**MACROPHAGE DEPOSITION OF CHOLESTEROL INTO THE EXTRACELLULAR MATRIX - A PATHWAY FOR REVERSE CHOLESTEROL TRANSPORT**

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*Objective*: To investigate the potential for mobilization of extracellular cholesterol within atherosclerotic plaques.

*Background*: Atherosclerotic plaques develop as a result of an imbalance between cholesterol accumulation and cholesterol removal. The macrophage plays a central role in both of these processes. How macrophages eliminate excess cholesterol has been of great interest, and is important for understanding the cholesterol accumulation process in developing atherosclerotic plaques. Our previous research has identified a novel macrophage cholesterol processing pathway, in which macrophages deposit excess cholesterol into the extracellular matrix where it can accumulate unless mobilized by HDL. Apolipoprotein A-I (ApoA-I) is the major protein component of HDL. In this study, we examined the function of ATP-binding cassette transporter A1 (ABCA1) in ApoA-I mobilization of cholesterol deposited into the extracellular matrix by cholesterol-enriched macrophages. We have also determined whether an ApoA-I mimetic peptide can mobilize macrophage deposited cholesterol.

*Method*: Human monocyte-derived macrophages and mouse bone marrow-derived macrophages with and without ABCA1 were cultured and cholesterol enriched. Extracellular cholesterol deposited by cholesterol-enriched macrophages was detected with a monoclonal antibody.

*Results*: ABCA1 causes ApoA-I and ApoA-I mimetic peptides to complex with phospholipid, a cholesterol solubilizing agent. ApoA-I and the ApoA-I mimetic peptide, 5A, mobilized cholesterol deposited by macrophages, but this depended on ABCA1 function. In contrast, ApoA-I mimetic peptide 5A pre-complexed with sphingomyelin could mobilize cholesterol deposited by macrophages deficient in ABCA1.

*Conclusions*: Our findings show that extracellular cholesterol deposited by macrophages can be mobilized by both ApoA-I and an ApoA-I mimetic peptide, but that mobilization depends on macrophage ABCA1. Importantly, ApoA-I mimetic peptide already complexed with phospholipid can mobilize the extracellular cholesterol even in the absence of ABCA1, suggesting that this cholesterol acceptor could have efficacy even when ABCA1 activity in atherosclerotic plaques is limited.