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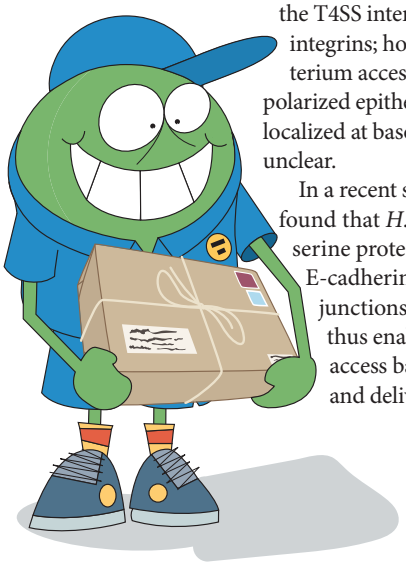
BACTERIAL PATHOGENESIS

Activating *Helicobacter* effector delivery

> *H. pylori* traverses the gastric epithelium and delivers its virulence factor CagA



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Helicobacter pylori is a human bacterial pathogen that colonizes the gastric mucosa and, in some infected individuals, can cause various diseases ranging from gastritis to gastric cancer. *H. pylori* uses a type IV secretion system (T4SS) to inject effector proteins into the cytoplasm of host cells, such as the cytotoxin-associated gene A (CagA) oncoprotein, and thus initiate a cascade of downstream events that contribute to its pathogenesis. *In vitro* studies using non-polarized cells have shown that the T4SS interacts with host cell integrins; however, how the bacterium accesses these receptors in polarized epithelia, in which they are localized at basolateral surfaces, was unclear.

In a recent study, Tegtmeyer *et al.* found that *H. pylori* uses the serine protease HtrA to degrade E-cadherin-based adherens junctions and tight junctions, thus enabling T4SS pili to access basolateral integrins and deliver effector proteins into the host cell. First, by using transmission electron microscopy (TEM) and immunogold staining to analyse biopsy samples from patients that were infected with *H. pylori*, the authors confirmed that HtrA was secreted *in vivo* and was found at cell-to-cell junctions and in deep intercellular clefts of the damaged gastric epithelium. In addition, they found that E-cadherin was strongly reduced by bacterial infection. Next, the authors showed that at 4 and 8 hours post-infection of cultured polarized epithelial cells, *H. pylori* localized to the apical surface of the epithelium, in proximity to cell-to-cell junctions, and that HtrA mediated the specific cleavage of the tight junction proteins occludin and claudin 8 to loosen the epithelium. In accordance with this, at 24 hours post-infection, bacteria were found both at the apical and basolateral surfaces of the polarized epithelium and T4SS pili specifically associated with transmigrated basolateral bacteria, which suggested that T4SS activation occurred at the basolateral surface of the epithelium and not at apical sites. To test this hypothesis, and to demonstrate that bacterial transmigration was necessary for the function of the T4SS of *H. pylori*, the authors tested the translocation of CagA, which is phosphorylated once internalized into host cells. Confocal scanning laser microscopy (CSLM) analysis showed that phosphorylated CagA colocalized with basolateral integrins, thus confirming that the T4SS was active and injected the oncoprotein into the host cell. Furthermore, by testing a *H. pylori* strain engineered to express a synthetic peptide that specifically inhibits HtrA protease activity, the authors showed that they could block bacterial transmigration across the epithelium and the consequent translocation and phosphorylation of CagA, further corroborating their findings. In summary, the results from this study reveal a novel molecular mechanism by which *H. pylori* traverses the gastric epithelium and delivers its virulence factor CagA to host cells to contribute to its pathogenicity.

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ORIGINAL ARTICLE Tegtmeyer, N. *et al.* *Helicobacter pylori* employs a unique basolateral type IV secretion mechanism for CagA delivery. *Cell Host Microbe* **22**, 552–560 (2017)