ENZYME RESCUED FOR FIRST TIME IN LIVE CELLS

Small molecule is used to partially restore lost activity of a disabled enzyme

A technique called chemical rescue has been used for the first time in living cells to partially restore the activity of a disabled enzyme.

The approach was demonstrated on a mutated form of the protein tyrosine kinase Src by graduate student Yingfeng Qiao, professor of pharmacology and molecular sciences Philip A. Cole, and coworkers at Johns Hopkins University School of Medicine (Science 2006, 311, 1293). In vivo chemical rescue represents a new way to probe in vivo enzyme function and could potentially lead to disease treatments.

In chemical rescue experiments, a key active-site residue of an enzyme is first modified to deactivate the enzyme. The enzyme is then reactivated by introducing a compound that binds to the active site and supplies some of the missing electronic or steric features there.

In vitro examples of the approach were demonstrated independently in the late 1980s by groups led by pharmaceutical chemistry professors Charles S. Craik and James A. Wells of the University of California, San Francisco, and Jack F. Kirsch, professor of molecular and cell biology and of chemistry at the University of California, Berkeley. The Johns Hopkins team's work extends chemical rescue to living cells.

The enzyme Src is known to be involved in a range of cellular processes, but its functional role is still incompletely understood. In their Science paper, Cole and coworkers show that the lost function of mutated Src expressed in engineered mouse cells can be rescued rapidly and reversibly by exposing the cells to the small molecule imidazole. The technique enabled them to obtain some new and unexpected insights on the cellular pathways that the enzyme helps control.

In vivo chemical rescue could ease studies of cell signaling and could one day make it possible "to find small molecules that rescue disease-related mutant enzymes in people" as genetic disease treatments, the researchers write. For example, they have shown that imidazole and several methylimidazole analogs can be used to chemically rescue Src modified with a type of inactive amino acid change that causes the genetic immune-deficiency disease agammaglobulinemia.

"This work is a good example of how chemical tools, combined with chemical insight of how enzymes work, can lead to new information regarding the role of enzymes in a biological setting," Craik comments. "In vivo chemical rescue can be a new tool in the chemical biologist's toolbox," assuming it can now be demonstrated to work for other enzymes, he notes.

The study "is an exciting demonstration of selective activation of a protein kinase with a small molecule to infer rapid downstream signaling events," Wells says. "The signaling field needs a better set of rapid signaling probes if we are to understand the immediate changes that these enzymes induce," and in vivo chemical rescue could aid in that effort.—STU BORMAN

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