. pylori* infection is less substantial and inconclusive. Although RA patients have a high risk of developing peptic ulcer disease (PUD), but the abundant use of non-steroidal anti-inflammatory drugs in the RA patient may also contribute to the risk for PUD development[26]. Furthermore, studies have shown that not only RA patients but also other connective tissue disease patients have a prevalence of *H. pylori* infection nearly similar to that of control group[25,26]. Hence, the overall data regarding the association of *H. pylori* infection with RA pathogenesis remains controversial. Further specific *in vitro* and large scale clinical trials are required to provide clear understanding of this relationship.

H. PYLORI-ASSOCIATED SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease affecting multi-system. Immunologic abnormalities include the production of a number of autoantibodies, such as anti-dsDNA and anti-nuclear antibodies[29]. A number of microorganisms such as parvovirus B19, EBV and cytomegalovirus are associated in the disease pathogenesis[24].

H. pylori prevalence has been studied in SLE patients, but unlike other infectious agents, results vary significantly in published literature. A study by Kalabay *et al*[30] demonstrated similar frequency of *H. pylori* infection in SLE patients and control group. Also a study by Showji *et al*[31] demonstrated that patients with SLE have lesser anti-*H. pylori* antibodies in contrast to patients with some other connective tissue diseases. However, Yamanashi *et al*[18] have shown *in-vivo* induction of anti-single stranded DNA antibodies by *H. pylori* urease. In contrast to this evidence of SLE related antibody induction by *H. pylori*, fewer studies have shown protective role of *H. pylori*-infection in patients with SLE. Such as, Sawalha *et al*[32] have compared 466 SLE patients to matched control showing lower anti-*H. pylori* sero-positivity in SLE patients (36.5%:42.9%). Furthermore, in this study African American old age sero-positive females developed SLE more frequently compared to sero-negative females. Hence suggesting that *H. pylori*-infection have a protective role in the development of SLE is specific to this population group.

H. PYLORI-ASSOCIATED FIBROMYALGIA

Fibromyalgia (FMG), a chronic pain disorder, is associated with widespread musculoskeletal pain, stiffness, fatigue, anxiety, cognitive dysfunction, sleep difficulties and depression. Etiology and pathogenesis of FMG remains unknown[33]. Studies have evaluated association of FMG with bacterial and viral infection, however literature regarding specific role of *H. pylori*-infection in FMG development is inadequate. Microorganisms might contribute to the development of FMG by activation of inflammatory cytokines leading towards neuroendocrine abnormalities[34].

A study by Malt *et al*[35] shows that about 33% of the subjects were *H. pylori* positive in both FMG and control

group, therefore they concluded that *H. pylori*-infection was not associated with psychological changes in both diseased and control subjects. A recent study by Akkaya *et al*[36] demonstrated an association of *H. pylori*-infection with FMG patients and compared to similar gender control group. The FMG patients demonstrated higher frequency of an anti-*H. pylori* antibody (IgG) was seen in when compared to the control group, (30.8% and 17.1% respectively. Further, amongst FMG patients' depression and anxiety levels were not different between *H. pylori*-infected FMG patients or un-infected FMG patients.

CONCLUSION

The unique ability of *H. pylori* to chronically infect human gastric mucosa to activate inflammation and host immunological response suggests its role in autoimmune diseases. Associations with few autoimmune diseases are strong[7], whereas association of *H. pylori* infection with autoimmune RD remains controversial. To develop better understanding of *H. pylori*-association with RD further molecular and clinical research studies with larger sample sizes are warranted.

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