# The floppy protein: When being out of shape finally pays off

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(Phys.org) —A protein that acts as a chaperone and escorts pathogenic bacteria through the acid bath of the human stomach actually needs to lose its shape in order to work.

A team of researchers at the University of Michigan has found evidence that a protein called HdeA becomes more active as it becomes disordered. HdeA is a crucial player in the fight between pathogenic bacteria and their human hosts. On their journey to infect a human's intestine, pathogenic bacteria like the notorious bacteria E. coli first have to a cross a gruesome barrier – the human stomach.

"These bacteria use HdeA as an insurance policy to survive this unpleasant acid bath," said James Bardwell, the lead investigator of the study that appeared online in the journal Proceedings of the National Academy of Sciences this week.

Understanding the structural basis for the relationship between protonation, conformation and activation of HdeA is critical in understanding the virulence of this bacterium. This knowledge could aid in the design of specific drugs targeting this vital protein to attenuate E. coli's virulence as well as that of other pathogenic bacteria, the researchers said.

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Proteins fulfill a myriad of different roles in the cell. For many years, it has been thought that proteins need to be highly structured in order to be functional. That this is always the case has been questioned. Nevertheless, it has been very difficult for scientists to show that a protein actually needs to be flexible in order to be active.

Most bacterial proteins take a big hit when exposed to stomach acid – they unfold and tend to clump together, making them useless to the bacterium. Unlike most other proteins however, the acid insurance protein HdeA becomes active upon contact with acid. In this state, HdeA wraps around other proteins like a candy wrapper around sticky candies and prevents the other proteins from clumping together.

While the naturally occurring form of HdeA is only active in acid, the team of researchers figured out a way of permanently activating the protein even at neutral pH.

"We essentially predicted which residues this protein uses to sense that it is exposed to acid", said Charles Brooks, a collaborator in the Department of Chemistry whose group was also involved in the study. "Once we knew what the pH switches in the protein were, we could flip these switches to permanently on and create an HdeA variant that is active also at neutral pH."

The group of researchers was excited to find that their permanently active version of HdeA was very unstable and had lost much of its structure. This is in stark contrast to the naturally occurring form of HdeA, which is very stable and inactive at neutral pH and is only switched on by the unfolding effects of acid.

"Scientists usually assume that proteins that become unfolded and unstable due to mutations are inactive. Here, the exact opposite is the case: unfolding goes hand in hand with a gain of activity, " said Linda Foit, first author of the study. "If you think about it though, it makes perfect sense. Flexibility allows HdeA to bind to and protect a large number of different proteins. Thus we have shown that in some cases it pays off for a protein to be floppy."

Provided by University of Michigan