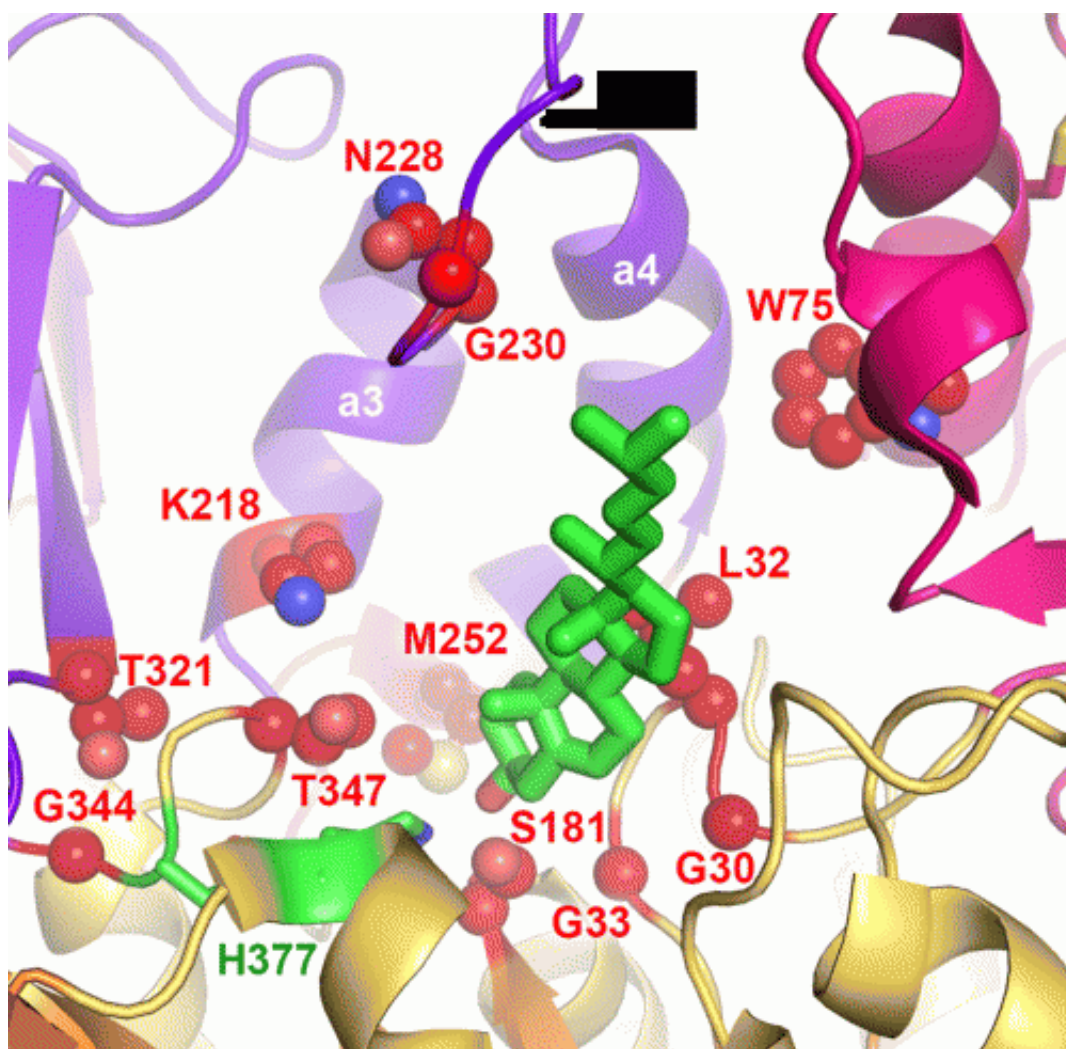


New views of enzyme structures offer insights into metabolism of cholesterol, other lipids

March 2 2015, by Ian Demsky



A model of cholesterol docked into the active site of lecithin:cholesterol acyltransferase (LCAT). The positions shown in red correspond to amino acids that are known to be mutated in human disease. Credit: Alisa Glukhova

With the aid of X-ray crystallography, researchers at the University of Michigan have revealed the structures of two closely related enzymes that play essential roles in the body's ability to metabolize excess lipids, including cholesterol.

The findings are an important step toward understanding and being able to therapeutically target disorders and drug side effects that cause lipids, including cholesterol, to build up in the body—leading to heart and kidney failure and other problems.

Investigators in John Tesmer's lab at the U-M Life Sciences Institute obtained a high-resolution picture of the atomic structure of lysosomal phospholipase A2, which is known as LPLA2, and a lower-resolution image of the structure of lecithin-cholesterol acyltransferase, which is known as LCAT. The enzymes share many structural similarities but perform different functions within the body.

Being able to see the structures for the first time gives scientists a better understanding of the role the two enzymes play in helping the body to break down and remove cholesterol and other lipids. The findings are scheduled for publication in *Nature Communications* on March 2.

In healthy people, LCAT facilitates the removal of cholesterol from the body. But LCAT doesn't function properly in people with genetic disorders that cause plaques to build up in the blood vessels of the heart and kidneys, and in the corneas.

Meanwhile, LPLA2 helps cells break down excess lipids. Side effects of certain drugs lead to inhibition of LPLA2, which in turn leads to a buildup of lipids within cells. Recent studies suggest LPLA2 may also play a role in lupus, a [chronic autoimmune disease](#).

"The structures reveal how the catalytic machinery of these enzymes is organized and how they interact with membranes and HDL particles," said the study's first author, Alisa Glukhova, who received a doctorate from U-M's Program in Chemical Biology last fall and who is now working as a research fellow at Monash University in Melbourne, Australia.

The high-resolution snapshot of LPLA2 can also help illuminate the impact of mutations within the enzyme.

"By knowing the architecture of these key enzymes, we can further understand how more than 55 known mutations of LCAT lead to dysfunction and disease," said study senior author John Tesmer, a research professor at the Life Sciences Institute, where his laboratory is located, and a professor of biological chemistry and pharmacology in the U-M Medical School. "These structures also suggest new approaches to develop better biotherapeutics to treat LCAT deficiency."

The researchers are now working on obtaining a higher resolution image of the LCAT structure to get a more refined understanding of how it functions.

Co-authors on the paper include Vania Hinkovska-Galcheva, Robert Kelly and James Shayman of the Department of Internal Medicine in the U-M Medical School and Akira Abe of the Department of Internal Medicine in the U-M Medical School and Sapporo Medical University in Japan.

Support for the research was provided by grants from the National Institutes of Health, an American Heart Association Predoctoral Fellowship, a Rackham Graduate Student Research Grant and a Merit Review Award from the Department of Veterans Affairs.

The Life Sciences Institute is a nucleus of biomedical research at U-M. LSI scientists use a range of tools and model organisms to explore the most fundamental biological and chemical processes of life. The institute houses an academic early drug discovery center, a cryo-electron microscopy laboratory, a comprehensive protein production and crystallography facility and a stem-cell biology center.

Provided by University of Michigan

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