

using flow cytometry. Explant-derived cells (EDCs) isolated from mdx hearts formed significantly fewer cardiospheres per 30 000 EDCs than those from wild-type hearts (19 ± 2.8 vs 26.7 ± 5.3 , $p < 0.01$), but generated more cardiosphere-derived cells (CDCs) ($2.9 \pm 1.7 \times 10^5$ vs $1.4 \pm 0.5 \times 10^5$, $p < 0.05$). Approximately 70% of CDCs expressed sca-1 in both groups. Interestingly, CDCs from mdx mice exhibited higher expression of c-kit ($16.1 \pm 6.3\%$ vs $8.9 \pm 3.4\%$, $p < 0.05$) and lower expression of CD90 ($44.3 \pm 15.8\%$ vs $77.9 \pm 10.6\%$, $p < 0.01$) compared with cells from wild-type hearts. In conclusion, the mdx mouse, a disease model of human DMD, is associated with impaired cardiac function and had increased c-kit and decreased CD90-expressing CDCs.

8 OSSIFICATION OF ATHEROSCLEROTIC PLAQUE: THE ROLE OF VESSEL DERIVED STEM CELLS

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Introduction Pericytes, although traditionally considered as supporting cells, have recently been proposed to have a more active role in the repair and pathogenesis of various vascular diseases. In this study, we hypothesised that a pericyte-like stem cell population, termed vessel derived stem cells (VSCs), with chondrogenic and osteogenic potential exists in the vessel wall and in the presence of the inflammatory cytokines seen in atherosclerotic environment contributes, along with the circulating mesenchymal stem cells, to the calcification of atherosclerotic plaque which occurs through the endochondral pathway.

Methods VSCs from aortae of ApoE^{-/-} mice and control C57BL/6 mice were isolated and characterised for cell surface markers by flow cytometry and immunocytochemistry. MSCs from the bone marrow of these mice were also isolated and characterised. Chondrogenic potential of these cells was investigated in presence or absence of inflammatory cytokines such as IL-6 and IFN- γ .

Results and Discussion Isolated VSCs were strongly positive for Sca-1, CD44 and negative for CD31 and CD34. A sub-population of VSCs also expressed 3G5, a specific pericyte marker. Differentiation assays demonstrated the ability of the cells to undergo osteogenesis and chondrogenesis. VSCs had significantly higher GAG/DNA ratio than MSCs indicating comparatively increased chondrogenesis. That both MSCs and VSCs from the ApoE^{-/-} atherosclerotic mice generate a more mature hypertrophic chondrocyte than cells from the C57BL/6 mice is interesting and suggests that the atherosclerotic environment may modulate the stem cell phenotype. Collagen-type II and aggrecan expression and effect of oxidised LDL on these cells in vitro will be investigated to further test this hypothesis.

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9 IGG ANTI-MALONEDIALDEHYDE-LDL ANTIBODIES ARE ASSOCIATED WITH LOW RISK OF CARDIOVASCULAR EVENTS IN A SUBSTUDY OF THE ANGLO-SCANDINAVIAN CARDIAC OUTCOMES TRIAL (ASCOT), AND ARE UNRELATED TO LDL, CRP LEVELS AND STATIN TREATMENT

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Health, NHLI, Imperial College London, UK; ³Department of Clinical Pharmacology Royal College of Surgeons of Ireland, Dublin

Background We aimed to determine whether measurement of anti-bodies to modified LDL predicts cardiovascular events.

Methods We studied ASCOT participants without diabetes with total cholesterol of ≤ 6.5 mmol/l and a total cholesterol/HDL ratio ≤ 4.5 . IgG and IgM antibodies against malondialdehyde-modified LDL (MDA-LDL) and phosphorylcholine (PC) were measured by ELISA at baseline and after one year on atorvastatin (10 mg daily; n=100) or placebo (n=100). CRP, carotid intima-media thickness (CIMT), Framingham 10-year CVD Risk score (FRS) and total and LDL cholesterol (LDL) were determined.

Results Antibody levels did not correlate with baseline LDL, or LDL, CRP or CIMT at 1 year. Atorvastatin reduced LDL by 1.44 mmol/l ($p < 0.001$, 95% CI 1.31 to 1.58 adjusted for age and sex), but did not influence IgG or IgM antibodies against MDA-LDL ($p = 0.74$ and $p = 0.38$) or PC ($p = 0.26$ and $p = -0.556$). However, following adjustment for classical risk factors, baseline IgG anti-MDA-LDL levels predicted protection from cardiovascular events (HR=0.22, 95% CI 0.052 to 0.92; $p = 0.04$). There was also a trend for IgG anti-MDA-LDL being protective after adjustment for FRS, (HR=0.33, 95% CI 0.089 to 1.20; $p = 0.09$).

Conclusion IgG anti-MDA-LDL antibody levels are unrelated to LDL cholesterol levels, CRP, CIMT, and are not affected by treatment with atorvastatin. However, elevated levels are associated with significant protection against cardiovascular events and may be useful in clinical risk stratification for cardiovascular disease.

10 CERTOLIZUMAB PEGOL INHIBITS TUMOUR NECROSIS FACTOR-INDUCED ENDOTHELIAL CELL ACTIVATION

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Rationale Rheumatoid arthritis (RA) is associated with accelerated atherosclerosis and premature cardiovascular death. Chronic inflammation mediated by tumour necrosis factor (TNF) may contribute to this by promoting endothelial activation, dysfunction and leukocyte recruitment. Anti-TNF therapy has been associated with improved vascular function in RA patients. However, the specific effects of TNF inhibitors on endothelial cell function are largely unknown. We aim to establish whether the anti-TNF therapy certolizumab pegol (CZP) (Cimzia®; UCB, Belgium) modulates the inflammatory response by activated human endothelial cells.

Methods and Results Human aortic endothelial cells (HAoECs) were cultured in vitro and exposed to (i) TNF alone, (ii) TNF plus CZP, or (iii) neither agent. Microarray analysis detected at least twofold higher expression of 115 genes after exposure of HAoEC to TNF, compared to control untreated cells. 22.6% of the increased genes were associated with the immune response and 9.6% encoded adhesion/cell surface molecules. In particular, genes for E-selectin, VCAM-1 and ICAM-1 were significantly upregulated by TNF treatment, which was validated by qPCR. Notably, treatment of HAoEC with the TNF/CZP cocktail prevented the up-regulation of these genes, resulting in an expression pattern similar to that detected in control cells. Immunocytochemistry confirmed the NF κ B pathway as a downstream target of TNF-induced HAoEC activation, since the TNF-induced nuclear translocation of NF κ B was prevented in the presence of CZP.



9 IgG anti-malonedialdehyde-LDL antibodies are associated with low risk of cardiovascular events in a substudy of the anglo-scandinavian cardiac outcomes trial (Ascot), and are unrelated To LDL, CRP levels and statin treatment

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