Viral Commensalism in Humans?

Martin J. Blaser1,2 and Fred T. Valentine1

1Departments of Medicine and Microbiology, New York University School of Medicine, and 2VA Medical Center, New York, New York

(See the article by Matsumoto et al., on pages 10–5.)

In this issue of the Journal, Matsumoto et al. [1] asked whether human T lymphotropic virus type 1 (HTLV-1) antibody status is associated with the risk of developing gastric cancer. In a cohort of >5000 patients aged >40 years who were enrolled during 1989–1992 in an HTLV-1–endemic area, they identified 1812 subjects who underwent endoscopy of the upper gastrointestinal tract before 2003. Of those who were free of gastric cancer on that examination, 497 HTLV-1 antibody positive patients were selected and matched with 497 control patients who were HTLV-1 antibody negative. Both groups were followed for ~9.5 years to determine who would develop gastric cancer. The major finding of the study was that gastric cancer developed less frequently among HTLV-1–positive subjects than among HTLV-1–negative subjects (2.8% vs. 7.0%). The findings are convincing because no sources of differential bias were obvious, the results confirm and are similar to those of a previous study [2], the time courses in Kaplan-Meier analysis are internally consistent, and the results for men and women were parallel with similar levels of inverse association (odds ratio, 0.38). Thus, the inverse association between HTLV-1 infection and development of gastric cancer that was uncovered in this prospective study should be considered correct.

What do these findings mean? First, the findings may be flawed by confounders, but we could not find any. Second, it is possible that a preexisting host property that predisposes to HTLV-1 infection may lower the risk for gastric cancer development and that HTLV-1 positivity is just a marker for that host phenotype. Although this is plausible, there is no obvious mechanism to account for this possibility, especially when considering the transmission of HTLV-1 and the major gastric cancer–modifying agent, H. pylori.

Third, HTLV-1 infection may offer protection against gastric cancer. If this is correct, what could be the protective mechanisms? To address this possibility, we must consider the relationship of HTLV-1 with H. pylori.

We now know that gastric colonization with H. pylori, especially cagA-positive strains, is the major risk factor for typical (noncardia) gastric cancer [3], with attributable risk of ~80%. Could there be an interaction between HTLV-1 and H. pylori? This study and several previous studies provide evidence that HTLV-1–positive hosts carry H. pylori less often than do HTLV-1-negative hosts [1, 4, 5]. Thus, one potential explanation is that the immunological context created by HTLV-1 is inhibitory to H. pylori. This explanation, although attractive, probably is not sufficient, because the size of the H. pylori positivity rate differences with respect to HTLV-1 status may not be sufficiently large to account for the magnitude of the inverse association. An alternative possibility is that the immunologic context provided by HTLV-1 alters the host-H. pylori interaction in a way that lessens the risk of oncogenesis. This could occur by reduction of the extent or distribution of gastric inflammatory responses to H. pylori or, possibly, of the progression of inflammation into atrophy and intestinal metaplasia. Since HTLV-1 is acquired early in life [1, 2], its acquisition could affect the milieu in which a subsequent H. pylori colonization takes root; a precedent for early life phenomena to affect H. pylori–associated risk of gastric cancer decades later recently has been reported [6].

The interactions of HTLV-1 and humans are complex. Only 0.1%–3% of HTLV-1 infections result in T cell leukemia. Most often infection is chronic and indolent with little viral replication, exceeded by larger amounts of latent, integrated provirus [7]. HTLV-1 infection also is associated with some degree of immunosuppression [8, 9], possibly because of its propensity to establish a clinically silent low-grade infection in T lymphocytes distorting cytokine production [10]. HTLV-1 also stimulates polyclonal activation of lymphocytes without infecting
them [11], can transform cells because of its transactivating tax protein [6, 10], and, uncommonly, may infect cells other than T lymphocytes [12–14]. HTLV-1 infection may also have nonmalignant consequences, including tropical spastic paraparesis (HTLV-1–associated myelopathy) [15], polyarthritis [16], and uveitis [17]. Each of these manifestations is characterized by substantial local lymphocytic infiltration.

How then might HTLV-1 decrease the prevalence of *H. pylori* infection (in males) and decrease the incidence of gastric cancer in males and females? An effect of the virus on the microenvironment affecting *H. pylori* growth or on gastric epithelial cells might account for Matsumoto and colleagues’ observation. Although it is possible that HTLV-1 might decrease *H. pylori*–induced chronic inflammation, HTLV-1 usually induces lymphocytic infiltrates, despite its association with immunosuppression. Comparison of gastric histologic findings in the presence or absence of HTLV-1 and *H. pylori* might provide initial clues as to the nature of the interaction.

HTLV-1–specific cytotoxic lymphocytes are present in the blood of asymptomatic infected individuals [18]. Cross-reacting immunity might modify responses to *H. pylori*, or an immune response to the virus might activate innate immune mechanisms that could modulate the preneoplastic process. Some viruses are biologically active even when not replicating [19], and HTLV-1 may disrupt normal cellular functions. In addition to its potential for integration within a gene encoding a host protein, the HTLV-1 tax protein can modulate several cellular signaling pathways [10]; viral polypeptide translation might interfere with cellular protein functions, or, if expressed on the cell surface, render it susceptible to cytotoxic CD8 lymphocytes [19]. Archival sequences of human endogenous retroviruses are present in the human genome, and RNA transcripts of these sequences can be detected at low levels in the plasma of some healthy individuals and at much higher levels in immunosuppressed patients infected with HIV. Cytotoxic lymphocytes directed against peptides encoded by these retroviral genes can be detected in the blood of HIV-infected individuals [20].

What are the implications of finding an interaction between HTLV-1 and *H. pylori*? Both microbes are rapidly disappearing because of public health measures (in the case of HTLV-1) [21] and because of changes extant in modern life, possibly driven by antibiotic use (in the case of *H. pylori*). As such, the epidemiologic significance of the interaction between these 2 microbes may lessen over time. Nevertheless, the linkage has important implications in human cancer biology. The concept of a protective effect suggests that HTLV-1 may be a form of viral commensal of humans, protecting hosts through interference with *H. pylori*–induced pathology. The value of our indigenous commensal microbiota has been recognized at least since the 19th century [22], but only now are we beginning to understand its scope and complexity [23–25]. Most attention has focused on the bacterial species that are major constituents of our microbiota, with bacterial cells substantially outnumbering “human” cells in our bodies [24–26]. Research efforts such as the recently announced Human Microbiome Project (HMP), sponsored as part of the National Institutes of Health Roadmap, and parallel efforts in other countries will provide new knowledge and insights into the relationships.

It is important to recognize that although our indigenous (i.e., commensal) microbiota provides benefit to us, there also are biological costs [26]. For example, α-hemolytic streptococci help protect against invading oral pathogens (such as β-hemolytic streptococci) but also may kill their hosts when they attach to heart valves. We presume that natural selection has endowed us with indigenous microbial populations that on balance maximize our survival as a species [27].

However, do we have commensal viruses? We know that there is biological cost to our persistent carriage of viruses, including Epstein-Barr virus, cytomegalovirus, and HTLV-1, which comes in the form of inflammatory diseases and neoplasia. Could there be benefits as well? The article by Matsumoto et al. [1] ultimately raises this question. Since the time of Koch, the advances of medical science have made it easier to recognize new pathogens to understand their pathogenic effects. However, unraveling of the potential benefits to us of our long-term cohabitants, whether eukaryotic, prokaryotic, viral, or prion, will require a greater emphasis on epidemiology to address more-subtle questions. In this regard, the work of Matsumoto et al. [1] may be seen as a model, exploring long-term biological interaction between prevalent microbes to understand issues of clinical synergy or antagonism. Ultimately, epidemiology will help us better understand human microbiology: since our world is changing so rapidly [26], it is especially important.

Elucidation of mechanisms explaining Matsumoto and colleagues’ observation of an interaction between HTLV-1 and *H. pylori*–associated gastric cancer should provide insights into the pathogenesis of each of these individual processes. This work also poses the possibility that the largely asymptomatic equilibria with our commensal microbiota might be influenced by the silent presence of other viral or retroviral elements. As we continue to learn about the rich diversity of life within humans, it is increasingly likely that such interactions will have clinical significance.

References


