Equilibria of Humans and Our Indigenous Microbiota Affecting Asthma

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It is becoming increasingly clear that our residential microbes, the key constituents in the human microbiome, are centrally involved in many aspects of our physiology. In particular, the ancient and dominant gastric bacteria *Helicobacter pylori* are highly interactive with human physiology. In modern times, *H. pylori* has been disappearing, which consequently affects the interactions between luminal bacteria and epithelial, lymphoid, and neuroendocrine cells. A growing body of evidence indicates that *H. pylori* protects against childhood-onset asthma, probably through the gastric recruitment of regulatory T cells. The phenomenon of disappearing ancient microbiota may be a general paradigm driving the diseases of modernity.

Keywords: allergy; T cells; *Helicobacter pylori*; microbiota; immunity

The totality of cells in the human body has been estimated as 10¹⁴. Remarkably, 90% of these cells are the bacteria that we carry. These commensal bacteria are highly diverse, and the different types of genes that they collectively possess outnumber the different genes in the human genome by an estimated 100 to 1. Consequently, the study of the interactions of our collective microbes (termed the microbiome) and their genes (the metagenome) with human tissue has received considerable attention in recent years. In this brief report, I will focus on *Helicobacter pylori*, gram-negative bacteria that have been the dominant members of the microbiome colonizing the human stomach. The relationships between our dominant organisms and human biology are not accidental but likely have been highly programmed over long time periods (1). *H. pylori* serves both as an example of the ways in which our microbiota interact with us and as an important factor likely causally related to the risk of childhood-onset asthma.

H. pylori, AN ANCIENT CONSTITUENT OF THE HUMAN MICROBIOTA, IS INVOLVED IN GASTRIC PHYSIOLOGY

It now is clear that mammals carry gram-negative bacteria of the genus *Helicobacter* in their acid-producing stomach; *H. pylori* is the human representative. A large body of evidence now indicates that *H. pylori* has been colonizing humans since before the major “out-of-Africa” about 50,000 years ago, and that as our ancestors migrated around the planet, they took their *H. pylori*

strains with them (2). There are thus important geographic differences in the *H. pylori* strains that are carried. *H. pylori* have an intimate relationship with the gastric epithelium, with several adhesins, and a type IV secretion system that injects *H. pylori* constituents directly into host gastric epithelial cells (3). The constituents, including the CagA protein, affect the flow of cellular information in major signal transduction pathways. The *H. pylori*-induced epithelial cell interactions recruit inflammatory and immune cells to the gastric lamina propria. The interactions affect neuroendocrine (e.g., gastrin, somatostatin), inflammatory (e.g., multiple cytokines), and immune (both B- and T-cell) functions (3).

THE DISAPPEARANCE OF *H. pylori* AND ITS EFFECTS ON DISEASES OF THE UPPER GASTROINTESTINAL TRACT

Despite its long coexistence with humans and its dominance of the gastric niche (4), *H. pylori* has progressively become less prevalent over the last 100 years (5). The reasons for this trend have not been determined definitively, but changes in human lifestyles and practices (e.g., clean water, antibiotic use) likely play an important role (6). Now, with the ability to detect the presence or absence of *H. pylori* in individual hosts, we can determine its pathophysiologic significance. For the last 20 years, we have known that *H. pylori* increases risk of both peptic ulcer disease and gastric cancer (7–9). More recently, there has been evidence that *H. pylori* is inversely associated with gastroesophageal reflux disease and its neoplastic consequences, Barrett esophagus and adenocarcinomas of the esophagus and at the gastroesophageal junction (10, 11).

EPIDEMIOLOGIC STUDIES OF THE RELATIONSHIPS BETWEEN *H. pylori* AND ASTHMA AND RELATED DISORDERS

Asthma has been rising in prevalence (12) as *H. pylori* has been disappearing. *H. pylori* generally is acquired in the first few years of life, so lack of acquisition has the potential to change human physiology in some important ways. In three large, blinded independent epidemiologic studies that we performed, seropositivity to *H. pylori* was associated with decreased risk of childhood-onset (but not with adult-onset) asthma, as well as with allergic rhinitis and cutaneous allergies (5, 13, 14). The strongest inverse association was with CagA⁺ strains, consistent with their greater interaction with host cells. An increasing number of studies from many countries are showing such inverse associations with asthma and atopic disorders (15) of childhood. One interpretation of these findings is that childhood-onset asthma is primarily an allergic disorder, whereas adult-onset asthma is much more multifactorial, involving smoking, air pollution, and other environmental insults.

(Received in original form August 16, 2011; accepted in final form September 21, 2011)

Supported by National Institutes of Health grant R01GM63270 and by the Diane Belfer Program in Human Microbial Ecology.

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Proc Am Thorac Soc Vol 9, Iss. 2, pp 69–71, May 1, 2012

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DOI: 10.1513/pats.201108-048MS

Internet address: www.atsjournals.org

***H. pylori* AND IMMUNITY IN RELATION TO ASTHMA**

We have postulated four types of host interactions with the microbiome including regulated equilibria with well-evolved relationships (6). We hypothesized that the *H. pylori*-free stomach cross-signals in very different ways from the *H. pylori*-positive stomach. In 2011, Arnold and colleagues reported that age makes a difference in experimental *H. pylori* infections of mice (16). Compared with mice infected as adults, mice infected as neonates have higher levels of the organism and lower levels of humoral and cellular immune responses. In studies to define the role of *foxP3*⁺ helper T cells and transforming growth factor- β , Arnold and colleagues found that both were necessary for the tolerogenic response. These studies provide evidence that the host is responding to *H. pylori* with T-reg functions that induce a level of tolerance to *H. pylori*.

In clinical studies, Robinson and colleagues showed that gastric biopsies from *H. pylori*-positive patients had higher levels of T-helper cells and of their responses than did *H. pylori*-negative subjects (17). Similarly, markers for gastric T-reg function are significantly higher in *H. pylori*-positive compared with *H. pylori*-negative subjects (17), an effect that also may be reflected by circulating T-regs (K. Robinson and colleagues, unpublished observation). In 2006, Wunder and colleagues identified a glycolipid (P157) unique to *H. pylori* that has an effect on host immune responses (18). Chang and colleagues studied the role of P157 in an experimental murine model of asthma, based on sensitization to inhaled ovalbumin (19). It now is clear P157 recruits natural killer T cells into the inflammatory exudates. Importantly, exposure to P157 ameliorated asthma expression (in the graduated methacholine assay) as well as eosinophilic infiltrates. Chang and colleagues also showed that transfer of natural killer T cells from P157-exposed (or control-exposed) mice but not unexposed mice ameliorated the inflammatory responses in recipient mice subjected to the ovalbumin challenge (19). These studies provide direct evidence that a unique *H. pylori* constituent has immunomodulatory functions that can reduce the inflammatory cascade in experimental asthma.

Continuing their studies of experimental murine asthma using the ovalbumin challenge model, Arnold and colleagues explored the effects of *H. pylori* infection, especially comparing infection in early life (neonatal) or in adulthood (20). Their work clearly shows a protective role of persistent early life *H. pylori* infection, with a lesser effect from adult-acquired infection. Parallel results were obtained in a house dust-mite antigen exposure model. Finally, they showed that they could adaptively transfer the protection using purified CD4⁺ CD25⁺ T cells from the mice that were neonatally infected with *H. pylori*. In total, those recent studies provide experimental evidence that supports the hypothesis that *H. pylori* protects against childhood-onset asthma.

CONCLUSIONS

There is increasing evidence that gastric *H. pylori* colonization protects against common infections, including those leading to diarrheal diseases of childhood (21), and perhaps against tuberculosis (22). The studies of Perry and colleagues provide evidence that gastric *H. pylori* colonization enhances *Mycobacterium tuberculosis*-specific immunity and decreased reactivation in a primate model (20).

In conclusion, as humans are moving from *H. pylori*-positive to *H. pylori*-negative status, gastric physiology is changing (23). There now are well-documented differences in somatostatin, gastrin, ghrelin, and leptin regulation as well as in gastric acidity and T-regulatory populations (3, 24). These changes in physiology appear to be contributing to changes in incidence of several

diseases. Gastric cancer and peptic ulcer disease are becoming less common, but gastroesophageal reflux disease and its sequelae, asthma, and obesity all are increasing. The possibility that *H. pylori* (especially *cagA*⁺) is protective against childhood-onset asthma and that its disappearance is helping to fuel the worldwide asthma epidemic is especially attractive. Perhaps early life antibiotics are playing a role (25).

Is *H. pylori* good or bad for humans? Evidence is accumulating that *H. pylori* is beneficial by protecting against diseases acquired in early life (infections, asthma, obesity, and reflux) but is costly later in life (including peptic ulcer disease and gastric cancer) (3). Perhaps one day physicians will be restoring *H. pylori* to young children and eradicating it when they reach the age of 30 or 40 years, to maximize early life benefit and to minimize late-in-life risk. These are speculations at this point; however, this is the direction in which the data are pointing. If the disappearance of *H. pylori* is fueling the development of a disease (childhood-onset asthma) that is epidemic in our post-modern world, might disappearances of other ancient members of our microbiota be contributing to other ongoing epidemics? We need to address this issue.

Author disclosures are available with the text of this article at www.atsjournals.org.

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