



Helicobacter pylori Infection: Regulatory T Cells and Their Participation in the Immune Response

Tania Beatriz Romero-Adrià^{1,*}, Jorymar Leal-Montiel²

¹ Faculty of Medicine, University of Zulia, Maracaibo, Venezuela

² Institute of Biological Research, Faculty of Medicine, University of Zulia, Maracaibo, Venezuela

*Corresponding author: Tania Beatriz Romero-Adrià, 69 B, Avenue 77, 49th Street, Panamericano Sector, Maracaibo, Venezuela. Tel: +26-17532659, E-mail: betrizromero@cantv.net.

ABSTRACT

Helicobacter pylori (*H. pylori*) is a Gram-negative bacterium that colonizes the human stomach and affects more than half of the global human population. This microorganism shows variations in its geographical distribution and causes chronic gastritis, peptic ulcer, gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma. The development of these clinical entities depends on the bacterial strain and its virulence, the host genetic predisposition, immunological response, concurrent infections and infestations.

In the immune response for the eradication of *H. pylori* different types of cells and mediators are involved. Studies reveal that the bacterial infection predominate the cytokines of Th1 phenotype with secretion of abundant levels of IFN-gamma and IL-2 by mucosal T cells. The inability of patients to clear *H. pylori* infections is a consequence of active immunosuppression and evasive mechanisms of bacteria. Many immune factors are involved: chronic exposure of the DCs to *H. pylori* leading to DC exhaustion, influence of regulatory T (Treg) cells through immunosuppressive cytokines, and the mast cells that change the gastric mucosal environments among others.

In the current review, the focus is restricted to Tregs and their participation in the anti-bacterial response. These cells are a heterogeneous T-cell subpopulation with biological actions determinants in the pathogenesis of *H. pylori* infection. Studies have demonstrated that the activation of Treg cells cause down-regulation of adaptive immunity facilitating the persistence of infection by *H. pylori*. Even, the regulations of the Th1/Treg and Th1/Treg balances are important in the immune response against the pathogen, in the persistent colonization of the bacterium and in the affectation of the gastrointestinal system.

Keywords: *Helicobacter pylori*; Regulatory T cells; Cytokines

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►Article type: Review Article; Received: 03 May 2012; Revised: 17 Jul 2012; Accepted: 08 Aug 2012; Epub: 01 Jun 2013; Ppub: Jun 2013

►Implication for health policy/practice/research/medical education:

Studies of Regulatory T cells in *Helicobacter pylori* infection can stimulate further research to search new treatments that affect the immune system and control the bacterial infection. Factors that contribute to the failure of the immune response to clear the bacterial organism have not been fully elucidated. The generation of a marked Treg has recently been postulated as key factor in this failure. The implementation of health policies and the disclosure of knowledge are the result of new research contributions

►Please cite this paper as:

Romero-Adrià T, Leal-Montiel J. *Helicobacter pylori* Infection: Regulatory T Cells and Their Participation in the Immune Response. Jundishapur J Microbiol. 2013;6(4):e5183. DOI: 10.5812/jjm.5183.

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1. Introduction

Helicobacter pylori is a motile Gram-negative spiral bacterium that colonizes the human gastric epithelium. It was first reported to be successfully cultured from patient biopsies under micro-aerophilic conditions in 1984 (1). Infection is believed to occur predominantly in early childhood, and it persists for life unless successfully treated with antimicrobial therapy. In developing countries more than 80% of the adult population can be infected (2). In Waro communities of Venezuela, the seroprevalence of the infection was 38% in children and 84% in their mothers (3, 4). *H. pylori* has been classified by the WHO as a Group I carcinogen (5).

H. pylori outer membrane proteins, including *BabA*, *SabA*, *AlpA*, *AlpB*, and *HopZ*, can mediate *H. pylori* adherence to gastric epithelial cells for the activation of numerous signaling pathways (6) and permits efficient delivery of toxins or other effector molecules into the cells. Studies in an animal model indicate that attachment of *H. pylori* to epithelial cells is involved in gastric mucosal inflammation, production of autoantibodies, and parietal cell loss (7). Several *H. pylori* factors are known to interact directly with immune cells and modulate immune responses to *H. pylori*. For example, *VacA* alters the function of T lymphocytes, B cells, macrophages, and mast cells (8-11) and *HP-NAP* acts on neutrophils, mast cells, and monocytes (12, 13).

For many years, studies have been conducted involving the subset of T cells and cytokines in different physiological and pathological clinical entities (14-22). In *H. pylori* infection all investigations indicate the predominance of the Th1 response (14, 21, 23). However, other cellular phenotypes such as Th2, Th17 and Treg that secrete immunomodulate cytokines may participate (21). In the setting of *H. pylori* infection, multiple cytokines in the gastric mucosa (including TNF, IFN- γ , IL-1 β , IL-6, IL-8, and IL-18) are predicted to have proinflammatory effects, whereas IL-10 and TGF- β are cytokines that may limit the inflammatory response (21). Early studies suggest that IL-2 is specifically required for the development and maintenance of nTregs (24). Research shows that interactions among epithelial cells, DC and T cells bridged by cytokines are important for the generation of thymic nTregs (25). Preserved functionality of Treg cells can facilitate the immune response against infectious agents due to their regulatory effects on other subpopulations of T lymphocytes and recruitment of cells at the site of infection (26).

2. Regulatory T cells: General Characteristics

With the development of new technologies in the 1990s convincing evidences are presented in relation to the existence of immunosuppressive cells called Regulatory T cells (27).

There are different subsets of Treg cells. CD4+CD25^{high}

Treg cells are the best-described subset. A key characteristic of CD4+CD25^{high} Treg cells is its ability to induce anergy in vitro and suppress immune responses (28, 29). Some studies suggest that CD4+CD25^{high} Treg cells inhibit proliferation of effector CD4+CD25-T cells and CD8+ T cells by arresting the proliferation of these cells at G1-S interphase of the cell cycle (30). Recent data also indicate that CD4+CD25^{high} Treg cells regulate through their cytokines to Th17 cells (31). The total number of CD4+CD25^{high} Treg cells in human peripheral blood increases with age, despite thymic involution (32). Surface markers associated with CD4+CD25^{high} Treg cells are of identification, homing/trafficking, activation/cell death and suppressive function. These cells have been classified into into natural (n) and inducible (i). The first originated in the thymus and the second coming of naive T cells. Natural Treg cells represent 5-10% of CD4+CD8- thymocytes in humans, mice, and rats (33).

CD4+CD25^{high} Treg cells participate in immune responses against malignant cells (34, 35) allogeneic organs, stem-cell grafts (36) and infectious agents (37). Although CD4+CD25^{high} Treg cells regulate both Th1 and Th2 immune responses, Th2 cells may partially escape this suppressive activity by regulating protein, such as IL-4, IL-7, and IL- contrast, the proliferation of Th1 cells is only restored by the administration of IL-15 (38). Under appropriate conditions, CD4+CD25^{high} Treg cells are able to confer suppressive capacity on CD4+CD25- T cells, converting them to either Th3 or Tr1 cells (39, 40). Also, Treg cells possess properties of plasticity and interconvertibility under certain circumstances. These cells are transformed into others phenotypes such as Th1, Th2 and Th17 (41, 42).

3. Role of Regulatory T cells in the *Helicobacter pylori* Infection

Investigations have implicated Treg cells in the pathogenesis of the *Helicobacter pylori* infection. Treg cells suppress excessive activation of CD4+ as well as CD8+ to control gastric inflammation and persistent colonization of the bacterium (43, 44).

Studies show that *H. pylori*-infected individuals have increased frequencies of CD4+CD25^{high} T cells in both the stomach and duodenal mucosa compared to uninfected controls. These cells express FOXP3, a key gene for the development and function of Treg cells, as well as high levels of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) proteins. Mucosal CD4+CD25^{high} T cells are present in individuals with asymptomatic *H. pylori* infections as well as in duodenal ulcer patients. The frequencies of CD4+CD25^{high} cells are also increased in the stomachs of *H. pylori*-infected patients with gastric adenocarcinoma (45). These findings suggest that regulatory T cells may suppress mucosal immune responses and thereby contribute to the persistence of *H. pylori* infections (46).

A recent study has demonstrated the elevation and positive correlation of Tregs with histological grade of chronic gastritis, atrophic gastritis and adenocarcinoma, and its decrease and negative correlation with histological grade of intestinal metaplasia. However, the relationship between CD4+CD25+ Tregs and precancerous lesions of the stomach remain unclear (47).

Researchers have shown that the decrease of the gastric inflammation in infected children is associated with a marked increment in the number of Treg cells and the levels of their cytokines such as IL-10 and TGF- β . IL-10-producing T lymphocytes are important in the control of inflammation induced by *H. pylori* and facilitate persistence of the bacterium on the gastric mucosa. This is not observed in mice with IL-10 “knockout” (48, 49). Investigations have shown that TGF- β acts inhibited the secretion of pro-inflammatory cytokines: Th1 and Th17. “Knockout” mice for TGF- β develop a deadly generalized inflammation (50). Study has demonstrated that the naïve CD4+ T cell development into Treg was enhanced in the presence of GECs (Gastric Epithelial Cells) derived TGF- β . This cytokine may be among the key factors which direct the T cell response during *H. pylori* infection (51). Treg cells regulate and maintain the tissue injury and overwhelming infection in balance. Excessive Treg activity is observed in persistent infections such leishmaniasis, malaria, tuberculosis (52-54), *H. pylori* infection, Human Immunodeficiency Virus (HIV) and Hepatitis C Virus (HCV) infections (46, 55-57), suggesting the possibility of a link between pathogen persistence and Treg mediated suppression.

Studies have revealed that *H. pylori*-infected patients express increased levels of FOXP3 mRNA and protein in gastric lymphocytes. The induction of the Treg response contributes to equilibrium between the host and the bacterium not only the survival of *H. pylori* but also the prevention of the destructive inflammation (58). Other studies agree with these results and show an inverse relationship between the risk of peptic ulcer disease and the frequency of regulatory T cells. Even, indicate that the reduction of Treg increases bacterial colonization (45). The induction of Tregs by *H. pylori* may prove to be a major adaptation to evade host immunity. The bacterium is able to stimulate DCs to prime Tregs and the functional significance of *H. pylori*-induced Treg response is the restriction of Th17 priming. Inhibition of Th17 immunity may allow chronic persistence of the bacteria (59), Researchers (45) indicate that the potent Treg response may affect the development of vaccine against *H. pylori*.

Studies show that Tregs did not increase in peripheral blood in *H. pylori*-infected patients, but the activation of humoral immunity and Th2 polarization was appreciated. These changes may induce systemic autoimmune diseases (60).

It can be hypothesized that the regulations of the Th17/

Treg and Th1/Treg balances are important in the response immune in the *H. pylori* infection. The Tregs cells exert their immunosuppressive effects on other cellular phenotypes (Th1, Th2 and Th17) based on the functional activity and secretion of cytokines. Therefore, to understand the development of Tregs during infection with *H. pylori* it is crucial to interpret not only the immunopathogenic mechanisms involved but also multiple outcomes of the infection. Certainly, the *H. pylori* infection is a multi-factorial pathology and each of the host (genetic and nutritional state) and bacterium (virulent strains and multiple strains) dependent factors have their influences on the immune system. Also, a concomitant helminthic infection that triggers Th2 phenotype may affect the Th1 cell responses associated with *H. pylori* infection and limit the pathological consequences of *H. pylori* gastric colonization; in particular, gastric atrophy (21, 61).

The identification of regulatory T cells and their cytokines at the site of *H. pylori* infection in humans may also have important implications to understand to understand immune responses to other infections.

4. Conclusions

Many cells and mediators are involved in the pathogenesis of *H. pylori* infection. Inflammation of the gastric mucosa is dependent on T lymphocytes. Studies have shown that mice deficient in T cells and infected by the bacteria do not develop gastritis. It is considered that specific regulatory T cells that suppress memory T cells could contribute to the persistence of the pathogen. Studies have demonstrated that Tregs have different regulatory mechanisms at their disposal. They can be divided into four basic modes of action such as inhibitory cytokines, cytolysis, metabolic disruption and modulation of APC function. The consequences of Treg mediated suppression of the immune response during infection are controversial. Studies show that while Treg cells, limit local tissue damage and prevent sterilizing immunity against the pathogen, allow the persistent of infection.

This results in protective immunity against a subsequent bacterial challenge. While this ‘symbiotic relationship’ may be beneficial to the host, there is also evidence to suggest that Tregs can be detrimental to the host. The regulations of the Th17/Treg and Th1/Treg balances may influence intestinal immunity and tolerance, dictating the outcome of luminal bacterial infection. More knowledge about the molecular mechanisms driving Treg cell proliferation, activation, and survival is required.

Acknowledgements

We are grateful to research staff at the Institute of Biological Research Faculty of Medicine University of Zulia, Maracaibo, Venezuela for its constructive advice in the preparation of the manuscript.

Financial Disclosure

This work was funded by the Institute of Biological Research Faculty of Medicine University of Zulia, Maracaibo, Venezuela.

Funding Support

None Declared.

Authors' Contribution

None declared.

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