1918 virus, and the resultant data further support the conclusions made by McAuley et al. that the PB1-F2 of 1918 virus contributes to the extreme virulence of the virus in mice. However, none of the recent work on PB1-F2 and more specifically on the PB1-F2 of the 1918 pandemic virus provides a molecular mechanism for the ability of the 1918 PB1-F2 to cause macrophage and neutrophil infiltration into the lung or increase morbidity. Furthermore, there have been no studies connecting the known apoptotic function of PB1-F2 in vitro to the increased in vivo pathogenesis, or to the ability of PB1-F2 to bind PB1 (S. Ludwig, personal communication).

It seems the more we know about PB1-F2, the more puzzling questions there are to ponder. How could we prevent the detrimental effects of PB1-F2? Would it be possible to inhibit the activity of PB1-F2 through smart design of small-molecule drugs? What role does cytokine dysregulation have in increasing lung pathology, and can we prevent it by abrogating the function of PB1-F2? Exactly how is the C-terminal PB1-F2 peptide getting into cells to impact cell recruitment, or alternatively, is C-terminal PB1-F2 even entering cells at all? Lastly, could this peptide or full-length PB1-F2 be found extracellularly in a natural infection? Truly exciting work is now being done with PB1-F2, but there are still many holes in the knowledge we have about influenza's smallest protein.

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Orchestration of Dysregulated Epithelial Turnover by a Manipulative Pathogen

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Chronic *Helicobacter pylori* infection is the strongest known risk factor for the development of gastric cancer. In order to survive and propagate under the harsh conditions of the gastric niche, this pathogen has evolved numerous means to interact with host epithelium. In this issue, Mimuro et al. shed light on mechanisms by which *Helicobacter pylori* attenuates apoptosis in the gastric epithelium to facilitate its persistence within the human stomach.

Helicobacter pylori (*H. pylori*) has infected human stomachs for more than 55,000 years, with colonization typically lasting for the lifetime of its host (Linz et al., 2007). This bacterium colonizes more than 50% of the world's population, thereby establishing itself as one of the most successful human pathogens. *H. pylori* has developed numerous strategies to colonize and thrive within the hostile environment of the stomach. These include evasion of the host immune response, gaining access to nutrients, protection against the inherent acidic environment, adherence to the gastric epithelium, and resisting peristalsis and rapid cellular turnover. Several lines of evidence have also indicated that, within gastric mucosa, *H. pylori* is able to modify signaling events that couple epithelial and mesenchymal cells in order to tailor an environment optimal for its own survival. However, although all colonized individuals develop chronic gastritis, only a mere subset will develop gastric adenocarcinoma (Peek and Crabtree, 2006). *H. pylori* virulence constituents clearly modify disease risk, and strains that possess the *cag* island, a type IV secretion system that functions to translocate its substrate CagA into host cells, further

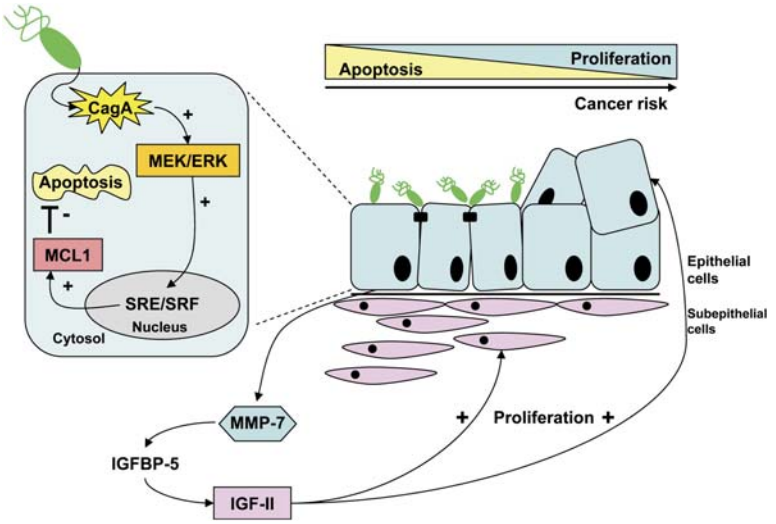

Figure 1. Translocation of CagA by *H. pylori* into Gastric Epithelial Cells Disrupts the Balance between Apoptosis and Proliferation

Translocation of CagA into gastric epithelial cells increases expression of MCL1 in pit cells via a mechanism involving MEK/ERK activation and SRE/SRF transcription, resulting in a prosurvival phenotype. *H. pylori* may also contribute to increased pit cell number by increasing MMP-7 production by epithelial cells. MMP-7 subsequently cleaves the binding protein IGFBP-5, resulting in biologically active IGF-II and increased proliferation of epithelial and subepithelial cells.

augment the risk for gastric cancer (Blaser et al., 1995).

The gastric epithelium consists of a single layer of cells that invaginates to form highly organized tubular structures (gastric glands), which contain a distinct variety of cell types. The region in closest proximity to the gastric lumen is termed the pit and is primarily composed of surface mucous cells. The region adjacent to the pit is the isthmus, which contains stem cells that spawn differentiated cell lineages. The isthmus is bordered by the neck region containing mucous neck cells, and the base of the gland, which consists primarily of chief cells. Parietal cells and endocrine cells are scattered throughout the gland (Karam and Leblond, 1995). Gastric epithelial cells undergo constant turnover, the rate of which increases following damage to the epithelium. As such, it is imperative that a tightly regulated balance is maintained between apoptosis, proliferation, and differentiation to prevent normal healing from transitioning into disease states. From the standpoint of a chronic microbial pathogen, the efficiency of colonization is increased if cell survival is supported. Mimuro and colleagues now report that *H. pylori* can attenuate gastric epithelial cell apoptosis and sustain cell survival in a CagA-dependent manner and that these events increase bacterial colonization (Mimuro et al., 2007).

In this study, the chemotherapeutic agent Etoposide was used to induce gastric pit cell apoptosis in the stomachs of Mongolian gerbils, a robust rodent model of *H. pylori*-induced injury. *H. pylori* infection alone for 8 weeks did not significantly affect levels of apoptosis. However, precolonization with *H. pylori* prior to Etoposide administration protected gastric pit cells from apoptosis. Moreover, infection with an isogenic *cagA*$^-$ mutant *H. pylori* strain revealed that CagA was required for this antiapoptotic response. Utilizing Mongolian gerbil and in vitro gastric epithelial cell models, the authors further demonstrated that CagA translocation into gastric epithelial cells activated the MEK/ERK pathway and increased Serum Response Element (SRE)/Serum Response Factor (SRF)-driven gene transcription, which promoted cell survival (Figure 1). The antiapoptotic protein Myeloid cell leukemia sequence-1 (MCL1) is a SRE/SRF target that is tightly regulated by growth and differentiation factors and functions to promote cell survival (Craig, 2002). Consistent with their previous results, Mimuro et al. found that MCL1 levels were also regulated in a CagA-dependent manner via a pathway that involved activation of MEK/ERK and SRE/SRF transcription. Of interest, increased expression of MCL1 localized predominantly to the pit region. *H. pylori* infection in humans leads to increased proliferation rates with extension of the proliferative zone from the isthmus toward the pit region of gastric glands. The results generated by Mimuro et al. now suggest that hyperplasia observed in response to *H. pylori* infection is not only due to increased cellular proliferation, but may also be due to antiapoptotic responses exerted by *H. pylori* CagA-positive strains.

Dynamic and intimate interactions occur between gastric epithelial and subepithelial cells (including fibroblasts and myofibroblasts), and such interactions are crucial for maintaining mucosal organization. Endocrine and paracrine mediators regulate gastric epithelial architecture, but recently it has been demonstrated that proteolytic enzymes are also important (McCaig et al., 2006; Varro et al., 2007). Matrix metalloproteinases (MMPs) are capable of degrading all components of the extracellular matrix (ECM), are involved in the physiological turnover of ECM, and have a crucial role in pathophysiological processes, such as tumor invasion and metastasis (Nagase and Woessner, 1999). MMPs are typically produced by subepithelial cells; however, MMP-7 is predominantly expressed by epithelial cells. Recent evidence indicates that *H. pylori* exploits MMP-7 to aberrantly regulate interactions between epithelial and subepithelial cells (McCaig et al., 2006). *H. pylori* increases MMP-7 expression in gastric epithelial cells (Crawford et al., 2003; Wroblewski et al., 2003), and elegant work by McCaig et al. has demonstrated that these elevated levels of MMP-7 cleave insulin-like growth factor-binding protein (IGFBP)-5 secreted from myofibroblasts, leading to increased extracellular concentrations of insulin-like growth factor (IGF)-II, which subsequently increases gastric epithelial cell proliferation in a positive feedback system (Figure 1). Since MMP-7 can also exert antiapoptotic effects

(Mitsiades et al., 2001), it will be important to determine whether epithelial-mesenchymal signaling is involved in the survival phenotype reported by Mimuro et al. and others.

The present study by Mimuro and colleagues has enhanced our understanding of the complex and active interplay that occurs between *H. pylori* and epithelial cells. However, it is clear that there are still many viable questions regarding the biology of *H. pylori* and mechanisms by which this bacterium is able to manipulate the highly regulated organization of the gastric epithelium, which over time can promote the progression from normal gastric mucosa to gastric adenocarcinoma.

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Symbiont Genes in Host Genomes: Fragments with a Future?

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While lateral transfer is the rule in the evolutionary history of bacterial and archaeal genes, events of transfer from prokaryotes to eukaryotes are rare. Germline-transmitted animal symbionts, such as *Wolbachia pipientis*, are well placed to participate in such transfers. In a recent issue of *Science*, Dunning Hotopp et al. identified instances of transfer of *Wolbachia* DNA to host genomes. It is unknown whether these transfers represent innovation in animal evolution.

Lateral gene transfer (LGT; also known as horizontal gene transfer) is a major feature of bacterial and archaeal genome evolution. Through this mechanism, lineages can acquire important functions wholesale from other lineages, and thus improve their relative fitness. While LGT has an ancient history in prokaryotes, it is an ongoing process, as evidenced by the emergence of drug-resistant pathogens in human communities. In contrast, lateral gene transfer in eukaryotes appears to be rare. For animals, the early segregation of germline cells in development is likely to make LGT events rarer than in eukaryotes without a segregated germline. One textbook example, the acquisition of cellulase genes by termites from a bacterial source, has recently been shown to be erroneous (Davison and Blaxter, 2005), and initial excitement about "bugs in our genome" from the initial analysis of the human genome (Lander et al., 2001) has evaporated, as these genes have been shown to be present in other eukaryotes and thus more probably part of the core eukaryote genome (Salzberg et al., 2001). Is LGT a significant, ongoing process in animal genomes?

Animals can be infected with germline-transmitted symbionts, and these bacterial genomes are thus in just the right position to be donors in LGT events. There are several groups of animal germline symbionts, and the best studied are the α-proteobacterial *Wolbachia* parasites of arthropods and nematodes. First discovered in mosquitoes, *Wolbachia pipientis* induces a range of reproductive manipulation phenotypes in infected hosts (such as mating type incompatibility, feminization of genetic males, and induction of parthenogenesis) that increase the relative fitness of the host, and thus