A scientific breakthrough on the control of the bad cholesterol

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A study performed by the team of Dr. Nabil G. Seidah, Director of the Biochemical Neuroendocrinology Research Unit at the IRCM, shows for the very first time that the degradation by PCSK9 of the LDLR receptor, which is responsible for removing the bad cholesterol (LDL-cholesterol) from the bloodstream, may be inhibited by a third protein, annexin A2. This major discovery co-authored by Gaétan Mayer, a postdoctoral fellow, Steve Poirier, a doctoral student, and Dr. Seidah was published on November 14 in the *Journal of Biological Chemistry*.

Genetic studies on humans have clearly shown that PCSK9 is a prime therapeutic target for the prevention and treatment of cardiovascular diseases. PCSK9 proprotein convertase promotes the degradation of the receptor responsible for eliminating LDL-cholesterol particles. Thus, the presence of PCSK9 leads to a surplus of bad cholesterol in the bloodstream and contributes to plaque formation, leading to blockage of blood vessels and arteries. This phenomenon is a major risk factor that can lead to cardiovascular diseases, such as heart attack, atherosclerosis and stroke.

Mutations of human genes have demonstrated that a rise in PCSK9 activity results in a major increase in LDL-cholesterol and familial hypercholesterolemia. Conversely, in people with a non-functional mutation in the gene coding for PCSK9, a decrease in its activity brings down the LDL-cholesterol concentration levels in the bloodstream and diminishes by up to 88% the risks of developing cardiovascular diseases.

"By performing a series of biochemical experiments, we discovered that annexin A2 binds strongly to PCSK9 and inhibits its function," remarks Gaétan Mayer, the article's first author. This discovery should pave the way toward the development of a new drug that would lower blood cholesterol to recommended levels. Currently, cholesterol lowering drugs known as "statins" are used by more than 25 million people worldwide.

Statins decrease cholesterol synthesis and increase the number of LDL-receptors, thus efficiently decreasing plasma cholesterol levels; however, they also increase the amount of PCSK9, which degrades those receptors, thus reducing the effect of statins. A drug that would block PCSK9 could either be used alone or jointly with statins and would be highly beneficial to patients in whom statins do not work or are unable to take this drug.

Reference: Mayer G, Poirier S, and Seidah NG. (2008) Annexin A2 is a C-terminal PCSK9-binding protein that regulates endogenous low density lipoprotein receptor levels. *J Biol Chem*, November 14; 283(46): 31791-801.
The on-line version of this article is available at: www.jbc.org/content/vol283/issue46/index.shtml .

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