

to which strong interactions become weak at very short distances. In this 'perturbative' regime, we understand (at least in principle) how to work with QCD. But for the strong coupling that occurs over larger distances, one has to resort to computer-simulation techniques, known as lattice QCD. These techniques have been rather successful (for instance, in explaining the spectrum of hadron masses), but rigorous results remain hard to come by: despite years of effort, we still cannot explain, for example, why there are no free, single quarks in nature. Such unresolved puzzles are coming into renewed focus with the scheduled start of experiments at the Large Hadron Collider at CERN in Geneva next year.

The new approach that revives the link to string theory first suggested itself in 1998, when Juan Martín Maldacena conjectured¹² a link between a close relative of QCD and a 'superstring' living in a ten-dimensional curved space-time. Although the theory in question, known as supersymmetric $N = 4$ gauge theory, is sufficiently different from QCD to be of no direct interest to experiment, the link raised the prospect of a general connection to some form of compactified string theory. This equivalence is now commonly referred to as the AdS/CFT (Anti-de-Sitter/conformal field theory) correspondence. If true, it would mean that string theory was originally not so far off the mark after all — its ingredients just need to be interpreted in the correct way.

The Maldacena conjecture raised a lot of interest, but seemed for a long time to be quantitatively unverifiable. This was because it takes the form of a duality in which the strongly coupled string theory corresponds to weakly coupled QCD-like theory, and vice versa. But to verify the duality, one would need to find a quantity to compare in a regime of intermediate coupling strength, and calculate it starting from both sides. No such quantity was obvious.

Help came from an entirely unexpected direction. Following a prescient observation¹³, the spectrum of the $N = 4$ theory has been found^{1,2} to be equivalently described by a quantum-mechanical spin chain of a type discovered by Hans Bethe in 1931 when modelling certain metallic systems. There are not many quantum-mechanical systems that can be solved analytically — the hydrogen atom is the most prominent example — but Bethe's *ansatz* immediately applied in a much wider context, and constructed a bridge between condensed-matter physics and string theory (in this context, see the recent News & Views article by Jan Zaanen¹⁴ on the nascent connection to high-temperature superconductivity). Indeed, even though the mathematical description of the duality on the string-theory side is completely different from that on the condensed-matter side, a very similar, exactly solvable structure has been identified here as well^{3–5}.

Puzzling out the details of the exact solution

is currently an active field of research. But in one instance, that idea had already been put to such a hard test that a complete solution now seems within reach. The context is a special observable entity, the 'cusp anomalous dimension', which was argued^{6,7} to be ideally suited as a device to test whether string and gauge theory really connect. Some of its structure at strong coupling was also worked out. Just recently, Beisert, Eden and Staudacher⁸ have extracted the analogue of this observable on the field-theory side, and have been able to write down an equation valid at any strength of the coupling. Since then, work has established that their 'BES equation' does indeed seem, for the first time, to offer a means of reformulating theories such as QCD as string theories.

Much still needs to be learned from this one exactly solvable case. There is justifiable hope that this solution will teach us how to go back to the physically relevant case of QCD and finally arrive at the long-sought dual description by a string theory. It may even take us closer to realizing the quantum-field theorist's ultimate dream, unfulfilled for more than 50 years: completely understanding an interacting relativistic quantum-field theory in the four space-time dimensions that we are

familiar with. Progress towards this goal can be judged independently of loftier attempts to use strings in the construction of a theory of everything. ■

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MICROBIOLOGY

Preparing the shot

Christof R. Hauck

Direct injection of proteins into host cells is one of the tricks bacteria use during infection. It seems that, to achieve this, the stomach pathogen *Helicobacter pylori* first grabs the cell by its surface receptors.

The bacterium *Helicobacter pylori* successfully colonizes the stomach of about every third person. Infection with this ubiquitous microorganism can cause acute and chronic gastritis, as well as stomach ulcers¹. Moreover, up to 90% of cases of stomach cancer are associated with *H. pylori* infection. The bacterium's main weapon is an elaborate apparatus on its surface called the type-IV secretion system, which acts as a nano-syringe (Fig. 1a). Using this apparatus, the bacterium delivers a cancer-associated protein, CagA, directly into its host cells. But whether the bacterium anchors the secretion system to the surface of host cells before injection, and if so, how, has remained unclear. On page 862 of this issue, Kwok *et al.*² report that transfer of CagA is made possible by another *H. pylori* protein, CagL, which binds to integrin receptors on gastric epithelial cells.

So far, CagA is the only *H. pylori* protein known to be injected into the host cell. In the bacterial chromosome, the *cagA* gene is part of a stretch of DNA called *cagPAI*, which also encodes the structural components of the

type-IV secretion machinery³. Bacterial strains harbouring *cagPAI* are considered to be more virulent than other strains⁴.

Previous work^{5–7} had shown that, once CagA is delivered into the host cell, kinase enzymes of the Src family add a phosphate group to it. The presence of phosphorylated CagA results in several changes that might promote *H. pylori* virulence and an unfavourable outcome for infection with this bacterium^{4,8}. These changes include the assembly of signalling complexes, reduced cell–cell adhesion and induction of cell migration.

Examining the localization of phosphorylated CagA in isolated gastric epithelial cells, Kwok *et al.*² found that it occurs almost exclusively at focal adhesion sites — discrete regions of the cell where integrin receptors 'glue' cells to the supporting extracellular matrix. The authors speculated that CagA might not move through the cytoplasm of the infected cells to these sites, but instead be injected directly at these places. Support for this idea came from experiments demonstrating that CagA is not transferred into host cells if *H. pylori* cannot

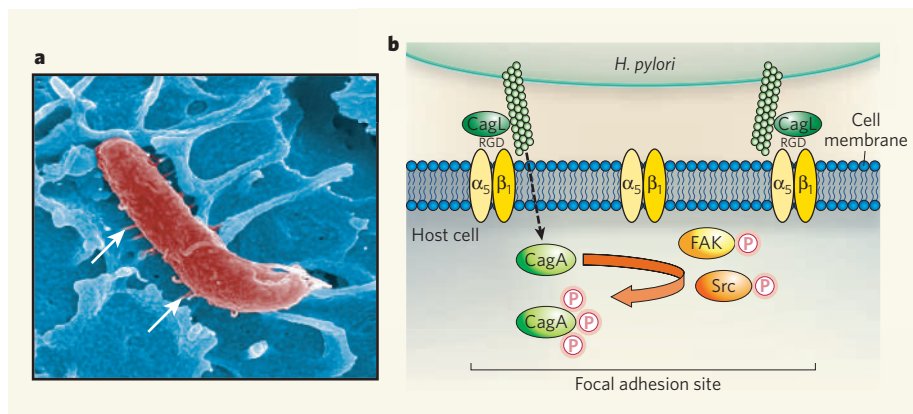


Figure 1 | Translocation of the CagA protein of the bacterium *Helicobacter pylori* into host cells. **a**, Electron micrograph of *H. pylori* (red) attaching to the surface of a host gastric epithelial cell. The type-IV secretion apparatus, in the form of needle-like projections (arrowed), mediates the transfer of the bacterial protein CagA into the host cell. (Image courtesy of M. Rohde.) **b**, Kwok *et al.*² find that, to achieve transfer, the CagL protein on the surface of the secretion apparatus binds to host-cell integrins ($\alpha_5\beta_1$) through its RGD structural motif, thereby directing the injection of CagA precisely into focal adhesion sites in the cell. Moreover, CagL seems to stimulate integrin-mediated signalling, such as activation of FAK and Src-family kinases, ensuring the phosphorylation of translocated CagA, and thus its activation.

access a particular type of integrin known as integrin $\alpha_5\beta_1$.

The authors went on to show that CagL — a little-studied protein encoded by a sequence within *cagPAI* — is the crucial molecular link between the type-IV secretion apparatus of *H. pylori* and host-cell integrins, mediating CagA translocation. CagL occurs on the surface of *H. pylori* together with the type-IV secretion apparatus. It contains a three-amino-acid sequence motif known to mediate binding to, and activation of, integrin $\alpha_5\beta_1$. This tripeptide motif in CagL consists of arginine-glycine-aspartate (RGD in single-letter code) — a sequence that is present in several proteins found in the extracellular matrix, such as fibronectin and vitronectin, that bind to integrins to activate them⁹.

Kwok and colleagues showed that, like the physiological stimulation of integrins, normal, RGD-containing CagL — but not mutant CagL (containing RGA instead) — activates integrin-associated kinases such as FAK and Src, which then phosphorylate CagA (Fig. 1b). Therefore, CagL not only holds on to integrins to precisely position the type-IV secretion apparatus, but, by stimulating integrin-mediated signalling, it also ensures that the translocated CagA encounters active host kinases for its subsequent phosphorylation.

A number of pathogenic bacteria enter host cells by exploiting integrins and integrin-initiated signalling events¹⁰. So a remaining question is how *H. pylori* avoids being internalized in this way. In the intact tissue, preformed integrin-rich focal adhesion sites occur on the basolateral surface of gastric epithelial cells, facing away from the stomach lumen. Other unknowns are therefore how, once in the stomach, *H. pylori* reaches integrin-rich focal adhesion sites on the basolateral surface, and how CagL induces the *de novo* formation of integrin clusters on the cell's apical

surface, which faces the stomach lumen.

A type-IV secretion apparatus or a functionally similar type-III secretion system is present in many other bacteria, and interactions with host-cell integrins have been documented¹¹. So the race will now be on to search for CagL-

related proteins in these microbes. Furthermore, to understand how CagL helps position the *H. pylori* type-IV secretion apparatus, it will be crucial to dissect the interactions between CagL and the structural components of this apparatus.

Regardless of the unresolved questions, Kwok and colleagues' work² neatly highlights the thrifty elegance with which a bacterial pathogen uses a single virulence factor, together with exploitation of the host-cell components, to secure intracellular positioning and activation of the noxious CagA protein. ■

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ASTRONOMY

Black holes go extragalactic

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The mass of a black hole beyond our Galaxy has been calculated, thanks to the presence of an associated star. The hole is the weightiest yet, placing intriguing constraints on how this binary system developed.

Weighing celestial bodies is a goal of many astronomers, and it is an especially fascinating task in the case of black holes. On page 872 of this issue¹, Orosz *et al.* announce a significant advance — they have measured the mass of a black hole lying far beyond our own Galaxy.

The best method for weighing a black hole is to measure the strength of its gravity. This can be done by observing how it affects the motion of a second object, usually a blob of hot gas, or a star, that is locked into a binary system with it. It's a well-worn method: the radial velocity and orbital period of the two objects must first be measured, along with their eccentricity (the deviation of their orbits from a perfect circle). This measurement sets a joint constraint on the masses of the objects and their inclination (the angle between their orbital paths and some reference plane). But it does not tell us what the values of the masses and inclination are.

In the case of eclipsing binaries, where one object periodically passes in front of the other, the inclination can be tightly constrained: in

a binary, both objects must, by definition, be observed nearly in the plane of their orbits. But such instances are rare, and the lack of reliable information on the orbital inclination of most black holes remains a great source of uncertainty in the measurement of their mass. A final ingredient for the calculation is a direct measurement of the mass of the companion object. If it is a star, an estimate can be made from its luminosity and the spectrum of radiation that it emits. Astronomers cannot measure the absolute luminosity directly, only its radiation flux at Earth; so they first need an estimate of its distance from us.

Several binary systems hosting extremely compact, massive objects are known in our Galaxy, as revealed by their characteristic high and variable luminosity at X-ray wavelengths. None is eclipsing, but the objects' masses have been determined using the classic method outlined above. The values cluster at around 10 times the mass of the Sun, significantly higher than the 2.5 to 3 solar masses thought to