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Promising New Directions for Gallstone Treatment

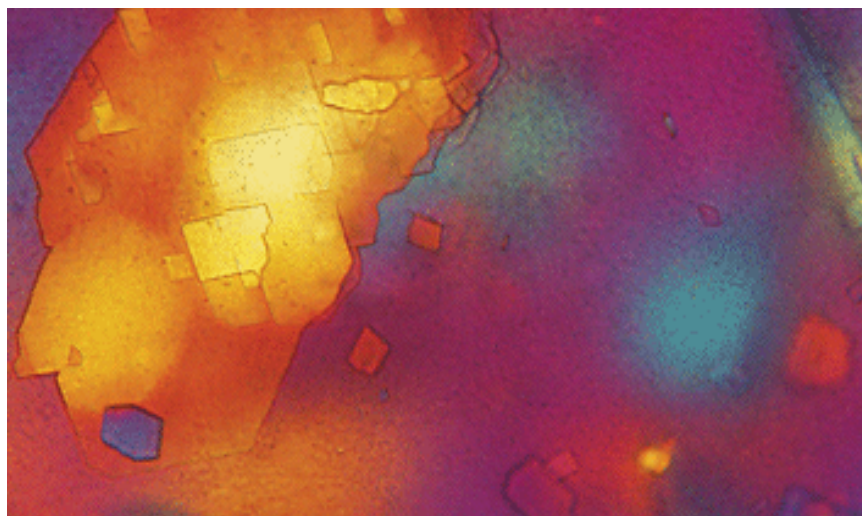


Image Title: Polarizing light microscopy of gallbladder bile shows the deposition of cholesterol crystals, which can form gallstones under the right biochemical conditions. - Courtesy of David Mangelsdorf/HHMI at UT Southwestern Medical Center

A promising experimental compound prevents cholesterol gallstone disease in mice by stimulating the biochemical pathway that controls bile acid secretion by the liver, according to new studies by Howard Hughes Medical Institute researchers.

The findings suggest new approaches to developing drugs to prevent the disease, which afflicts some 20 million people a year. The studies also propose novel strategies for developing diagnostic tests to identify people with a genetically increased risk for developing gallstones.

A research team led by David J. Mangelsdorf, a Howard Hughes Medical Institute (HHMI) investigator at the University of Texas Southwestern Medical Center at Dallas, published its findings November 21, 2004, in the advance online version of the journal *Nature Medicine*. Co-authors of the paper included HHMI research associate Antonio Moschetta and Angie

Bookout in Mangelsdorf's laboratory.

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- David J. Mangelsdorf

"What we saw was remarkable," said Mangelsdorf. "After just five to seven days of treatment, these animals, which were on a diet that would normally produce cholesterol gallstone disease, showed no trace of the disease."

Gallstones are formed by a disruption in the normal balance of bile acids and phospholipids that are pumped from the liver into the gall bladder. Bile then becomes supersaturated with cholesterol, which is still being pumped into the bile under control of another metabolic pathway. This supersaturation causes the cholesterol to precipitate as crystals, which, under conditions created by the chemical imbalance, can form gallstones. The subsequent change in biochemical conditions and gallstone formation then triggers inflammation, which is the major symptom of patients suffering from cholesterol gallstone disease (CGD).

In their studies, the researchers sought to determine the role of a protein known as farnesoid X receptor (FXR), which controls genes whose proteins regulate the transport of bile acids and phospholipids from the liver into the gallbladder. Previous studies had indicated that FXR's activity is low in strains of mice that are more susceptible to gallstone disease.

To study FXR's function, the researchers used a knockout mouse that lacked the *FXR* gene. They then fed the mice a "lithogenic" diet, which is designed to induce gallstone formation because it is high in cholesterol and other components of bile.

Mice are good models for CGD, said Mangelsdorf, because mice and humans have the same genetic regulatory pathways to control the components of bile. Also, the mouse version of CGD physiologically mimics the disease that is observed in humans.

The researchers' analyses of bile components in the knockout mice revealed cholesterol saturation and lower levels of biliary lipids, resulting in cholesterol crystals—conditions that closely matched those seen in humans with CGD. They also found that the bile acids created the same hydrophobic conditions and inflammation that are hallmarks of the human disease.

Finally, the researchers measured the activity of genes known to be regulated by FXR in the knockout mice. Among these, they found low activity in those involved in the transportation of lipid components of bile.

“Once we had established that the FXR-deficient animals were much more susceptible than normal animals to getting all the sequelae of CGD, we decided to explore the effects of enhancing FXR activity in a strain of mouse that was known to have FXR, but which was also susceptible to the disease,” said Mangelsdorf. “We wanted to determine whether such a drug could reestablish the proper equilibrium of the bile components.”

To do this, the researchers gave CGD-susceptible mice, which were fed a lithogenic diet, a synthetic compound—code-named GW4064—known to mimic the natural chemical that switches on FXR.

Mangelsdorf said the compound's effects were dramatic. “Their cholesterol saturation, bile lipids, and bile hydrophobicity were normal. And they showed no cholesterol crystal precipitation or inflammation,” he said. In contrast, susceptible mice that did not receive GW4064 showed evidence of gallstone formation. Mangelsdorf said the studies also showed that FXR-knockout mice - in which the drug was not expected to work - developed CGD more rapidly than the susceptible mice.

“While we have not shown in this study that the drug that activates FXR cures the disease once it starts, it does prevent gallstones from occurring,” said Mangelsdorf. Although further studies will be needed to determine whether the FXR-activating drug could dissolve gallstones, their findings have clinical implications for both diagnosis and prevention of CGD, he said.

“Humans are known to have a genetic component to risk of CGD that has never been identified,” he said. “While surgical removal of the gallbladder will remain the major treatment for existing CGD, if we can identify those at genetic risk, we might be able to prevent the disease. The lack of FXR might well be a diagnostic marker for genetic predisposition to CGD.”

Also promising, said Mangelsdorf, is the potential for such a drug to prevent pancreatic inflammation and “microlithiasis” in people who have had their gallbladders removed because of gallstones. In this disorder, a sludge of cholesterol-supersaturated bile inflames the bile duct because of its abnormal properties. By restoring the normal properties of bile, the drug would render it less viscous and inflammatory.

While the drug used in the experiments is an expensive experimental compound, said Mangelsdorf, “I have no doubt that the pharmaceutical industry will use these findings as a basis for commercial drug development, provided there are no serious side-effects in humans.”