The Language Used by *Helicobacter pylori* to Regulate Human Cells

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(See the article by Keates et al., on pages 95–103.)

Although it was not isolated in culture until 1982, *Helicobacter pylori* has colonized the human stomach since ancient times [1]. Moreover, *H. pylori* has dominated its gastric niche (table 1). On no other internal or external surface of the human body—neither the colon, mouth, esophagus, nor skin—does a single species dominate so overwhelmingly [5–7]. That *H. pylori* now is disappearing from socioeconomically advantaged human populations (a phenomenon at once multifactorial and modern) [8] does not diminish the powerful biological features that have long made it the dominant member of the gastric biota.

How did *H. pylori* become so successful [9], thwarting both the human immune responses that recognize it readily [10] and the vast competing human microbiota [4]? Evolutionary pressures have selected intrinsic *H. pylori* phenotypes that protect against gastric acidity, resist the peristalsis that threatens to sweep the bacteria away, and aid in the acquisition of nutrients (reviewed in [11]). Although these are essentially defensive strategies, it is becoming equally clear that *H. pylori* actively interacts with its host, sending (and receiving) a variety of chemical signals. How such interactions evolved remains uncertain, but *H. pylori* has been an excellent student of human biology and has developed a complex dialogue with human gastric cells. Among the most important of these signals is the protein CagA, which is introduced by *H. pylori* into its host cell through a specialized secretion system [11]. The intensity and sophistication of *H. pylori*–gastric cell interactions imply an extensive coevolution of the 2 species, to the benefit of *H. pylori* and *Homo sapiens* alike. For example, if *H. pylori* helped defend against lethal enteric pathogens or supported the regulation of nutrition, there would be selection for its presence, and if *H. pylori* could be sustained at low metabolic cost to its host throughout the human reproductive life span, a robust symbiotic relationship would be expected to evolve [8]. Such a model is consistent with *H. pylori*’s dominance of its niche.

In this issue of the *Journal*, Keates et al. [12] explore a specific facet of the *H. pylori*–host interaction. Like other epithelial, gastric epithelial cells express the epidermal growth factor receptor (EGFR). Ligation of epithelial EGFR is important in normal gastric physiology, because activation of EGFR initiates signaling pathways (most prominently, Ras-dependent Erk activation) that are at once promitotic and antipapoptotic and may serve to sustain the gastric mucosa. EGFR activation may be a double-edged sword, however, because excessive EGFR signaling (as can be seen in EGFR overexpression) may lead to unrestrained proliferation and has been associated with gastric neoplasia [13].

Because *H. pylori* persistently colonizes the gastric epithelium and *cagA*+ strains in particular increase risk for atrophic gastritis and gastric adenocarcinoma [14, 15], Keates et al. asked whether *H. pylori* induces EGFR. They demonstrate that this is indeed the case, to a greater extent in *cagA*+ strains. Interestingly, the mechanism through which *H. pylori* induces EGFR expression appears to depend on the presence and indirect activation (transactivation) of preexisting plasma membrane EGFR, which suggests an amplification cycle. Specifically, EGFR up-regulation may act as a mechanism by which *H. pylori* sensitizes its target host cells for enhanced *H. pylori* effects. That is, if *H. pylori* up-regulates EGFR via transactivation of the EGFR itself, then the resultant increases in EGFR population would, in turn, likely produce enhanced signaling in response to ongoing *H. pylori* contact. Presumably, the increased EGFR population also would be
Table 1. Dominance of the human gastric niche by Helicobacter pylori.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Observation [reference]</th>
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<tr>
<td>History</td>
<td>Colonization of humans for &gt;50,000 years [1]</td>
</tr>
<tr>
<td>Proportion of population</td>
<td>Essentially universal (in developing countries) [2]</td>
</tr>
<tr>
<td>Duration of colonization</td>
<td>&gt;90% of life span [3]</td>
</tr>
<tr>
<td>Proportion of niche</td>
<td>&gt;70% of gastric clones [4]</td>
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susceptible to direct activation by EGF itself.

In both the present and previous work, Keates et al. have also addressed the mechanism of H. pylori–induced EGFR transactivation, which appears to resemble the transactivation of EGFR in other cell types, in response to ligands of G protein–coupled receptors (GPCRs) [16]. Engagement of GPCRs induces metalloproteinase–dependent shedding of HB-EGF, an EGF family member that can engage the EGFR [17]. Similarly, Keates et al. show that colonization of gastric cells with H. pylori leads to EGFR transactivation as a consequence of metalloproteinase–dependent HB-EGF shedding and EGFR autoengagement [18]. Erk activation, a consequence of EGFR activation, also is required for the transactivation of EGFR; thus, Erk serves as both an activator and effector for EGFR. Whether H. pylori transactivation of EGFR is GPCR dependent is unknown, but such a mechanism would be consistent with the common requirement of Src kinase for EGFR activation in response to both H. pylori and GPCR ligands [19]. HB-EGF shedding is not the only mechanism for EGFR transactivation, because GPCRs also have the capacity to assemble a multireceptor scaffold that may include both the EGFR and MAP kinase (Erk) pathway elements [20, 21]. Whether similar scaffolding mechanisms exist for H. pylori–induced EGFR activation is worth investigating.

One implication of the present work is that the mechanisms for EGFR up-regulation, and for gastric epithelial cell responses to H. pylori in general, are more complex and indirect than has previously been appreciated. For example, H. pylori induces increased expression of proinflammatory cytokines in gastric tissues, presumably through the activation of transcription factors such as NF-κB [22]. In turn, these cytokines are themselves capable of activating gastric cell signaling pathways. For example, both interleukin-1β and tumor necrosis factor–α stimulate gastric cells to activate Erk and other proinflammatory signaling elements, to some extent mimicking the effects of H. pylori and EGF [23]. During persistent colonization, as opposed to the short-term state that Keates et al. have studied, induced inflammatory cytokines may be at least as important as EGFR activation in driving intrinsic gastric cell responses (figure 1).

It remains to be determined whether cytokines can up-regulate EGFR, rendering cells more susceptible to both growth factors and H. pylori.

The earliest stages of H. pylori coinfection (minutes) may initiate “immediate early” signaling in the gastric cells, in contrast to the slightly longer time periods (1–6 h) that Keates et al. address. One unresolved area concerns whether gastric cell Erk activation in response to H. pylori is CagA dependent [24] or independent [25, 26]. Our own studies [27] indicate that there is both CagA-dependent and -independent Erk activation and that these events are temporally distinguishable, with the earliest Erk activation (minutes) being CagA independent. Because Keates et al. show both that Erk activation is necessary for EGFR up-regulation and that EGFR up-regulation occurs mainly in response to cagA+ strains, the ability of cagA+ strains to stimulate Erk suggests that Erk may be necessary, but not sufficient, for EGFR up-regulation. What additional signals are re-

Figure 1. Alternative mechanisms for Helicobacter pylori induction of gastric cancer. Although the presence of H. pylori is strongly associated with the development of gastric adenocarcinoma, the mechanisms are unknown. Most work has examined the relationship of H. pylori with epithelial cells (pathway a), but the host responses to the colonizing microbial population may also affect epithelial cells directly (pathway b) or via atrophic gastritis (pathway c). An alternative, and little-explored, possibility is that host response–induced atrophic gastritis selects for a differing microbiota that signals in a more aggressive and unregulated manner than does H. pylori, affecting epithelial cells more profoundly (pathway d).
quired for EGFR up-regulation? One must be Src activation, given that Src inhibition blocks EGFR expression. Other candidates might include molecules known to play roles in inflammation involving other cell types. For example, in rheumatoid arthritis synovial fibroblasts [28], not only Erk [29] but also the other MAP kinases Jnk [30] and p38 [31] play important roles in the regulation of cellular inflammatory responses. Indeed, both Jnk and p38 are activated in gastric cells exposed to *H. pylori* in a manner that does not itself require EGFR activation [18].

High EGFR levels are associated with a poor prognosis in patients with gastric cancer [32], and Keates et al. suggest that cells with EGFR induction may be more susceptible to growth factor–driven malignant progression. By contrast, it is possible that EGFR up-regulation in gastric cells is adaptive for healthy humans, because the antiapoptotic signal provided by the active EGFR might stabilize the gastric lining. In a biological sense, the antiapoptotic effect of EGFR up-regulation may be useful to the host early in life, during the reproductive life span, but costly later in life, leading to an enhanced gastric cancer risk. In the complex *H. pylori*–host interaction, the degree of EGFR up-regulation and the context in which it occurs may determine the extent to which *H. pylori* is beneficial or harmful.

The studies by Keates et al. enhance our understanding of the interplay between gastric epithelial cells and *H. pylori*, which also may serve as a model for the interaction of other coevolved microbes with their adjacent host tissues. In analogy with the widespread medical use of botulinum toxin (an example of harnessing microbial products for therapeutic purposes), greater appreciation of the beneficial effects of *H. pylori* cell signaling may someday lead to the derivation of Helicobacter products with potential medical utility [33]. As noted earlier however, *H. pylori* is disappearing rapidly from populations in developed countries, such as the United States [8]. That it has profound interactions with human cells predicts that there will be consequences. The decrease in rates of gastric cancer is a benefit, but the increase in rates of adenocarcinomas at the gastroesophageal junction, metabolic diseases, asthma, and other disorders [11, 34, 35] may reflect the disordered biology of humans deprived of our long-time partner and physiologic regulator [8]. Careful exploration of the specific interactions of *H. pylori* with host cells, as in the article by Keates et al. [12], will permit greater understanding of the mechanisms that underlie these differences in disease and health.

References


