questions. Compensatory mechanisms and redundant pathways in the knockout mice could obscure the function of the *SHP* gene; therefore conditional knockouts of the *SHP* gene will be of great interest. As SHP can interact with several nuclear receptors, the exact molecular targets through which SHP modulates bile-acid synthesis *in vivo* remain to be identified. However, the regulatory effects and molecular targets of SHP are not necessarily conserved between mice and humans. Species-dependent differences in promoter and cellular context and in relative NR expression levels may thus confound extrapolations of experiments in mice to human beings.

Because SHP is expressed not only in the liver but also in other tissues, additional functions for SHP may yet come to light. The association of genetic variation in the *SHP* gene with mild obesity and high birth weight in humans[12] is an indication that such additional functions exist. Although SHP is presently still an orphan NR, its conserved ligand-binding domain suggests the existence of SHP ligands. Likewise, additional agents that modulate SHP expression might be identified. Such compounds might interfere with SHP's capacity to bind or modulate other NRs. SHP ligands and/or compounds that alter SHP expression might have the potential to modulate bile-acid production. Their eventual therapeutic value should be tested in conditions such as cholestasis, hypercholesterolemia and atherosclerosis. Similarly, the alternate pathways described in these papers might serve as therapeutic targets to lower cholesterol.

With the availability of these SHP-deficient mice, we know that it takes more then SHP alone to control the feedback inhibition of bile-acid synthesis. We now need to find out more about how these additional and redundant feedback pathways steer the metabolism of bile acids and, indirectly, cholesterol.

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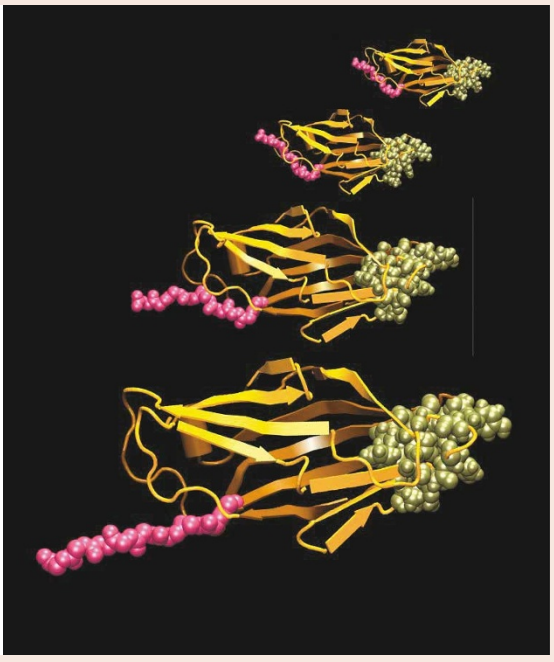
E. coli hangs on tight



The protein FimH sits at the tip of projections on the surface of many enterobacterial strains and grips human cells. It has been thought that bacteria lose that grip when flushed out by body fluids such as saliva. But Thomas *et al.* now show that the stress of getting caught mid-stream can actually make *E. coli* clasp on tight, and it's FimH that does the grasping.

In the 28 June issue of *Cell*, the authors revisited a decades-old observation that shaking up bacteria with red blood cells in a flask causes the red blood cells to clump. If the flask is then left to sit, Thomas *et al.* discovered that certain strains of *E. coli* fall off the red blood cells, causing them to disaggregate. The reason for this counter-intuitive behavior has to do with the mechanics of FimH.

The authors delved into the mechanics of FimH by applying a new computational method to the previously solved structure of the protein. That method, called steered molecular dynamics (SMD), stretches a known protein structure under an external force. The authors performed SMD simulations designed to mimic tension mediated by the sheer stress of fluids. As in this image, sheer force stretches the segment (in pink) that connects FimH to bacterial fimbrial projections. The authors describe the mechanism as a "finger-trap" in which the harder you pull, the more your finger gets stuck in a trap. Sheer stress could shift the binding site (in green) from a "low-affinity" to a "high-affinity" conformation, or expose an additional binding site, speculate the researchers. The authors note that with this mechanism, bacteria are well adapted to not only clamp down under stress, but to pick up and move under their own power when the coast is clear.

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