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Turning off key piece of genetic coding eliminates toxic effect of statins

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In research funded by the National Institutes of Health and the American Heart Association and published in *EMBO Molecular Medicine*, Saint Louis University investigator Ángel Baldán, Ph.D., found that the microRNA miR-33 plays a key role in regulating bile metabolism. Further, the research suggests that, in an animal model, the manipulation of this microRNA can improve the liver toxicity that can be caused by statins.

"As we learn more about the way cholesterol is moved and metabolized through the body, we have more tools at our disposal to try to limit potential side effects of cholesterol-managing drugs like statins," said Baldán, who is assistant professor of biochemistry and molecular biology at Saint Louis University.

This study continues Baldán's exploration of the microRNA miR-33, which is expressed from within SREBP-2, an important gene in the body that previously had been shown to regulate cholesterol metabolism. In earlier research, the Baldán laboratory found that miR-33 plays a key role in regulating cholesterol. In particular, his team found that decreasing the levels of the microRNA (which is a piece of genetic coding) helped to raise HDL, or "good cholesterol," in an animal model. Five laboratories, including Baldan's, simultaneously reported these results in 2010.

Now, as Baldán continues to study the role of miR-33, he has examined two particular bile transporters, ABCB11 and ATP8B1, and found that

miR-33 directly regulates these transporters. The research team found that when they silenced miR-33, turning off the microRNA's signal, they caused increases in bile secretion from the liver, so more bile was recovered in the gallbladder.

Further confirming the suspicion that this pathway was responsible for regulating the flow of bile, researchers treated two groups of mice with an anti-miR-33 drug and tracked radioactively labeled cholesterol as it moved through and was eliminated by these animals.

"We hypothesized we should see changes in the amount of radioactivity in the cholesterol that was eliminated in the mice's feces, depending on whether they were given placebo or anti-miR-33," Baldán said. "That is in fact what we found. When the microRNA is silenced, the pathway is enhanced and more cholesterol is passed through."

Bile is produced by the liver to help the body digest dietary lipids. Bile is itself made up, in part, of cholesterol and cholesterol-derived bile acids, and it also serves a key function in controlling the body's balance of cholesterol.

When the body doesn't secrete and transport bile well, due to an obstruction like a gallstone, or, as examined in this study, because of a genetic variation or medication side effect, bile cannot flow from the liver to the small intestine. The resulting blockage causes cholestasis, a kind of liver damage.

In the final segment of the study, researchers took note of a genetic condition, called progressive familial intrahepatic cholestasis (PFIC), an inherited disease that causes cholestasis and can lead to liver failure. PFIC is caused by defects in the biliary transporters, such as ABCB11 and ATP8B1, the very genes that are regulated by miR-33. Interestingly, the same group of symptoms can occur in a less severe form, called

benign recurrent intrahepatic cholestasis (BRIC) in some people with less severe genetic mutations.

"Intriguingly, a very small number of patients who take statins develop a syndrome identical to BRIC, a milder version of the same illness experienced by people who have the genetic disease PFIC," Baldán said. "In this case, though, statins caused the condition pharmacologically.

"We further hypothesized that conditions that induce miR-33 could, under certain circumstances, also induce a BRIC-like syndrome, by reducing the expression of ABCB11 and/or ATP8B1."

To test this theory, researchers fed mice a special high fat, high cholesterol diet, in the presence or absence of statins (which induces miR-33). As expected, animals that did not receive statins tolerated the diet with no problems, but those mice that did receive the drug developed liver damage, mimicking the cholestasis found in some human patients.

"To conclusively prove that this was due to the induction of miR-33, we treated the animals with anti-miR-33, and, when we did, their livers recovered," Baldán said. "In effect, miR-33 encourages some of the undesired, hepatotoxic effects of statins and by silencing this signal we were able to avoid these toxic side effects.

"This discovery may ultimately lead to treatment options both for those with BRIC, and more broadly, those who suffer from statin side effects."

The researchers' next step will be to test patients who experienced cholestasis after taking statins to see if they do, indeed, have a particular genetic alteration related to miR-33 signaling.

To sum up, researchers found that:

- Statins induce miR-33.
- MiR-33 decreases expression of bile transporters ABCB11 and ATP8B1, which can lead to cholestasis.
- Silencing the microRNA with anti-miR-33 eliminated the toxic side effects from taking statins in an animal model.

Provided by Saint Louis University

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