Cholesterol's other way out

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Many of us are simply overloaded with cholesterol, and now a report in the July issue of *Cell Metabolism* brings what might be good news: There is more than one way to get rid of that cholesterol, which can otherwise lead to atherosclerosis and heart disease.

"Cholesterol really can't be broken down," said Mark Brown of Wake Forest University School of Medicine. To get rid of it, it must be excreted, and now Brown and his colleagues have new evidence for an alternate way to deliver cholesterol into the feces. The findings revise scientific dogma about cholesterol loss that goes back almost 40 years.

Textbooks say that white blood cells known as macrophages gobble up cholesterol from artery walls. That cholesterol is then delivered to high-density lipoprotein [HDL, aka good cholesterol], which takes it back to the liver where it goes into bile.

"Bile is necessary under the model to deliver cholesterol to the intestine," Brown said.

There were some hints that might not be the whole story. A model of cholesterol loss first proposed way back in the 1920s suggested the existence of a route that didn't rely on bile. And indeed, studies in dogs unable to get cholesterol into bile showed that the animals actually experienced an increase in cholesterol loss. More recent studies in mice showed a similar thing.

Even so, the researchers said that an alternative pathway has largely been

ignored. As a result, scientists have made very little progress in defining the molecular pathways and players involved.

Now, Brown and his colleagues offer new evidence that helps support and clarify this alternate path for cholesterol. They report that mice made unable to secrete cholesterol into bile through genetic manipulation or surgery still lose cholesterol through the feces at a normal rate. Macrophages in those animals also continued to take up cholesterol from blood vessels.

The researchers believe that alternate path delivers cholesterol from the liver to the intestine directly through the bloodstream.

"The classic view of reverse cholesterol transport involved the delivery of peripheral cholesterol via HDL to the liver for secretion into bile," the researchers wrote. "In parallel, we believe that the liver also plays a gatekeeper role for nonbiliary fecal sterol loss by repackaging peripheral cholesterol into nascent plasma lipoproteins that are destined for subsequent intestinal delivery."

For the purposes of cholesterol-lowering drug discovery, it may prove fruitful to consider those two pathways as "separate and complementary," Brown said.

There is some reason to think that drugs aimed to increase cholesterol loss without relying on bile might come with fewer side effects. That's because an excess of cholesterol in bile can lead to gallstones.

"You don't necessarily want to increase cholesterol in the bile," Brown said. And now it seems, there might be a way to get rid of cholesterol without having to.

More information: Temel et al.: “Biliary Sterol Secretion Is Not

Required for Macrophage Reverse Cholesterol Transport." Publishing in Cell Metabolism 12, 96-102, July 7, 2010. DOI 10.1016/j.cmet.2010.05.011