METABOLOGY OF HELICOBACTER PYLORI INFECTION:
ROLE OF GASTROKINES

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Trillions of bacteria, collectively referred to as the microbiota, reside in gastrointestinal tract. Helicobacter (Campylobacter) pylori (H. pylori) is a Gram negative bacillus which infects about half of the world’s population. Its causative role in gastroduodenal disease is well known. Recent studies also implicated H. pylori infection in the pathobiology of autoimmune diseases such as rheumatoid arthritis and idiopathic thrombocytopenic purpura. However, little is known about H. pylori-associated alterations in metabolic pathways and food intake as related to cardiometabolic diseases such as atherosclerosis, obesity, diabetes, and metabolic syndrome. This novel approach is conceptualized as metabology of H. pylori infection. Here we Dance Round this specific topic, with special reference to possible roles played by gastric cell-secreted molecules such as leptin, ghrelin and various cytokines, collectively designated gastrokines. Biomed Rev 2006; 17: 123-128.

Keywords: Helicobacter pylori, cardiometabolic disease, cytokines, ghrelin, leptin, metabolism

INTRODUCTION

History of the stomach colonization by Helicobacter pylori

Trillions of bacteria, collectively referred to as the microbiota, reside in the gastrointestinal tract, Helicobacter (Campylobacter) pylori (H. pylori) being a member of this microbial society. In 1983 and 1984 Lancet published the first papers of two Australian physicians, Marshall and Warren (1,2), demonstrating H. pylori infection in biopsy specimens from patients with gastritis. In paper published in 1985, Marshall and colleagues (3) reported a personal experiment using oral administration of H. pylori suspension by Dr Marshall himself, resulted in the development of gastritis shortly after

*These authors contributed equally to this Dance Round.
infection (see also 4). In fact, the presence of spirochete-like bacteria in the stomach has been recognized since 1892 (see 5) (Table 1).

Here we Dance Round possible role of gastrokines in metabolic pathways and food intake as related to cardiometabolic diseases associated with *H. pylori* infection or its eradication.

**H. PYLORI INFECTION AND GASTOKINES**

**Biology of *H. pylori***

*H. pylori* is a curved or spiral shaped Gram negative, mobile bacterium. It measures 3-5 µm in length and approximately 0.5 µm in diameter. *H. pylori* colonizes the stomachs of roughly half of the world’s population and usually persists in the gastric mucosa of human hosts for decades or life. Family unit is generally accepted as one of the contributors to *H. pylori* infection that is most frequently acquired in childhood. Although most *H. pylori*-positive people are asymptomatic, the presence of *H. pylori* is associated with increased risk for the development of peptic ulcer disease, gastric adenocarcinoma and gastric lymphoma (reviewed in 5). The development of a sustained gastric inflammatory and immune response to *H. pylori* infection appears to play a pivotal role for the development of these diseases. During its long co-existence with humans, *H. pylori* has evolved complex strategies to maintain a low-grade inflammation of the gastric epithelium. Important local factors implicated in the pathobiology of *H. pylori* include urease-dependent NH$_3$ production and the bacterial cytotoxin associated gene A (CagA).

**Gastrokines: what in the name?**

Today, the number of “-kine” bioactive molecules as well as “-omics” sciences is dramatically increased. Generally referred to as cytokines and chemokines (Table 2), various molecules, depending on the cellular source of their secretion (synthesis, store, and release), were more specifically dubbed adipokines (6-10), myokines (11,12) or enterokines (13). Here we introduce the term “gastrokines” to connote the bioactive molecules secreted by selected gastric cells, using both paracrine and endocrine pathway (Table 3).

The host’s immune-inflammatory response, involving paracrine overproduction of pro-inflammatory cytokines such

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**Table 1. History of the discovery of Helicobacter pylori**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1892</td>
<td>Bizzozero: snake-line bodies in a dog stomach</td>
</tr>
<tr>
<td>1906</td>
<td>Krienitz: spirochete-like bodies in human stomach</td>
</tr>
<tr>
<td>1919</td>
<td>Kasai and Kobayashi: animal model for <em>H. pylori</em> infection and first <em>H. pylori</em> eradication</td>
</tr>
<tr>
<td>1936</td>
<td>Doenges: isolation of from a human stomach</td>
</tr>
<tr>
<td>1954</td>
<td>Palmer: completely disproved the presence of bacteria in stomach; the gastric lumen was believed to be aseptic about 30 years thereafter</td>
</tr>
<tr>
<td>1982</td>
<td>Warren and Marshal: detection and isolation form human stomach biopsy</td>
</tr>
<tr>
<td>1984</td>
<td>Recommendation of eradication therapy for all patients with peptic ulcers</td>
</tr>
<tr>
<td>1994</td>
<td>WHO: recognition as a carcinogen involved in the etiopatogenesis of gastric cancer</td>
</tr>
<tr>
<td>1997</td>
<td>Tomb: total genome analysis</td>
</tr>
<tr>
<td>2002</td>
<td>Marshal awarded the Keio Medical Prize</td>
</tr>
<tr>
<td>2005</td>
<td>Warren and Marshall awarded the Nobel prize in physiology or medicine</td>
</tr>
</tbody>
</table>

Modified from Suzuki et al (5). Note the gap between the years of 1954 and 1982, when the scientific progress in the field is blocked, a known phenomenon in science.
Metabolism of *H. pylori* infection

**Table 2. A selected list of anti- and pro-inflammatory signals**

<table>
<thead>
<tr>
<th>Anti-inflammatory signals</th>
<th>Pro-inflammatory signals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin</td>
<td>Tumor necrosis factor-α</td>
</tr>
<tr>
<td>Interleukin-10</td>
<td>Interleukin-1, -6, -18</td>
</tr>
<tr>
<td>Interleukin-1 receptor antagonist</td>
<td>Leptin</td>
</tr>
<tr>
<td>Nerve growth factor</td>
<td>FIZZ-1*, Resistin (FIZZ-3)</td>
</tr>
<tr>
<td>Prohibitin</td>
<td>MCP-1 (CCL2)**</td>
</tr>
<tr>
<td>Adrenomedullin</td>
<td>Interleukin-8 (CXCL8)</td>
</tr>
<tr>
<td></td>
<td>Eotaxin (CCL11)</td>
</tr>
<tr>
<td></td>
<td>RANTES** (CCL5)</td>
</tr>
</tbody>
</table>

Modified from Chaldakov *et al* (6). Note that all the listed mediators may also be secreted by adipose tissue cells (6-10,34-41).

* FIZZ, found in inflammatory zone – a member of FIZZ family of secreted proteins

** Monocyte chemoattractant protein-1 (cysteine cysteine modif chemokine ligand)

*** RANTES, regulated on activated normal T-cell expressed and secreted

**Table 3. A selected list of gastrokines and enterokines**

**Gastrokines***

Leptin, Ghrelin
Gastrin, Histamine
Somatostatin, Pancreastatin
IL-1, IL-6, IL-8, TNF-α
Neurotrophins (NGF, BDNF, NT-3, -4/5, -6)

**Enterokines***

Cholecystokinins
Peptide tyrosine tyrosine (PYY)
Orexin A and B
Incretins
 – glucagon-like protein-1
 – glucose-dependent insulino tropic protein

* As indicated (36-43,45,46)

** In agreement with “-kines” terminology, cholecystokinins, PYY, and orexins (30) and incretins (44), secretory products of specific populations of gut endocrine cells, may be classified as enterokines (13); their likely links to the metabolism of *H. pylori* infection remain to be examined
as interleukin-1 (IL-1), IL-6, tumor necrosis factor-alpha (TNF-α) and the chemokine IL-8 (CXCL8), is accompanied by the enhanced epithelial cell proliferation; these events being involved in the processes of gastric mucosal alterations, including carcinogenesis (5). Additionally, an H. pylori-induced chronic low-grade inflammation is involved in the pathogenesis of autoimmune diseases (14-16) and also cardiometabolic diseases such as atherosclerosis, obesity, diabetes, and metabolic syndrome (17-23).

The discovery of adipokines (6-10) and gastrointestinal cell-secreted factors (24-30) promotes investigations of possible relationship among inflammation, obesity-related diseases, and H. pylori infection. Under healthy conditions, the gastrointestinal mucosa is in a state of “controlled inflammation” regulated by a delicate balance of pro- and anti-inflammatory mediators, examples being shown in Table 2.

**H. pylori and gastric leptin**

A selected list of gastro(entero)kines is presented in Table 3, ghrelin and leptin being signature examples of these molecules (24-30,36-44). The “classical” leptin, an ob gene product, is adipocyte-secreted protein/cytokine (31). Leptin, via its yin-yang action on specific hypothalamic neurons, exerts an anorexic effect also associated with acute and chronic inflammation (32-35). Gastric leptin, in tandem with a local pro-inflammatory cytokine/chemokine network, may be involved in local and systemic inflammatory response to H. pylori infection. Several studies have indeed found (positive or negative) relations between H. pylori and risk of obesity and related diseases. For instance, eradication of H. pylori is associated with (i) decreased gastric leptin levels and subsequent weight gain (19), and (ii) an increase in both body mass index and cholesterol and triglyceride levels (40). Moreover, H. pylori infection is associated with upregulation of adipocyte genes, including those encoding for leptin, adiponectin, and resistin; an adipocentric insight (6-10,29-35) into H. pylori infection is a matter of our ongoing work.

**H. pylori and gastric ghrelin**

Although several other potent orexigenic peptides, including neuropeptide tyrosine (NPY) and agouti-related peptide, have been characterized in the brain, ghrelin is the first appetite-stimulating signal originating from the stomach (reviewed in 29,30). Ghrelin (“ghre”, meaning grow) is a 28-amino acid peptide (3.3 kD) that is synthesized predominantly in mucosal endocrine cells called A-like cells, which are located in the gastric corpus. Ghrelin was discovered in 1999 (27) and named for its ability to stimulate growth hormone (GH) secretion via activation of GH secretagogue receptor (5,28-30). However, ghrelin is much more that simply a natural GH secretagogue. Contrary to leptin, ghrelin has profound orexigenic properties, increasing food intake and reducing fat utilization; likewise, it exerts many effects similar to those of endocannabinoids, known food-intake-stimulating molecules (30). Altogether, leptin-ghrelin tango hypothesis of obesity was proposed (25; also 24,26); it may also be danced during H. pylori infection. Note that a prolonged period of breastfeeding has been shown to reduced the risk of obesity development, whereas gastric and plasma ghrelin concentration are maintained at a lower level by delayed weaning in rats (28).

Suzuki et al (5) studied the kinetics of ghrelin in animal model of H. pylori infection and found a gradual decrease in ghrelin-immunoreactive gastric cells, whereas clinical studies demonstrated that plasma ghrelin levels may be used as a marker for subjects at high risk of atrophic gastritis or gastric cancer. This remains to further be pursued in cardiometabolic disease (17-23,45,46).

**CONCLUSION**

Cardiometabolic disease is multifactorial in nature. Here we discussed that one important factor that may affect the metabolic pathways of glucose and lipids and also food intake comprise an altered secretion of gastrokines possibly triggered by H. pylori infection. In perspective, a possible involvement of enterokines and adipokines, other essential dancers in metabolism, inflammation, and food intake, may also be studied. Further, a metagenomic (human genome and microbial genome/microbiome) approach (47,48) to metabology of H. pylori infection may provide new insights into obesity and related cardiometabolic diseases.

**ACKNOWLEDGMENTS**

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