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SCAVENGER RECEPTORS MEDIATE UPTAKE OF MODIFIED LDL BY CIRCULATING BLOOD MONOCYTE SUBSETS: CONSEQUENCES FOR ATHEROSCLEROSIS.W Jackson, R Khamis, D Haskard, K Woollard *Imperial College London*

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A major risk factor for cardiovascular disease (CVD) is elevated LDL-cholesterol, which can undergo oxidative modification (mLDL). Experimental models show that mLDL in atherosclerotic

prone vascular beds leads to increased monocyte derived macrophage foam cell formation and atherosclerosis. However, an increasing appreciation of blood monocyte functional heterogeneity has complicated this model and the subset specific functions of blood monocytes in atherosclerosis is unknown. In humans, 3 circulating monocyte subsets can be identified based on CD14 and CD16 expression and 2 subsets in mice based on Gr1 expression. CD14^{high}CD16^{low} (Gr1^{high}) monocytes are well-characterized inflammatory monocytes that respond to bacterial cues, while CD14^{low}CD16^{high} (Gr1^{low}) monocytes can crawl on the vascular endothelium in the steady state, although their role in homeostatic conditions is largely unresolved. CD14^{high}CD16^{high} are poorly described in mice, but are shown to have increased frequency in human inflammatory disease. We aimed to characterise the blood monocyte subset response to mLDL by addressing the quantitation and mechanisms of uptake, subsequent functionality and how intravascular crawling monocytes may regulate mLDL endothelial deposition.

We have demonstrated differential intracellular uptake kinetics of mLDL in vitro by human monocyte subsets via quantitative imaging and flow cytometry. CD14^{high}CD16^{high} monocytes showed greatest uptake after 2 hours, via the scavenger receptor CD36. In-vivo experiments in mice showed similar uptake in monocyte subsets, peaking at 4 hours post mLDL infusion (Gr1^{high}: 4hrs 6.9+/-2.8, 24hrs 5.7+/-3.9; Gr1^{low}: 4hrs 10.3+/-4.4, 24hrs 4.3+/-2.8. Percentage cells mLDL positive, mean +/-SEM, n=3). Currently, we are developing whole body imaging modalities and high-resolution intravital microscopy in mice to attempt to understand the fate and function of 'LDL-loaded' blood monocytes. Preliminary data suggests LDL loaded monocytes localise to discrete tissues and that crawling Gr1^{low} (CD14^{low}) monocytes can scavenge LDL at the endothelial interface. Further work will determine whether they transmigrate into the arterial wall, undergo differentiation or apoptosis, localise to draining lymph nodes and/or efflux lipid to anti-inflammatory HDL. In summary, these complementary approaches add to existing knowledge on the role of mLDL and blood monocytes in atherosclerosis.