H.PYLORI INDUCE GASTERIC CARCINOMA CORRELATION BETWEE SERUM IL17 AND NK CELL ACTIVATING FACTOR IL15 LEVEL

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INTRODUCTION

Helicobacter pylori

is a gram-negative, helically-shaped, microaerophilic bacterium usually found in the stomach.[6] Its helical shape (from which the genus name, helicobacter, derives) is thought to have evolved in order to penetrate the mucoid lining of the stomach and thereby establish infection.[7][8] The bacterium was first identified in 1982 by Australian doctors Barry Marshall and Robin Warren, who found that it was present in a person with chronic gastritis and gastric ulcers, conditions not previously believed to have a microbial cause.[9][10][11] HP has been associated with the mucosa-associated lymphoid tissue in the stomach, esophagus, colon, rectum, or tissues around the eye (termed extranodal marginal zone B-cell lymphoma of the cited organ),[12][13][14] and of lymphoid tissue in the stomach (termed diffuse large B-cell lymphoma).[15]

Signs and symptoms

Up to 90% of people infected with *H. pylori* never experience symptoms or complications.[24] However, individuals infected with *H. pylori* have a 10 to 20% lifetime risk of developing peptic ulcers.[25][26] Acute infection may appear as an acute gastritis with abdominal pain (stomach ache) or nausea.[3] Where this develops into chronic gastritis, the symptoms, if present, are often those of non-ulcer dyspepsia: stomach pains, nausea, bloating, belching, and sometimes vomiting.[27][28] Pain typically occurs when the stomach is empty, between meals, and in the early morning hours, but it can also occur at other times. Less common ulcer symptoms include nausea, vomiting, and loss of appetite. Bleeding in the stomach can also occur as evidenced by the passage of black stools; prolonged bleeding may cause anemia leading to weakness and fatigue. If bleeding is heavy, hematemesis, hematochezia, or melena may occur. Inflammation of the pyloric antrum, which connects the stomach to

the duodenum, is more likely to lead to duodenal ulcers, while inflammation of the corpus (i.e. body of the stomach) is more likely to lead to gastric ulcers.[29][30] Individuals infected with *H. pylori* may also develop colorectal[31][32] or gastric[33] polyps, i.e. a non-cancerous growth of tissue projecting from the mucous membranes of these organs. Usually, these polyps are asymptomatic but gastric polyps may be the cause of dyspepsia, heartburn, bleeding from the upper gastrointestinal tract, and, rarely, gastric outlet obstruction[33] while colorectal polyps may be the cause of rectal bleeding, anemia, constipation, diarrhea, weight loss, and abdominal pain.[34]

Individuals with chronic *H. pylori* infection have an increased risk of acquiring a cancer that is directly related to this infection.[13][14][25][26] These cancers are stomach adenocarcinoma, less commonly diffuse large B-cell lymphoma of the stomach,[15] or extranodal marginal zone B-cell lymphomas of the stomach,[35][36] or, more rarely, of the colon,[14][36] rectum,[37] esophagus,[38] or ocular adenexa (i.e. orbit, conjunctiva, and/or eyelids).[39][40] The signs, symptoms, pathophysiology, and diagnoses of these cancers are given in the cited linkages

Morphology

Helicobacter pylori is a helix-shaped (classified as a curved rod, not spirochaete) Gram-negative bacterium about 3 µm long with a diameter of about 0.5µm. *H. pylori* can be demonstrated in tissue by Gram stain, Giemsa stain, haematoxylin–eosin stain, Warthin–Starry silver stain, acridine orange stain, and phase-contrast microscopy. It is capable of forming biofilms[41] and can convert from spiral to a possibly viable but nonculturable coccoid form.[42]

Helicobacter pylori has four to six flagella at the same location; all gastric and enterohepatic *Helicobacter* species are highly motile owing to flagella.[43] The characteristic sheathed flagellar filaments of *Helicobacter* are composed of two copolymerized flagellins, FlaA and FlaB.[44]

Pathophysiology

Adaptation to the stomach

To avoid the acidic environment of the interior of the stomach (lumen), *H. pylori* uses its flagella to burrow into the mucus lining of the stomach to reach the epithelial cells underneath, where it is less acidic.[54] *H. pylori* is able to sense the pH gradient in the mucus and move towards the less acidic region (chemotaxis). This also keeps the bacteria from being swept away into the lumen with the bacteria's mucus environment, which is constantly moving from its site of creation at the epithelium to its dissolution at the lumen interface.[58]

H. pylori urease enzyme diagram

H. pylori is found in the mucus, on the inner surface of the epithelium, and occasionally inside the epithelial cells themselves.[9] It adheres to the epithelial cells by producing adhesins, which bind to lipids and carbohydrates in the epithelial cell membrane. One such adhesin, BabA, binds to the Lewis b antigen displayed on the surface of stomach epithelial cells.[6] *H. pylori* adherence via BabA is acid sensitive and can be fully reversed by decreased pH. It has been proposed that BabA's acid responsiveness enables adherence while also allowing an effective escape from unfavorable environment at pH that is harmful to the organism.[51] Another such adhesin, SabA, binds to increased levels of sialyl-Lewis x antigen expressed on gastric mucosa.[42]

In addition to using chemotaxis to avoid areas of low pH, *H. pylori* also neutralizes the acid in its environment by producing large amounts of urease, which breaks down the urea present in the stomach

to carbon dioxide and ammonia. These react with the strong acids in the environment to produce a neutralized area around *H. pylori*.[43] Urease knockout mutants are incapable of colonization. In fact, urease expression is not only required for establishing initial colonization but also for maintaining chronic infection.[44]

Cancer

Two related mechanisms by which *H. pylori* could promote cancer are under investigation. One mechanism involves the enhanced production of free radicals near *H. pylori* and an increased rate of host cell mutation. The other proposed mechanism has been called a "perigenetic pathway",[9] and involves enhancement of the transformed host cell phenotype by means of alterations in cell proteins, such as adhesion proteins. *H. pylori* has been proposed to induce inflammation and locally high levels of TNF-α and/or interleukin 6 (IL-6). According to the proposed perigenetic mechanism, inflammation-associated signaling molecules, such as TNF-α, can alter gastric epithelial cell adhesion and lead to the dispersion and migration of mutated epithelial cells without the need for additional mutations in tumor suppressor genes, such as genes that code for cell adhesion proteins.[8]

The strain of *H. pylori* a person is exposed to may influence the risk of developing gastric cancer. Strains of *H. pylori* that produce high levels of two proteins, vacuolating toxin A (VacA) and the cytotoxin-associated gene A (CagA), appear to cause greater tissue damage than those that produce lower levels or that lack those genes completely.[6] These proteins are directly toxic to cells lining the stomach and signal strongly to the immune system that an invasion is under way. As a result of the bacterial presence, neutrophils and macrophages set up residence in the tissue to fight the bacteria assault.[41]

H. pylori is a major source of worldwide cancer mortality.[22] Although the data varies between different countries, overall about 1% to 3% of people infected with *Helicobacter pylori* develop gastric cancer in their

lifetime compared to 0.13% of individuals who have had no *H. pylori* infection.[3 3][7] *H. pylori* infection is very prevalent. As evaluated in 2002, it is present in the gastric tissues of 74% of middle-aged adults in developing countries and 58% in developed countries. Since 1% to 3% of infected individuals are likely to develop gastric cancer, *H. pylori*-induced gastric cancer is the third highest cause of worldwide cancer mortality as of 2018.[52]

Infection by *H. pylori* causes no symptoms in about 80% of those infected.[47] About 75% of individuals infected with *H. pylori* develop gastritis Thus, the usual consequence of *H. pylori* infection is chronic asymptomatic gastritis.[19] Because of the usual lack of symptoms, when gastric cancer is finally diagnosed it is often fairly advanced. More than half of gastric cancer patients have lymph node metastasis when they are initially diagnosed.[9]

Diagnosis

Colonization with *H. pylori* is not a disease in and of itself, but a condition associated with a number of disorders of the upper gastrointestinal tract.[26] Testing for *H. pylori* is not routinely recommended.[26] Testing is recommended if peptic ulcer disease or low-grade gastric MALT lymphoma is present, after endoscopic resection of early gastric cancer, for first-degree relatives with gastric cancer, and in certain cases of dyspepsia.[] Several methods of testing exist, including invasive and noninvasive testing methods.

Noninvasive tests for *H. pylori* infection may be suitable and include blood antibody tests, stool antigen tests, or the carbon urea breath test (in which the patient drinks ^{14}C—or ^{13}C-labelled urea, which the bacterium metabolizes, producing labelled carbon dioxide that can be detected in the breath). [16] It is not known which non-invasive test is more accurate for diagnosing a *H. pylori* infection, and the clinical significance of the levels obtained with these tests are not

clear.[26] Some drugs can affect *H. pylori* urease activity and give false negatives with the urea-based tests.

An endoscopic biopsy is an invasive means to test for *H. pylori* infection. Low-level infections can be missed by biopsy, so multiple samples are recommended. The most accurate method for detecting *H. pylori* infection is with a histological examination from two sites after endoscopic biopsy, combined with either a rapid urease test or microbial culture.[17]

Transmission

Helicobacter *pylori* is contagious, although the exact route of transmission is not known. Person-to-person transmission by either the oral–oral or fecal–oral route is most likely. Consistent with these transmission routes, the bacteria have been isolated from feces, saliva, and dental plaque of some infected people. Findings suggest *H. pylori* is more easily transmitted by gastric mucus than saliva.[8] Transmission occurs mainly within families in developed nations, yet can also be acquired from the community in developing countries.[10] *H. pylori* may also be transmitted orally by means of fecal matter through the ingestion of waste-tainted water, so a hygienic environment could help decrease the risk of *H. pylori* infection.[8]

Treatment

Gastritis

Superficial gastritis, either acute or chronic, is the most common manifestation of *H. pylori* infection. The signs and symptoms of this gastritis have been found to remit spontaneously in many individuals without resorting to *Helicobacter pylori* eradication protocols. The *H. pylori* bacterial infection persists after remission in these cases. Various antibiotic plus proton pump inhibitor drug regimens are used to eradicate the bacterium and thereby successfully treat the

disorder[18] with triple-drug therapy consisting of clarithromycin, amoxicillin, and a proton-pump inhibitor given for 14–21 days often being considered first line treatment.[11]

IL-17 is involved in *Helicobacter pylori*-Induced Gastric Inflammatory Responses

***Helicobacter pylori* (*H. pylori*) is the major cause of chronic active gastritis and peptic ulcer disease. Recent studies have shown that *H. pylori* produces various cytokines that are related to neutrophil or mononuclear cell accumulation. Interleukin-17 (IL-17) is the founding member of an emmerging family of inflammatory cytokines whose biological activities remain incompletely defined. In this study, the contributions of IL-17 to the induction of gastric inflammation and to the protection from *H. pylori* infection were investigated using IL-17 gene-knockout (IL-17$^{-/-}$).**

IL-17 is the founding member of an emmerging family of inflammatory cytokines whose biological activities remain incompletely defined [1]. IL-17 is a T cell-drivered cytokine produced predominantly by the T memory compartment(1). IL-17 has pleiotrophic activities including the induction of proinflamatory cytokines such as TNF-α, IL-1β, and IL-6, and chemokines like IL-8 and monocyte chemoattractant protein 1 on various cell types. In addition, IL-17 is involved in the induction of inducible nitric oxde synthase and cyclooxygenase 2 in chondrocytes, induction of prostaglandin E2-mediated osteoclast differentiation factor expression in osteoblasts, up-regulation of intracellular adhesion molecule 1 and HLA-DR expression in kerationocytes, promotion of stem cell factor and granulocyte-colony stimulating factor-mediated granulopoiesis, promotion of tumor rejection by natural killer cell activation, and enhancement of allorejection via promotion of dendritic cell maturation. IL-17 stimulates IL-8 release by gastric epithelial cells and facilitates the chemotaxis of neutrophils through an IL-8-dependent

mechanism, and contributes to the enhancement of IL-8 levels in *H. pylori*-colonized gastric mucosa [2].Recent studies reported that IL-17 stimulates IL-8 release by gastric epithelial cells and facilitates the chemotaxis of neutrophils through an IL-8-dependent mechanism, and contributes to the enhancement of IL-8 levels in *H. pylori*-colonized gastric mucosa.[3,4].However, in vivo studies using IL-17 gene-knockout mice has not reported to investigate the role of IL-17 in *H. pylori* infection. In the present study, we designed a *H. pylori*-infected IL-17 gene-knockout mouse model and investigated the role of IL-17 in the development of gastric inflammation.

Interleukin 15: Its Role in Inflammation and Immunity

Interleukin 15 (IL-15) is a 14–15 kDa polypeptide that belongs to the 4 α-helix-bundle family of cytokines and was originally discovered due to its T cell proliferative activity. It utilizes the signal-transducing β/γ polypeptides of the IL-2 receptor complex, thus sharing many biological activities with IL-2, in addition to its high-affinity private receptor subunit IL-15Rα. Accumulating evidence indicates that the biological relevance of IL-15 may not solely be confined to T lymphocytes, but to a variety of cell populations within the immune system as well as outside the immune system of the host. The expression of both IL-15 and its high-affinity receptor component, IL-15Rα, are readily demonstrable in a wide variety of tissues and appear to be augmented in response to environmental/stress stimuli and infectious agents. There is increasing evidence to suggest that IL-15 may play an important role in protective immune responses, allograft rejection and the pathogenesis of autoimmune diseases, where mononuclear cell infiltration is a hallmark feature. Herein, the effects of IL-15 on cells associated with host defense, immunity and inflammation are reviewed and support a central role for this cytokine in orchestrating multiple aspects of effector functions in immunity and inflammation.(5)

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