Preventing cholesterol absorption

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Because cholesterol plays a central role in the development of cardiovascular disease, the different types of cholesterol and their appropriate serum levels have become an important focus in the prevention of cardiovascular events. An understanding of the physiologic synthesis of cholesterol led to the discovery of drugs that inhibit this process: among other actions, HMG-CoA reductase inhibitors (statins) decrease hepatic formation of cholesterol, specifically low-density lipoproteins, and are widely used to treat dyslipidemia.

However, the process of cholesterol absorption from the gut has not been well understood. It is known that cholesterol is absorbed from the proximal jejunum, and it has been postulated that it is absorbed via a carrier protein in the gut endothelium.

Altmann and colleagues performed a series of experiments in an attempt to identify this carrier. They analyzed thousands of DNA sequences from rat intestine looking for sequences with features anticipated to be important in cholesterol interaction and transport. They were able to narrow their search to the rat homolog of the human gene, *NPC1L1*.

To determine the role of *NPC1L1*, the authors obtained a line of mice that lacked the gene (homozygous); they bred this line with wild mice who possessed the gene (also homozygous) to create a line of heterozygotes. They then fed the 3 lines of mice with radiolabelled cholesterol and found that the homozygotes who possessed *NPC1L1* absorbed 51% of the cholesterol, the heterozygotes absorbed 45%, and the homozygotes lacking the gene absorbed only 16% of the cholesterol.

The experiments were repeated after the mice were given ezetimibe, a drug known to interfere with cholesterol transport. In the mice with *NPC1L1*, the drug dramatically decreased the amount of cholesterol absorbed; in the mice lacking the gene, there was no difference. The authors therefore hypothesized that the drug's mechanism of action centred on the NCP1L1 protein.

Although these findings are promising, it is likely that treatments targeting the transport of cholesterol from the gut will be only one component of treating dyslipidemia treatment. The authors noted that decreased transport of cholesterol from the gut to the liver in mice lacking *NCP1L1* caused an almost 4-fold up-regulation of hepatic HMG CoA synthase. It is evident that the interplay of multiple biochemical processes characterizes cholesterol metabolism, a detailed understanding of which will allow future therapies to be developed and refined. (Altmann et al. *Science* 2004;303:1201-4.)

— Compiled by *Stephen Choi*, CMAJ

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