Endogenous peptide lowers cholesterol

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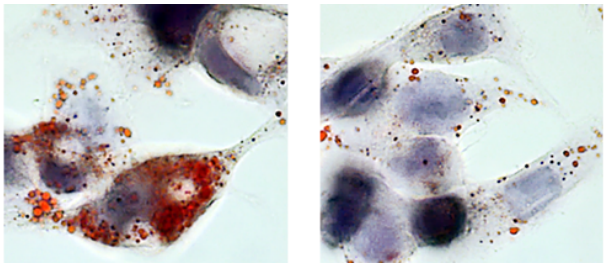

Uptake of human LDL by HepG2 cells in presence (left) or absence (right) of HNP1. LDL uptake was quantified following Oil Red O staining. Credit: Nicole Paulin, LMU

Cells of the innate immune system that play an important role in development of atherosclerosis contain a protein that reduces levels of cholesterol in mice – and thus helps to inhibit or mitigate the disease.

Atherosclerosis remains one of the primary causes of premature death in modern Western societies. The term itself refers to insoluble, fat-rich deposits that form on the inner wall of major blood vessels resulting in a chronic, localized inflammation. These so-called plaques obstruct blood flow and can ultimately lead to heart attacks and strokes. The unresolved inflammatory reactions that lead to atherosclerosis are initiated by immune cells in response to perturbations in lipidmetabolism owing to the presence of excess cholesterol (hypercholesterolemia) in the circulation. Researchers led by LMU's Oliver Söhnlein have now shown in mice that one of the cell types involved produces a protein that inhibits atherosclerosis by intervening in cholesterol metabolism. The new finding, reported in the journal *EBioMedicine*, could open up new options for the treatment of atherosclerosis.

Initiation and progression of atherosclerosis are closely linked to the activation of specific classes of cells that are part of the immune system. In earlier experiments, Söhnlein and his colleagues had shown that white blood cells called neutrophils play an important role in the process. The most abundant protein found in human neutrophils is human neutrophil peptide 1 (HNP1), which is known to have anti-microbial and pro-inflammatory functions. In contrast, mouse neutrophils normally do not express this protein at all. "This observation provided us with a unique opportunity to study the function of this protein. To do so, we genetically constructed a mouse strain that is not only prone to atherosclerosis, but also produces high levels of HNP1," Söhnlein explains. Much to their surprise, the LMU team found that the atherosclerotic lesions that formed in these mice were much smaller than those seen in the mice that lacked HNP1. "We expected to see exactly the opposite effect – in particular because we had previously discovered that HNP1 stimulates the recruitment of atherosclerosis-promoting monocytes to sites of inflammation," Söhnlein adds.

When they examined the HNP1-expressing mice more closely, the researchers discovered that the animals had lower levels of circulating cholesterol than control mice. Because cholesterol is not soluble in water, it is transported in the bloodstream in association with so-called lipoproteins. Lipoproteins are often divided into good guys and bad guys. The good guys, including HDL, transport cholesterol from the tissues to the liver and thus reduce the risk of atherosclerosis. The bad guys, like LDL, convey cholesterol in the opposite direction – from the liver to the tissues. High levels of circulating LDL thus enable more cholesterol to be delivered to endothelial cells that are especially prone to damage or are already damaged, and therefore tend to promote atherosclerosis. "Indeed, we were able to show that HNP1 binds to LDL in the bloodstream and induces rapid uptake of circulating LDL by the liver, thus reducing hypercholesterolemia," says Söhnlein. This can account for the reduction atherosclerotic lesions in HNP1-expressing mice.

The researchers believe that their findings may lead to new approaches to the treatment of

hyperlipidemia. "Since HNP1 is a natural constituent of the human body, therapeutic use of the protein would be expected to be relatively free of side-effects and should not compromise immune defenses," Söhnlein points out.

More information: Nicole Paulin et al. Human neutrophil peptide 1 limits hypercholesterolemia-induced atherosclerosis by increasing hepatic LDL clearance, *EBioMedicine* (2017). DOI: 10.1016/j.ebiom.2017.01.006

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