Why raising good cholesterol may not always protect against heart disease

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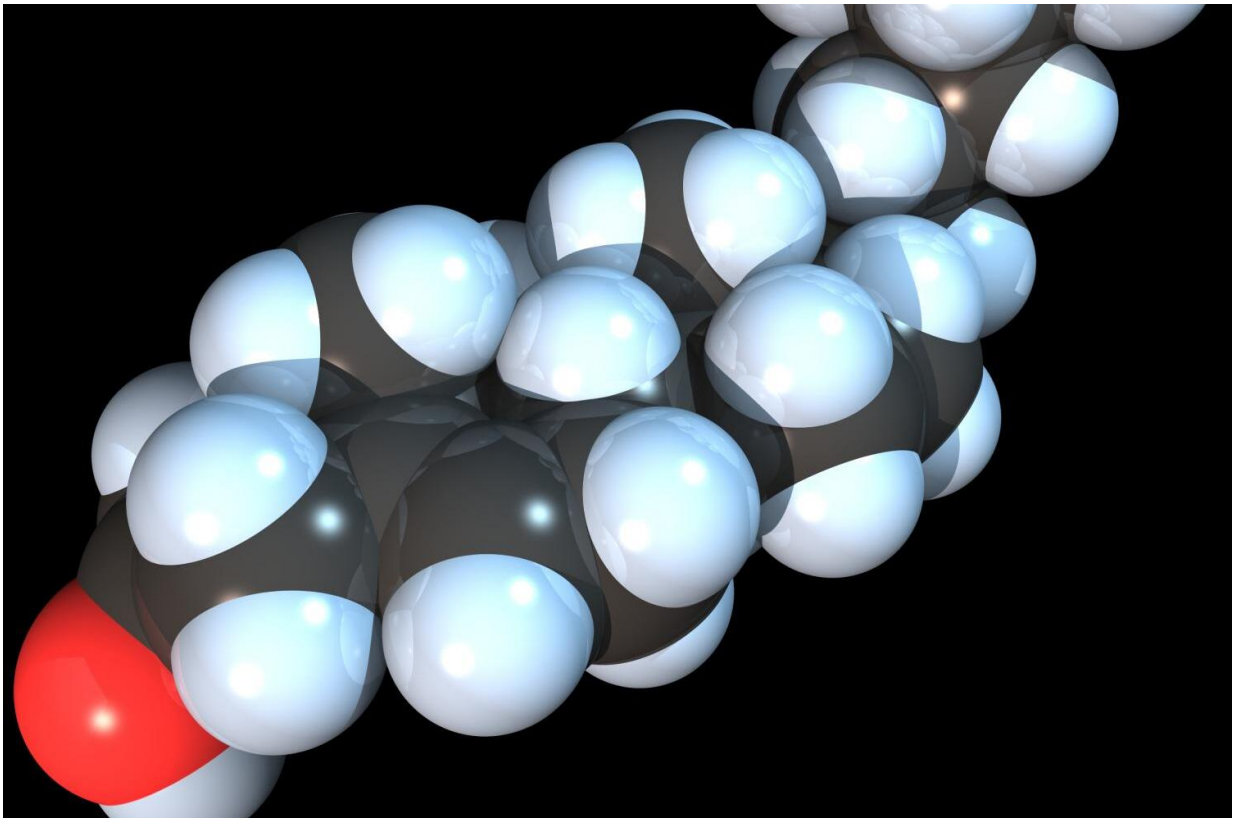

Space-filling model of the Cholesterol molecule. Credit: RedAndr/Wikipedia

Good cholesterol is well associated with lower cardiovascular disease risk, but just raising high-density lipoprotein (HDL) levels have produced disappointing results in recent clinical trials. A study published

November 17 in *Cell Metabolism* may explain why: HDL actually increases the inflammatory response of immune cells called macrophages, potentially counteracting its well-established anti-inflammatory effect in various other cell types.

"A main take-home message of our study is that HDL's functions are not as simple as initially thought, and appear to critically depend on the target tissue and cell type," says senior study author Marjo Donners of Maastricht University. "In the end, it is the balance between its pro- and anti-inflammatory effects that determines clinical outcome."

Based on decades of research in humans and animals, HDL has gained its now well-established reputation as the "good cholesterol." High HDL levels have been associated with a lower risk of atherosclerosis—an inflammatory disease that causes plaque to build up inside of arteries. In contrast to low-density lipoprotein, which is responsible for depositing cholesterol in vessel walls, HDL removes cholesterol and transports it toward the liver for degradation. Specifically, HDL protects against atherosclerosis by inhibiting inflammation in two important vascular wall cells: endothelial cells and smooth muscle cells.

However, macrophages are key immune cells contributing to the inflammation that characterizes atherosclerosis. Surprisingly, the effect of HDL on the inflammatory response in macrophages has not been clear. In the new study, Donners and first co-author Emiel van der Vorst of Maastricht University set out to address this question. Unexpectedly, they found that HDL treatment enhanced inflammation in macrophages, in contrast to its effects in other cell types. Similarly, macrophages taken from mice with elevated HDL levels showed clear signs of inflammation.

This pro-inflammatory effect induced by HDL had at least one benefit: enhanced pathogen protection. Lung macrophages ingested disease-

causing bacteria upon exposure to HDL. On the other hand, mice with low HDL levels were impaired at clearing these bacteria from the lungs. The results demonstrate that HDL's pro-inflammatory activity supports the proper functioning of macrophage immune responses. According to Donners, these findings suggest that patients with persistent infections or specific immune disorders might benefit from HDL-raising therapies.

However, several study limitations complicate clinical interpretations. For one, the study focused on acute inflammatory responses rather than the chronic inflammatory conditions that characterize cardiovascular diseases. Moreover, the researchers did not examine macrophages specifically in atherosclerotic tissue. "Whether HDL exerts beneficial or detrimental effects on the macrophage in a complex micro-environment, such as the atherosclerotic plaque, remains to be determined," Donners says.

The answer to this question may depend on disease stage and the net effect on all vascular wall cells. "For instance, in early atherosclerosis, a proper macrophage response could result in more effective scavenging and elimination of lipids and cellular debris, which may alleviate disease, whereas at later stages, such exaggerated responses may be detrimental because they destabilize the plaque," she says. "Moreover, the overt anti-inflammatory effects in other cell types should be taken into account, and it is the balance between these opposite effects of HDL that will determine clinical outcome for cardiovascular disease patients."

In the end, this research could lead to the development of cell-specific therapies that exploit the benefits of HDL-targeted therapies while avoiding the side effects. "Future studies will have to evaluate the delicate balance of HDL's cell-specific effects in humans and in various pathologies to get more insights and to develop and improve therapeutic strategies," Donners says.

More information: *Cell Metabolism*, van der Vorst and Theodorou et al.: "High-Density Lipoproteins Exert Pro-Inflammatory Effects on Macrophages via Passive Cholesterol Depletion and PKC-NF-kB/STAT1-IRF1 Signaling" www.cell.com/cell-metabolism/f … 1550-4131(16)30544-7 , DOI: 10.1016/j.cmet.2016.10.013

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