Early atherosclerotic plaques regress when cholesterol levels are lowered

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Early but not advanced forms of atherosclerotic plaques in the vessel wall disappear when the levels of 'bad' cholesterol are lowered, according to a study in mice from Karolinska Institutet, Sweden. The findings, published in *PLoS Genetics*, indicate that preventative cholesterol-lowering treatment could prevent more advanced, clinically relevant plaque to develop.

Almost half of all deaths worldwide are caused by strokes and heart attacks. The main underlying cause is atherosclerosis, where fat accumulates in the blood vessel walls in the so-called plaques. Atherosclerosis is a progressive disease where advanced and unstable plaques develop over time. When these plaques burst a blood clot is created, which in turn could cause stroke or heart attack, depending on how and where the blood clot is formed. It is therefore preferable to either prevent advanced plaque development, or to reduce and stabilise the plaques in those where they have already developed.

In the current study, the researchers used mice with elevated levels of 'bad' cholesterol (LDL cholesterol) which forms advance plaques, similar to what happens in humans with high LDL. With a genetic switch, researchers could also lower cholesterol levels in the blood at any desirable time point. They discovered that when LDL cholesterol was lowered, early plaques disappeared almost entirely, which to some extent surprised the researchers. However, mature and advanced plaques reduced but were still present. In humans, LDL cholesterol can be lowered by using cholesterol-lowering drugs such as statins.

"If lowering of LDL cholesterol affects atherosclerosis in humans in the same way, our observations mean that clinically advanced plaques could be prevented if cholesterol-lowering treatments are administered early enough in individuals with increased risk of cardiovascular disease. However, the perennial problem is to identify these individuals with certainty," says Dr Josefin Skogsberg at the Department of Medical Biochemistry and Biophysics, one of the principal researchers involved in the study.

The researchers also identified networks of genes that were activated by the cholesterol lowering procedure and caused the regression of the atherosclerotic plaques. There proved to be much greater differences in these networks between early, mature and advanced plaques than what researchers had believed.

"We believe that the regulators of the networks, "network wiring stations" may be suitable parallel treatment targets in order to improve the impact of the LDL cholesterol lowering on the regression of plaque in individuals with mature and advanced plaques," says Dr Skogsberg.

Provided by Karolinska Institutet