Aims: The chemokines CCL2, CCL5 and CX3CL1 stimulate vascular smooth muscle cell (vSMC) proliferation, the main driver of intimal hyperplasia. HDL have potent anti-inflammatory properties and inhibit the expression of the chemokines CCL2, CCL5 and CX3CL1 and their receptors in endothelial cells and monocytes. We therefore sought to determine the effect of rHDL on vSMC chemokine expression and proliferation and elucidate the signalling mechanisms involved.

Results: Pre-incubation of primary human vSMCs with reconstituted HDL (rHDL) containing apolipoprotein (apo)A-I and phosphatidylcholine (600µg/ml, final apoA-I concentration), prior to stimulation with TNF-α, inhibited the protein and mRNA levels of CCL2 (54%, 25%), CCL5 (55%, 54%) and CX3CL1 (34%, 38%) in vSMC cell lysates, as well as the secretion of CCL2 and CCL5 into culture media (30%, 38%, respectively) p<0.05 for all. Treatment with rHDL also suppressed the protein levels of chemokine receptors CCR2 (30%) and CX3CR1 (35%), p<0.05. The transcriptional regulators of chemokine expression p65 and pIkBα were reduced by rHDL (57% and 36% respectively, p<0.05). Upstream signalling proteins PI3K (37%) and pAkt (49%) were also suppressed, p<0.05. Pre-incubation with rHDL strikingly inhibited TNF-α-induced vSMC proliferation (84%) and ERK phosphorylation (30%), p<0.05. These effects appeared to be mediated via SR-B1, as siRNA knockdown of SR-B1 attenuated the inhibitory actions of rHDL on chemokine expression and proliferation.

Conclusion: These data suggest that via inhibition of vSMC chemokine expression and proliferation, rHDL may suppress inflammation-driven intimal hyperplasia. This has important implications for preventing the pathogenesis of restenosis that can lead to early vein graft/stent failure.