Helicobacter pylori Infection: Participation of Cytokines in the Immune Response and in the Consequences Pathological Clinic. Mini Review

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Abstract

Helicobacter pylori (*H. Pylori*) infection affects 50% of world population but shows variations in its geographical distribution, and is related to various gastric pathologies such as: symptomatic gastritis, peptic ulcers, and malignant tumors. The pathogenesis of *H. pylori*-related chronic gastritis and the mechanism responsible for the change into neoplasm are still debated. The roles of cytokines and chemokines in the carcinogenicity of *H.* pylori have been investigated. *H. Pylori* infection is a multi-factorial pathology and each of the host and bacterium dependent factors have their influences on the immune system. The inflammatory response in infection by *H. Pylori* determines: the production of gastric cytokines, the alteration of acid homeostasis, which directly impacts the colonization pattern of the bacterium and the extension of the gastritis. Studies on humans, non-human primates and rodents have reported that the Th1 phenotype predominates in the immune system response to infection by *H. pylori*. The cytokines produced by this phenotype, are not effective in eradicating the microorganism and furthermore, contribute to gastroduodenal pathogenesis. Factors involved in the failure of the immune response to clear the organism have not been fully elucidated; however, insufficient dendritic cells activation and the generation of a marked regulatory T (Treg) cells response have been postulated as key factors in this failure. Treg cells are important in the down- regulating adaptive immunity during the infection and may contribute to the long-term chronicity. For many years, studies have been conducted involving the subset of T cells and cytokines in different physiological and pathological conditions. The immune imbalance is key in pathology clinic consequences of the infection caused by *H. pylori*. However, it is must consider the inherent properties of the bacterial strain, the genetic predisposition, polymorphism of cytokines, the host nutritional state, the concurrent infections (protozoans) and the infestations (helminths) to evaluate the outcome final. A network of events leads to the establishment, development and consequences of infection.

Keywords: Helicobacter pylori; Cytokines; Immune Response; Lymphocytes; Gastrointestinal Diseases

Introduction

Helicobacter pylori (*H. Pylori*) infection has been diagnosed throughout the world and in all age groups. It is estimated that 50% of world population is affected but shows variations in its geographical distribution. In developing countries, where most children are infected before age 10, the adult prevalence reaches 80% before 50 years [1]. This infection is related to various gastric pathologies such as: symptomatic gastritis, peptic ulcers, and malignant tumors [1,2]. The World Health Organization has considered this bacterium as a class I carcinogen since 1994 [3]. The global prevalence of gastric cancer has increased from 1 to 3% among people infected with *H. Pylori* [4].

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The pathogenesis of *H. pylori*-related chronic gastritis and the mechanism responsible for the change into neoplasm are still debated. The roles of cytokines and chemokines in the carcinogenicity of *H. pylori* have been investigated in many researches. These regulating proteins which are related to the increased gastric carcinoma (GC) risk in the premalignant period, could explain the chronic inflammation-mediated neoplastic changes and its use as early predictive diagnostic molecular markers. The molecular mechanisms of local immune response initiated by *H. pylori* are complex, but it is believed that cytokines produced by both immune and non-immune cells amplify the ongoing inflammation [5].

Helicobacter pylori and participation of cytokines

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. In the bacterial infection, the participant cells are: neutrophils, epithelial cells, dendritic cells, monocytes, macrophages, lymphocytes, mast cells and NK. There are various effector CD4 Th cells that participate in the immune response during the infection: Th1, Th2, Th17, Th22 and regulatory T (Treg) cells which secrete different cytokine and chemokine profiles. Th1 pro-inflammatory cytokines are interleukin-2 (IL-2), interleukin -12 (IL-12), interferon gamma (IFN-γ), and tumor necrosis factor (TNF-α). They can cause tissue damage and elicit unwanted inflammatory disease and self-reactivity. Th2 anti-inflammatory cytokines are interleukin (IL-4), interleukin-5(IL-5), interleukin-6 (IL-6), interleukin-9 (IL-9), interleukin-10 (IL-10), interleukin-13(IL-13) and transforming growth factor beta (TGF-β) [6,7]. Th1 immunity is important in antitumor activity and antibacterial, and Th2 immunity is dominant in advanced carcinomas. Studies on humans, non-human primates and rodents have reported that the Th1 phenotype predominates in the immune system response to infection by *H. pylori* [8-10]. The cytokines produced by this phenotype, are not effective in eradicating the microorganism and furthermore, contribute to gastroduodenal pathogenesis [11]. It has demonstrated that concurrent infections with helminths parasites can determine a Th2 response that inhibits the Th1 phenotype and attenuates the gastric pathology induced by Th1 [12]. In the case of infection by protozoa such as *T. gondii*, which induces the Th1 phenotypes, gastric inflammation produced by *H. felis* is increased, as well as the atrophy and loss of parietal cells in balb/c mice [13]. Interleukin-4 (IL-4) an anti-inflammatory regulating protein inhibits to the Th1 phenotype and to the Treg cells. Also, this cytokine stimulus the somatostatin which decreases the gastric acid secretion. Th1 cytokines are important in immune defense anti-bacterial, and the Treg cells are involved in the tolerance and homeostasis. Treg cells secrete immunosuppressive regulating proteins, such as: IL-10 and TGF-β which are inhibitory and anti-inflammatory [6,7].

Researchers have demonstrated that the number of Treg cells are elevated and positively correlated with histological grade of chronic gastritis, atrophic gastritis and adenocarcinoma, but is decreased and negatively correlated with histological grade of intestinal metaplasia [14]. Th17 secretes: interleukin-8 (IL-8), interleukin-17 (IL-17), interleukin-21(IL-21), interleukin-22 (IL-22), interleukin-26 (IL-26), TNF- α, granulocyte colony stimulant factor (G-CSF) and various chemokines which are pro inflammatory [6]. Th22 secretes: IL-22 a member of the IL-10 cytokine family [15]. It can be expressed and secreted by others T cell subsets including Th1, Th17, γδ T cells, natural killer T cells [16,17]. While IL-22 acts synergistically with a number of cytokines including TNF- α, interleukin-1 beta (IL-1β) and IL-17A, it can also act independently [18]. IL-22 mainly acts on epithelial cells and hepatocytes [19-21]. Its functions include antimicrobial defense, cell regeneration and protection against tissue damage. Like other cytokines, IL-22 has both pro-inflammatory and anti-inflammatory effects [21]. In *H. Pylori* infection, the polymorphisms in IL22 were found to be associated significantly with gastric mucosa-associated lymphoid tissue (MALT) lymphoma.This study demonstrated that when *H. Pylori* patients had higher IL-22 expression they were more likely to respond to therapy [22].

The quantitative differences of the cytokines in *H. pylori*–induced gastric mucosal inflammation may play a pivotal role in determining the various clinical outcomes of this infection. Certainly, genotypes have been associated with clinical severity. The inflammatory response in infection by *H. Pylori* determines: the production of gastric cytokines, the alteration of acid homeostasis, which directly impacts the colonization pattern of the bacterium and the extension of the gastritis. In the bacterial infection many cells participate with different biological actions and outcome that depends on the factors involved (host and bacterium) already mentioned. In this regard, it has demonstrated that the chronic exposure of the dendritic cells (DCs) to *H. Pylori* causes a loss of capacity to induce a Th1 response, which

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contributes to the persistence of the infection. Treg cells are important in the down- regulating adaptive immunity during the infection and may contribute to the long-term chronicity. The local activation of NK cells in the infected mucosa can decrease the bacterial load and are, therefore, key elements in the immune defense against the pathogen [7].

Conclusions

Despite the development of immune responses against *H. Pylori* infection, the bacteria are rarely eliminated and the colonization is generally persistent. Factors that contribute to the failure of the immune response to clear the organism have not been fully elucidated; however, insufficient DCs activation and the generation of a marked Treg response have been postulated as key factors in this failure. Also, *H. Pylori* and their components have the capacity to cause apoptosis of cells of immune system [7].

For many years, studies have been conducted involving the subset of T cells and cytokines in different physiological and pathological conditions [5-11,15-22]. The immune imbalance is key in pathology clinic consequences of the infection caused by *H. pylori*. However, it is must consider the inherent properties of the bacterial strain, the genetic predisposition, polymorphism of cytokines, the concurrent infections (protozoans) and the infestations (helminths), among other factors. A network of events leads to the establishment, development and consequences of infection.

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