How drug that blocks cholesterol absorption from the diet works

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A new study in the June issue of *Cell Metabolism*, a Cell Press publication, sheds light on the action of the drug ezetimibe (trade name Zetia), which is used to treat high cholesterol. Ezetimibe is unique among cholesterol-lowering drugs in that it works by cutting the amount of cholesterol taken in from the diet rather than by blocking cholesterol's manufacture in the body.

Earlier studies had suggested that ezetimibe acts on an intestinal and liver protein recently found to play a critical role in cholesterol absorption. Now, the researchers reveal how that protein known as Niemann-Pick C1-like 1 (NPC1L1) carries cholesterol into the cell. They also show that ezetimibe bars NPC1L1's entry into the cell, thereby keeping cholesterol at bay.

" This is a breakthrough in terms of understanding how cholesterol is absorbed," said Bao-Liang Song of Shanghai Institutes for Biological Sciences. "Now we see how NPC1L1 is recycled between the cell surface and vesicles [inside the cell] and how it takes in cholesterol."

The findings might also have important implications for the search for new cholesterol absorption inhibitors, he added. "If we can uncover the players, we can try to identify new small molecules to interfere with the process."

Despite its bad reputation as a major risk factor for coronary heart disease, cholesterol is an essential component of most biological

membranes and is the precursor for synthesis of steroid hormones and bile acids produced by the liver to break down fat. Almost every kind of mammalian cell can synthesize cholesterol, but the process is an energy-intensive one. Therefore, mammals including humans obtain significant amounts of cholesterol from their diets.

Four years ago, scientists identified NPC1L1 as a critical player in cholesterol's absorption. Researchers also found that mice lacking NPC1L1 stop responding to ezetimibe. While there were clues that the drug interacts directly with the cholesterol absorption protein, the details remained unclear.

Song's group now finds that cholesterol specifically encourages cells to engulf and internalize NPC1L1 in a process known as endocytosis. In that process, part of the cell membrane pinches off to form a vesicle containing the protein.

By preventing NPC1L1's entry into the cell, the researchers showed they could dramatically reduce the amount of cholesterol taken up by cells. Ezetimibe accomplishes that by preventing NPC1L1 from incorporating into vesicles.

Although ezetimibe can dramatically decrease blood cholesterol concentrations in some people, it is barely effective in others, the researchers said.

" Therefore," Song said, "there is an urgent need for more cholesterol uptake inhibitory drugs. Our work provides the molecular basis for developing additional cholesterol absorption inhibitors. Moreover, the cell-based assay that we have established can potentially be used to screen for novel inhibitors of NPC1L1 endocytosis, which will block cholesterol uptake eventually."

Source: Cell Press