this arrangement is somewhat analogous to double-stranded DNA: both are right-handed helices with a binding groove running along the helix. Furthermore, recognition of peptides in elongated conformation may increase the specificity by exposing all functional groups, and may also result in higher binding affinities due to the large molecular surfaces covered in such interfaces.

It has been shown experimentally that the E-cadherin cytoplasmic domain is unstructured in the absence of β-catenin[5]. Given the extended conformations observed in the structures described here, it seems likely that many β-catenin groove-binding proteins will be unstructured alone. Huber and Weis[2] have suggested that interfaces between structured and unstructured binding partners should have a unique plasticity — a change in one region of the unstructured ligand (for example, phosphorylation) should not affect binding in other parts of the interface. In this way, they propose, post-translational modifications could regulate the interaction in a graded fashion, rather than as a simple on-off switch. Thus, β-catenin may serve as an integrator of information from different signals that could modulate these subsites independently.

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Gut-wrenching bugs

For some time, people believed that stomach ulcers were caused by excess gastric acid associated with emotional stress and/or diets that included spicy foods. Early treatment of this debilitating disease involved bed rest, a special diet of bland foods, and antacids. Unfortunately, for many patients the symptoms recurred, and stomach ulcers were considered an incurable disease.

In the late 1970s, an Australian pathologist, J. Robin Warren, noted the presence of curved rod-shaped bacteria in stomach biopsy samples. Curiously, the presence of bacteria appeared to correlate with inflammation of the tissue. Could these bacteria have actually inhabited the stomach, which had long been considered sterile because of the high acid concentration? Could they have caused the observed damage in the tissue?

To address some of these questions, Warren and a young physician, Barry J. Marshall, conducted systematic studies[1] to quantify the correlation between the presence of bacteria and stomach ulcers or chronic gastritis, and their results revealed a significant association between the two phenomena. They also isolated and successfully cultured the bacteria serendipitously in the laboratory — their early attempts to grow the bacteria over a two-day period failed, but when the plates were unintentionally left in the incubator over the Easter holidays for five days, colonies emerged. Based on their findings, Warren and Marshall proposed that the bacteria — now known as *Helicobacter pylori* — could be etiologically responsible for the upper digestive tract disease.

Although the link between *H. pylori* and stomach ulcers was proposed in 1984, the hypothesis remained controversial for the next 10 years. This was in part because a direct cause-and-effect relationship could not be established. In an attempt to prove the relationship, Marshall took the drastic step of ingesting *H. pylori*, and he subsequently developed a severe case of gastritis. Nevertheless, the result of this act fell short of proving the connection between *H. pylori* and stomach ulcers.

The Warren and Marshall studies provided a starting point for other researchers around the world to look for evidence linking *H. pylori* to stomach ulcers. Eventually, the connection was deduced from the accumulated data from epidemiological studies. Moreover, antibiotic treatment against *H. pylori* resolves the symptoms of ulcers with few cases of recurrence. In 1994, a consensus panel[2] at the NIH stated that "*H. pylori* infection is strongly associated with the predominant form of peptic ulcer disease...".

In addition to stomach ulcers, *H. pylori* seems to be involved in other diseases, such as gastric cancer and one type of non-Hodgkin's lymphoma. In fact, in 1994 the World Health Organization categorized this microbe as a group I carcinogen[3], a group of agents that are known to cause human cancers. Thus, it is important to understand how these bacteria are transmitted and how they can colonize the human stomach. The genome sequencing of *H. pylori*[4] completed in 1997, and the structure of the urease — an enzyme that protects *H. pylori* against acidic environment — reported on page 505 of this issue of *Nature Structural Biology*, represent two steps toward achieving this goal.

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