Discovery of enzyme activation process could lead to new heart attack treatments (w/ Video)

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Using a red pushpin, Thomas Hurley of the Indiana University School of Medicine demonstrates how a the compound Alda-1 works to restore functionality to a mutated form of the enzyme ALDH2, which plays an important role in metabolizing alcohol and other toxins in the body. Credit: Eric Schoch / Office of Public and Media Relations, Indiana University School of Medicine

Researchers at the Indiana University and Stanford University schools of medicine have determined how a "chemical chaperone" does its job in the body, which could lead to a new class of drugs to help reduce the muscle damage caused by heart attacks.

Such drugs would work by restoring the activity of a mutated enzyme, rather than taking the more common approach of blocking the actions of a disease-related protein.

The team, led by Thomas Hurley, Ph.D., associate chair and professor of biochemistry and molecular biology at IU, and Daria Mochly-Rosen, Ph.D., professor of chemical and systems biology at Stanford, report in the journal *Nature Structural Biology* published online Jan. 10 that the compound, called Alda-1, acts much like a shim to prop up a mutated form of a key enzyme, restoring the enzyme's function.

The enzyme, called ALDH2, plays an important role in metabolizing alcohol and other toxins, including those created by a lack of oxygen in the wake of a heart attack. It also is involved in the metabolism of nitroglycerin, which is used to prevent chest pain (angina) caused by restricted blood flow and oxygen to the heart.

However some people, including about 40 percent of people of East Asian descent, carry a mutated form of the ALDH2 enzyme that does not carry out its intended functions well. People with the mutated form of the enzyme are at increased risk of cardiovascular damage.

The IU and Stanford team reported in 2008 in the journal *Science* that in laboratory tests Alda-1 bypassed the body's usual signaling system and activated the ALDH2 enzyme directly, reducing damage to heart muscle tissue. That finding raised the possibility of new treatments for heart attacks, methods to protect hearts during open heart surgery, organ transplants, stroke and other situations in which blood flow is interrupted.

Their current paper describes how Alda-1 activates the ALDH2 enzyme in a process that Dr. Hurley likens to a woodworking procedure in which Alda-1 attaches to the ALDH2 enzyme at a crucial spot and acts like a

shim or wedge to prop it up.

"Because of the mutation in the gene, parts of the protein structure become loose and floppy. Alda-1 reactivates the enzyme by propping up those parts of the structure so they regain normal function," said Dr. Hurley, director of the Center for Structural Biology on the Indiana University-Purdue University Indianapolis campus.

Determining how the Alda-1 compound works will enable the researchers to begin working on alternative compounds that hold more promise as potential drugs. One primary improvement needed is the ability to give the drug orally, rather than by injection, Dr. Hurley said.

"Based on the information from these studies, we're now ready to sit down with medicinal chemists and start designing new analogues by applying our understanding of what we need to leave alone and what we can modify to improve the properties of Alda-1," he said.

He predicted that alternative compounds could be available for testing by mid-2010.

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