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LIPIDS

# HDL cholesterol—new insights

Levels of HDL cholesterol are inversely associated with cardiovascular disease. Given this relationship, the pharmaceutical industry is currently developing strategies to lower cardiovascular disease risk by targeting HDL metabolism. In this context, inhibitors of cholesteryl ester transfer protein (CETP) are a class of drugs that are being tested in several phase III clinical trials.

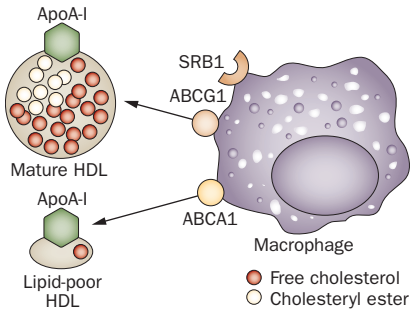
However, several reports have raised doubts about whether all HDLs have the same function and whether measures of HDL function might be more predictive of cardiovascular disease risk than levels of HDL cholesterol.

Together with George H. Rothblat (Children's Hospital of Philadelphia), Daniel J. Rader (University of Pennsylvania) had been working on cholesterol efflux capacity—the ability of an individual's HDL to extract cholesterol from macrophages—and asked if this efflux capacity is associated with cardiovascular disease even after adjusting for HDL cholesterol levels.

The investigators assessed efflux capacity and the thickness of the carotid wall, as a measure of atherosclerotic plaque, in 203 healthy participants. "In a second study, we compared patients with documented coronary disease by angiography to those with no coronary disease by angiography," explains Rader. "In both studies, we found that cholesterol efflux capacity was significantly inversely associated with cardiovascular disease even after adjusting for HDL cholesterol levels." In other words, HDL function is more important than HDL cholesterol levels for protection against cardiovascular disease.

"Not all persons with low HDL cholesterol are necessarily at increased cardiovascular disease risk, whereas not all persons with high HDL cholesterol levels are necessarily protected from cardiovascular disease," reflects Rader. "Not that HDL cholesterol is worthless, but the interpretation of HDL cholesterol levels in the individual patient should be made with some caution." Unfortunately, the test to measure cholesterol efflux capacity is highly laborious and not suitable for development as a clinical test at this time.

In a second study, Dutch investigators showed that a functional mutation in the scavenger receptor class B member 1 (*SRB1*; also known as *SCARB1*) in humans causes high HDL cholesterol levels, without apparent effects on atherosclerosis. In mice, Srb1 has long been established as a major receptor for HDL. "SRB1 was not expected to play an important role in humans," recounts senior investigator Jan A. Kuivenhoven (University of Amsterdam), as mice, which are naturally CETP-deficient, transport the majority of their cholesterol in HDL, whereas humans transport it in LDL. Strikingly, Kuivenhoven, together with Miranda Van Eck (Leiden University) found that, as in mice, HDL serves as a donor of cholesterol for the adrenal glands to produce corticosteroids in humans. Reduced corticosteroid levels were due to attenuated adrenal SRB1 protein function.

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**Original articles** Khera, A. V. *et al.* Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N. Engl. J. Med.* **364**, 127–135 (2011) | Vergeer, M. *et al.* Genetic variant of the scavenger receptor BI in humans. *N. Engl. J. Med.* **364**, 136–145 (2011)

CORRECTION

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In the version of this article initially published online on 1 March 2011, the doi in the citation line in the PDF was incorrect. The citation line originally read "… doi:10.1038/nrendo.2011.18" instead of "… doi:10.1038/nrendo.2011.28". The HTML version of the article has always been correct. The error has now been corrected in the PDF version of the article.