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Subclinical atherosclerosis and its progression are modulated by perilipin-2 through a feed-forward loop between LXR and autophagy

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Background: Hyperlipidemia is a major risk factor for cardiovascular disease and atherosclerosis is the underlying cause of both myocardial infarction and stroke. We have previously shown that the Pro251 variant of perilipin-2 reduces plasma triglycerides and may therefore be beneficial for atherosclerosis development.

Purpose: We sought to delineate putative beneficial effects of the Pro251 variant of perilipin-2 on subclinical atherosclerosis and the mechanism by which it acts.

Methods: A pan-European cohort of high-risk individuals where carotid intima-media thickness has been assessed was adopted. Human primary monocyte-derived macrophages were prepared from whole blood from individuals recruited by perilipin-2 genotype, or from buffy coats from the our University hospital blood central.

Results: The Pro251 variant of perilipin-2 is associated with decreased intima-media thickness at baseline and 30 months follow-up. Using human primary monocyte-derived macrophages from carriers of the beneficial Pro251 variant we show that this variant increases autophagy activity, cholesterol efflux, and a controlled inflammatory response. Through extensive mechanistic studies we demonstrate that increase in autophagy activity is accompanied with an increase in LXR activity and that LXR and autophagy reciprocally activate each other in a feed-forward loop, regulated by CYP27A1 and 27OH-cholesterol.

Conclusions: For the first time, we show that perilipin-2 affects susceptibility to human atherosclerosis through activation of autophagy and stimulation of cholesterol efflux. We demonstrate that perilipin-2 modulates levels of the LXR ligand 27OH-cholesterol and initiates a feed-forward loop where LXR and autophagy reciprocally activate each other; the mechanism by which perilipin-2 exerts its beneficial effects on subclinical atherosclerosis.