Multifunctional Regulation of Angiogenesis by High Density Lipoproteins

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Background: Angiogenesis can be both favourable and unfavourable. It is critical for collateral vessel formation in response to myocardial ischaemia (MI), however inflammatory-driven angiogenesis accelerates atherosclerotic plaque growth. High-density lipoproteins (HDL) are associated with improved survival and prognosis following MI and reduced plaque development. Herein, the potential multifunctional role of HDL in the regulation of angiogenesis under hypoxic and inflammatory conditions was investigated, in vitro.

Results: Hypoxia (1.2% O₂, 6h) increased human coronary artery endothelial cell (HCAEC) tubulogenesis (19%) and proliferation (31%), as expected. Pretreatment with reconstituted HDL (rHDL), containing apolipoproteinA-I and phosphatidylcholine, augmented hypoxia-driven elevations in tubulogenesis (14%) and proliferation (53%), p<0.05. Consistent with this, rHDL augmented hypoxia-driven elevations in the proangiogenic mediators HIF1α (39%), VEGF (1.5 fold) and SDFα (3.4 fold), p<0.05. In contrast to hypoxia, pre-treatment with rHDL significantly inhibited HCAEC tubulogenesis (75% & 70%), proliferation (47% & 39%) and migration (37% & 55%), following exposure to two inflammatory conditions: TNFα (0.7 ng/ml), and stimulated macrophage-conditioned media (CM). Preincubation with rHDL, before TNF-α and CM stimulation reduced the pro-angiogenic inflammatory mediators p65 (43% & 52%) and MCP-1 (33% & 30%), p<0.05. Significantly, rHDL also reduced HIF1α and VEGF protein levels in response to both inflammatory stimuli (p<0.05). Furthermore, rHDL pretreatment strikingly increased hemeoxygenase-1, a multifunctional regulator of angiogenesis, under both hypoxic and inflammatory conditions ~2-4 fold, p<0.05.

Conclusion: We have identified a unique multifunctional role for HDL in angiogenesis, characterised by enhancement of hypoxia-induced angiogenesis and, conversely, marked suppression of inflammation-associated angiogenesis.