BIOMEDICINE

Receptor Offers Clues to How 'Good' Cholesterol Works

Just about every health-conscious person knows by now that having lots of HDL cholesterol—the so-called good cholesterol—in the blood is just as important as having low levels of LDL cholesterol. LDL (low density lipoprotein), of course, predisposes to atherosclerosis and the problems it causes, including heart attacks and strokes, while HDL (high density lipoprotein) is protective. Exactly how HDL protects the arteries has been a mystery, but investigators now have their hands on a key to the answer: the receptor that enables cells to capture cholesterol from HDL particles in the bloodstream.

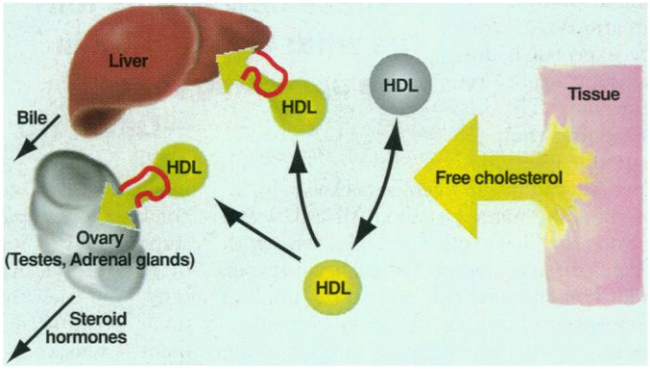

ILLUSTRATION: P. RIEHN SOURCE: M. KRIEGER

Shuttle service. HDL ferries cholesterol from tissue to receptors (red) on the liver and certain glands, where it discharges its load.

The leading theory of how HDL safeguards arteries is that it somehow removes excess cholesterol from blood and tissue, including the cholesterol-loaded cells of atherosclerotic plaques, then carries the excess through the bloodstream to the liver and other tissues. They take in the cholesterol from HDL and use it to synthesize other substances such as steroid hormones and bile acids. But actually proving this scenario was difficult, says cell and molecular biologist Monty Krieger of the Massachusetts Institute of Technology (MIT): "What has been missing is an HDL receptor to give a molecular and cellular handle on the HDL system."

Now, in the 11 November issue of the *Proceedings of the National Academy of Sciences* (*PNAS*), the Krieger team provides the best evidence yet that a receptor identified during other studies is the key to HDL transport. The clinching evidence came when they knocked out the mouse gene encoding the molecule, designated SR-BI. They found—as expected—that the mice's blood cholesterol levels increased dramatically, while concentrations in organs that pick up cholesterol from HDL, such as the steroid-producing adrenal gland, dropped.

With the HDL receptor positively identified, investigators should be able to study just how HDL protects against cholesterol deposition in atherosclerotic lesions and perhaps develop drugs that boost the protective effect. "This is a crucial step in obtaining a complete understanding of cholesterol transport," says Michael Brown of the University of Texas (UT) Southwestern Medical Center in Dallas, who shared the 1985 Nobel Prize in medicine with his longtime Texas colleague Joseph Goldstein for discoveries that revealed how LDL helps cause atherosclerosis.

Krieger and his colleagues didn't set out to find the HDL receptor. In their original work, which began in the mid-1980s, they were looking for so-called scavenger receptors, which macrophages use to vacuum up modified lipoproteins and other remnants of cells damaged by infection or disease. In 1994, they cloned the gene for what appeared to be the first of a new class of lipoprotein scavenger receptors, which they called SR-BI (for scavenger receptor BI).

But it soon became clear that SR-BI wasn't just another scavenger receptor. First, the researchers were surprised to find that it binds LDL. And when they then tested SR-BI binding to other lipoproteins, they found that it could bind HDL tightly, which raised the possibility that SR-BI might be the long-sought receptor that enables HDL to deliver its cholesterol load to liver and steroid-synthesizing cells.

Further studies supported that idea. When the team transferred the gene for SR-BI into cells that don't readily take up cholesterol from HDL, they found that the cells acquired that ability. What's more, the gene is expressed primarily in the right places for the proposed function, including the liver and glands that produce steroid hormones, such as the ovary and adrenals (*Science*, 26 January 1996, pp. 460 and 518). And in research reported in the 22 May issue of *Nature*, a group led by Krieger and one of his former graduate students, Karen Kozarsky, a gene therapy specialist at the University of Pennsylvania Medical Center in Philadelphia, used a modified adenovirus carrying the SR-BI gene to induce overexpression of the receptor in the liver cells of mice. As a result, nearly all circulating HDL disappeared from the animals' bloodstreams, while the concentration of cholesterol in their bile doubled.

But the gold standard for proving the function of a gene is the knockout mouse. SR-BI has passed this test. In their *PNAS* paper, Krieger and MIT colleagues Attilio Rigotti, Bernardo Trigatti, Marsha Penman, and Helen Rayburn, along with UT Southwestern researcher Joachim Herz, report that they've inactivated the SR-BI gene in mice and found that plasma cholesterol levels in the knockout animals more than doubled. Indeed, knocking out the gene had approximately the same effect on total serum cholesterol levels as a known contributor to atherosclerosis: loss of the LDL receptor, which causes blood cholesterol concentrations to soar.

At the same time, the knockout animals showed a dramatic drop in adrenal cholesterol, indicating that those tissues were being starved of HDL cholesterol. "Now it is doubly clear that this is the receptor" that takes up HDL cholesterol, says cholesterol researcher Daniel Steinberg of the University of California, San Diego.

The next big question facing researchers concerns whether SR-BI is as important for cholesterol transport in humans as it is in mice. Researchers will also want to know whether defects in SR-BI contribute to the development of human atherosclerosis.

But even if SR-BI is not directly involved in causing atherosclerosis, Krieger thinks that the receptor might still be a target for drugs to head off the condition. He notes that the work of Brown and Goldstein led directly to the enormously successful "statins," which lower bad cholesterol by increasing LDL receptor levels in the liver. SR-BI could also be manipulated, he suggests, to make good cholesterol levels even better.

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—Michael Brown

–Larry Husten

Larry Husten is a science and health writer in New York City.