Researchers discover a way to strengthen proteins

December 10 2009

Proteins, which perform such vital roles in our bodies as building and maintaining tissues and regulating cellular processes, are a finicky lot. In order to work properly, they must be folded just so, yet many proteins readily collapse into useless tangles when exposed to temperatures just a few degrees above normal body temperature.

This precarious stability leaves proteins and the living beings that depend upon them on the edge of a precipice, where a single destabilizing change in a key protein can lead to disease or death. It also greatly complicates the manufacture and use of proteins in research and medicine.

Finding a way to stabilize proteins could help prevent such dire consequences, reduce the very high cost of protein drugs and perhaps also help scientists understand why proteins are often so unstable in the first place. In a paper published in the Dec. 11 issue of the journal *Molecular Cell*, researchers at the University of Michigan and the University of Leeds describe a new strategy for stabilizing specific proteins by directly linking their stability to the antibiotic resistance of bacteria.

"The method we developed should provide an easy way to strengthen many proteins and by doing so increase their practical utility," said James Bardwell, a Howard Hughes Medical Institute investigator and professor of molecular, cellular and developmental biology at U-M.

In the new approach, the researchers found that when a protein is inserted into the middle of an antibiotic resistance marker, bacterial antibiotic resistance becomes dependent upon how stable the inserted protein is. This enabled the scientists to easily select for stabilizing mutations in proteins by using a simple life-or-death test for bacterial growth on antibiotics. The mutations the scientists identified rendered proteins more resistant to unfolding.

"This method also has allowed us to catch a glimpse of why proteins may need to be just barely stable," said Linda Foit, the graduate student at U-M who initiated the work. "The mutations that we found to enhance the stability of our model protein are mostly in key areas related to the protein's function, suggesting that this protein may need to be flexible and therefore marginally stable in order to work. It may be that, over the course of evolution, natural selection acts to optimize, rather than maximize protein stability."

Source: University of Michigan (news : web)