Study of alcohol reaction may revolutionize drug development

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(PhysOrg.com) -- Enzyme malfunctions are at the root of many serious health problems, but rarely do scientists come up with a way to repair them.

New research from the Stanford University School of Medicine and Indiana University shows how a particular molecule, known as Alda-1, repairs a common enzyme mutation that leads to a debilitating reaction to alcohol, increases the risk of some types of cancer and might also promote some neurodegenerative diseases.

What makes this so remarkable is the way the drug-like molecule Alda-1 works. While the typical drug development strategy is to find a molecule that binds to a key site on an enzyme and blocks the disease process, in this instance, the molecule actually changes the shape of a broken enzyme and revives it.

“We show how this small molecule fixes the structure of a dead enzyme and makes it function again,” said Daria Mochly-Rosen, PhD, professor of chemical and systems biology at Stanford, a co-author of the findings published online Jan. 10 in *Nature Structural Biology*. She and researcher Che-Hong Chen, PhD collaborated on the work with senior author Thomas Hurley, PhD, professor of biochemistry and molecular biology at Indiana University, and members of his laboratory.

Hurley’s team used an X-ray crystallography imaging technique to reveal how Alda-1 props up the broken enzyme’s flailing phalanges.

The discovery opens the door to the possibility of an entirely new class of drugs. Until now, using drugs to fix enzymes was widely viewed as impossible."It's one of the holy grails of drug development," said Steve Schow, PhD, who has worked in drug discovery and development for 35 years and is vice president of research at a biotechnology company not involved in the Alda-1 study. "I talked to a friend of mine about this earlier and he nearly jumped out of his seat. This approach points the way to solving problems that heretofore were not addressable."

While drug developers have strategies for fixing the other major types of proteins responsible for disease or discomfort, none exists for enzymes. Yet enzyme malfunctions are associated with a greater risk from a number of diseases including Alzheimer's disease, diabetic complications and certain types of oral and esophageal cancers, as well as an adverse reaction to alcohol.

Here's the background: A year ago, Mochly-Rosen's team reported that it had identified a small molecule (or a drug), which they named Alda-1, that repairs abnormal alcohol processing when an alcohol-processing enzyme, aldehyde dehydrogenase 2, malfunctions. Typically, ALDH2 metabolizes aldehyde molecules, a toxic byproduct of alcohol. But when the enzyme doesn't work, just one drink can cause unpleasant reactions—flushing, headaches, heart palpitations and nausea among other symptoms. The mutation that leads to this condition is common among people of Asian descent, appearing in about 40 percent of this population or about 1 billion people.

What's more, the mutation in drinkers can raise the risk of certain illnesses, including esophagus and liver cancers.

Perhaps most intriguing was the mutation's connection to heart disease. In fact, Mochly-Rosen first searched for Alda-1 because she was investigating why alcohol (in moderation) prevents damage from heart

attacks. Her experiments showed that the alcohol-processing enzyme plays an important role in mopping up damaging molecules that mount from heart attacks. In experiments in rats, she and her colleagues found that increases in the enzyme's activity decreased damage from heart attacks. A two-fold increase in activity led to a 60 percent drop in associated damage, she reported in 2008 in *Science*.

This suggests that people who lack normal activity of this enzyme would be more prone to heart failure and that a drug that fixes the enzyme could reduce that risk. For these reasons, drug developers are interested in the fix-it molecule. Mochly-Rosen is also considering creating a company to attempt to bring the drug to market herself.

The news now is that Hurley and his team have used X-ray crystallography to create 3-D images showing how Alda-1 fixes the enzyme. The first step in the project was the hardest: growing crystals made of the molecule formed by Alda-1 binding to the mutant enzyme. Hurley's team struggled with this for more than a year. "The enzyme is difficult to work with," said Hurley. "It's floppy, so it's hard to get into a crystal."

Once crystallized, the researchers bombarded the compound with X-rays and used the diffraction patterns to discover the compound's shape.

Hurley's team had previously revealed the shape of the normal enzyme, which resembles a four-leaf clover in basic structure. They had also shown that in the mutant version, the "leaves" droop and flap about.

The team's new work shows that Alda-1 molecules latch onto four identical binding sites near the center of the structure, one on each leaf, and buttress the waggling edges. "They come in, bind behind the disrupted structures, and pull them in," said Hurley.

And because of the way Alda-1 interacts with the broken enzyme, it opens drug developers' eyes to possibilities most hadn't dreamed of. Alda-1 falls into a new class of therapeutic agents that work not by blocking the disease process but by changing the shape of broken molecules and, as a result, improving their function. More traditional drugs work by binding to a protein's "active site," which essentially acts like a keyhole, waiting for the right molecular key to come along and unlock it. By binding to this site, drugs block the access of other molecules, essentially keeping the switch that starts the chain of molecular events turned off.

The beauty of the new approach is that it allows drugs to not only switch molecular interactions off, but to switch them on—which it accomplishes by fixing mutant versions of molecules. Mochly-Rosen is aware of only one other group that has reported success at using a drug to repair a broken enzyme: Yoshiyuki Suzuki, MD, PhD, and his colleagues at the International University of Health and Welfare Graduate School and Keio University in Japan. Their findings, published in May in Perspectives in Medicinal Medicine, show they used a similar approach to compensate for an enzyme malfunction that leads to Gaucher's disease and related conditions.

Now that Mochly-Rosen and Hurley have a clear picture of the interaction between the faulty enzyme and its helper, they plan to work together to make an even more effective molecular partnership. Ultimately, they hope to see the development of a drug to not only correct alcohol intolerance but also to decrease vulnerability to heart disease.

Provided by Stanford University Medical Center

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