High density lipoproteins exert pro-inflammatory effects on macrophages via passive cholesterol depletion and PKC-NF-κB/STAT1-IRF1 signaling

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Background: Membrane cholesterol is known to modulate a variety of cell signaling pathways and functions. While cholesterol depletion by High-Density Lipoproteins (HDL) has potent anti-inflammatory effects in various cell types, its effect on inflammatory responses in macrophages remains ill defined.

Methods & Results: Pre-incubation of human and murine macrophages in vitro with human recombinant apoA-I-phosphatidylcholine or native HDL significantly decreased LPS-induced anti-inflammatory IL-10 production, while the opposite was observed for the pro-inflammatory mediators IL-12 and TNF. We show that these effects are mediated by passive cholesterol depletion and lipid raft disruption, without involvement of ABCA1, ABCG1, SR-BI or CD36. These pro-inflammatory effects are confirmed in vivo in peritoneal macrophages from ApoA-I transgenic mice, which have high circulating HDL levels. In line, innate responses required for clearance of P. aeruginosa bacterial infection in lung were compromised in mice with low HDL levels. Native and reconstituted HDL enhances Toll Like Receptor-induced signaling by activating protein kinase C (PKC), since inhibition of PKC ablated the observed HDL effects. Using microarray analysis and macrophages from NF-κb luciferase mice, we observed that HDL induces NF-κB activation. Western blot and ChIP-PCR analyses showed that in particular the p65 subunit was activated. Using specific knock-out mice for the upstream activation pathways, we show that HDL enhances ADAM protease activity, thereby mediating TNF release.

Conclusion and Clinical Relevance: HDL exerts pro-inflammatory effects on macrophages via passive cholesterol depletion by activation of PKC, NF-κB and STAT1. These pro-inflammatory activities on macrophages could at least partly underlie the disappointing therapeutic potential of HDL raising therapy in current cardiovascular clinical trials.