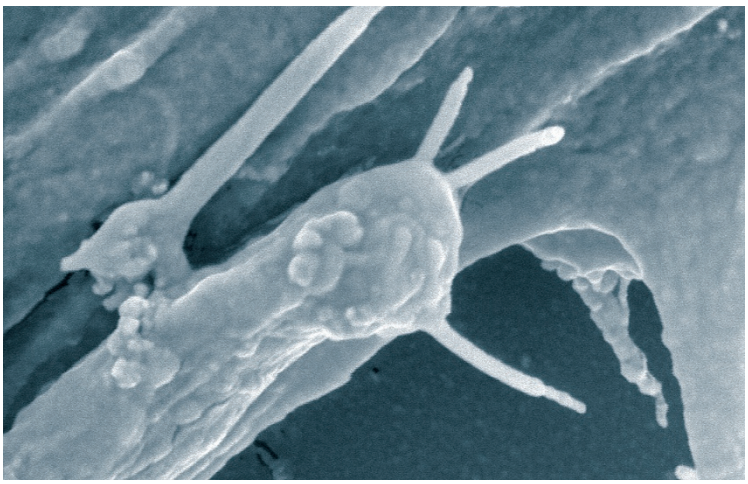
BACTERIAL VIRULENCE

The integrin connection

A new paper published in *Nature* has revealed that the gastric pathogen *Helicobacter pylori* hijacks a host-cell integrin receptor to inject the CagA oncoprotein into gastric epithelial cells and ensure that it is phosphorylated by a host tyrosine kinase.

H. pylori uses a type IV secretion system (T4SS) that is encoded by the *cag* pathogenicity island (PAI) to deliver the CagA oncoprotein into host cells. The events that occur downstream of CagA injection are well understood. However, whether a host-cell receptor is involved in positioning the T4SS or in any of the downstream signalling events has been an open question, and one that Steffen Backert, Terry Kwok and colleagues were interested in answering.

Once it is injected into gastric epithelial cells, CagA is tyrosine phosphorylated by the Src tyrosine kinase. Kwok *et al.* began by examining the subcellular localization of phosphorylated CagA in the AGS gastric epithelial cell line and found that it colocalizes with focal adhesion proteins. This was the first clue that an integrin might be involved in CagA injection, as integrins — transmembrane receptors that mediate various cell–cell interactions — are abundantly expressed at focal adhesions. An *Escherichia coli* strain expressing an integrin-β_1-binding *Yersinia* protein inhibited CagA phosphorylation in AGS cells, and both integrin-α_5- and integrin-β_1-function-blocking antibodies inhibited CagA phosphorylation. This indicates that the $\alpha_5\beta_1$ integrin receptor is involved in the type IV secretion and subsequent phosphorylation of CagA.



A scanning electron micrograph of *Helicobacter pylori* that shows the presence of T4SS pili at the tip. Image kindly provided by Steffen Backert, Otto von Guericke University, Magdeburg, Germany and Manfred Rohde, Helmholtz Centre for Infection Biology, Braunschweig, Germany.

So, which bacterial factor binds to the integrin receptor? The authors discovered that the only *H. pylori cag* PAI-encoded protein that contains the integrin-binding arginine-glycine-aspartic acid (RGD) motif is CagL. Immunofluorescence and scanning electron microscopy were used to show that CagL is expressed on the surface of *H. pylori*, where it associates with T4SS pili, and that the RGD motif is required for the formation of these pili. A series of *in vitro* binding assays and cell-culture experiments using purified recombinant CagL confirmed that this protein binds to $\alpha_5\beta_1$ integrin in an RGD-dependent manner. To investigate whether CagL has an active role in CagA secretion, Kwok and colleagues infected AGS cells with *H. pylori* strains in which the CagL RGD motif carried a point mutation, and found that this abolished both translocation of CagA into host cells and its subsequent phosphorylation. Finally, the authors looked at the signalling pathway that is responsible for CagA phosphorylation in AGS cells and found that CagL is essential for the activation of Src, the tyrosine kinase that phosphorylates CagA.

This work shows that CagL is responsible for the $\alpha_5\beta_1$-integrin-receptor-dependent delivery of CagA into gastric epithelial cells and the concomitant activation of the host-cell kinase that phosphorylates this oncoprotein. This is the first example of a host-cell receptor being involved in the type IV secretion function of a human bacterial pathogen.

Sheilagh Molloy

ORIGINAL RESEARCH PAPER Kwok, T. *et al.* *Helicobacter* exploits integrin for type IV secretion and kinase activation. *Nature* **449**, 862–866 (2007)