bination of one remodeling pattern in some areas of the plaque with absence of remodeling elsewhere (p < 0.001). Of plaques with homogeneous remodeling, 18.8% had Excessive ESS, 6.2% Compensatory ER, 12.5% Impaired proliferation; a pathological process integral to the development of vein graft failure and restenosis.

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Chemokine (c-x-c motif) ligand 10 deficiency causes impairment of perfusion recovery after local arterial occlusion

P. Van Den Born1, R.T. Haverslag1, M. Brandt2, C. Cheng2, H.J. Ducrê2, P.H.A. Quax2, I.E. Hoefler1, G. Pasterkamp2, D.P. Van Kleijn1,1

University Medical Center Utrecht, Division Heart and Lungs, Experimental Cardiology, Utrecht, The Netherlands; 2Erasmus Medical Center, Department of Cardiology, Vascular Surgery, Leiden, Netherlands

Purpose: In response to local tissue ischemia, adaptive collateral artery growth (arteriogenesis) is important to restore blood flow hampered by local arterial occlusion. Chemokine (C-X-C motif) ligand 10 (CXCL10) is secreted after Toll-like Receptor (TLR) activation and is involved in chemotraction of inflammatory cells as well as smooth muscle cell migration and proliferation. Previous studies have shown that TLRs are involved in arteriogenesis. In this study, we investigated the role of CXCL10 in the process of arteriogenesis.

Methods: Unilateral femoral artery ligation was performed in wildtype and CXCL10-/- mice and perfusion recovery was measured over 7 days using Laser-Doppler analysis. Histology was performed on hind limb muscles for quantification of vessel number and dimensions as well as influx of inflammatory cells. Chimerism experiments were performed to assess the role of bone marrow-derived CXCL10. Data are shown as mean±SEM.

Results: Perfusion recovery was significantly lower in CXCL10-/- (KO) mice compared to wildtype (WT) at day 4 and 7 after operation (WT vs KO: 81±6 vs 58±5 at day 4; p=0.002, 107±8 vs 57±12 at day 7; p=0.006). Dimensions of α-SMA positive vessels increased in time compared to baseline, but were only significantly higher at day 7 in WT mice compared to KO (WT vs KO: lumen area: 288±73 vs 109±37 at day 7; p=0.03, wall thickness: 3.5±1.4 vs 2.3±1.0 μm at day 7, p=0.001). Local macrophage and T lymphocyte infiltration did not significantly differ between WT and KO. Chimeric mice (KO bone marrow into WT) showed significantly lower perfusion recovery compared to WT (WT vs chimeres: 81±13 vs 46±4% at day 4 p=0.026, and 107±8 vs 61±6% at day 7, p=0.001). Compared to KO, chimeric mice (WT bone marrow into KO) showed impaired perfusion recovery (KO vs chimeres: 28%±6 vs 63±4% at day 4, p=0.001, and 57%±12 vs 74%±6 at day 7, p=0.025).

Conclusions: CXCL10 plays a causal role in arteriogenesis. Bone marrow-derived, as well as tissue derived CXCL10 both play a role in accelerating perfusion recovery after arterial occlusion in mice.

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G-protein coupled receptor 35 activation mediates human vascular smooth muscle migration

J.E. Lappin1, S.A. Nicklin1, G. Milligan1,1

University of Glasgow, Institute of Molecular, Cellular and Systems Biology, Glasgow, United Kingdom; 2University of Glasgow, BHF Glasgow Cardiovascular Research Centre, Glasgow, United Kingdom

Introduction: GPR35 is a poorly characterised G protein-coupled receptor endogenously activated by tyramine acid and selectively coupled to G13, a G protein involved in regulation of cellular motility and proliferation via the Rho kinase pathway. The role of GPR35 in cardiovascular disease (CVD) is poorly explored, though it has been proposed to regulate blood pressure in rodents. Ligands which activate GPR35 are orthogonal selective, however, we have identified potent novel protein human GPR35 specific ligands; agonist pamoic acid and antagonists CID-2745687 and ML145 for further dissection of GPR35 pharmacology.

Results: Endogenous expression of GPR35 was quantified in HVSVMC via RFP-QPCR and migration was measured in HVSVMCs stimulated with 10-50nM pamoic acid, +/- CID-2745687 and ML145 (100μM) or ROCK1/2 inhibitor Y-27632 (10μM) in scratch wound assays using ImageJ. HVSVMC proliferation was assayed via MTS assay. Changes in HVSVMC morphology and actin-cytoskeletal structure were assessed via tetramethyl rhodamine isothiocyanate (TRITC) actin staining.

Results: RET assays in FALG-HGPR35-eYFP cells demonstrated that pamoic acid was a potent, human selective GPR35 agonist (pEC50 7.28±0.07) while CID-2745687 (pIC50 7.16±0.12) were potent antagonists. KCa3.1 channles were assessed via whole cell patch clamp. Human GPR35 expression and activity was not detected. GPR35 activation induced a rearrangement of actin filaments consistent with HVSVMC migration. Quantification of HVSVMC migration revealed the GPR35 agonist pamoic acid induced a 30% increase in migration (p<0.01 vs -serum control) which was abolished in the presence of CID-2745687 and ML145 or the ROCK1/2 inhibitor Y-27632 (p<0.05 vs -serum control). GPR35 activation did not affect HVSVMC proliferation.

Conclusions: Here, we have described a novel role for GPR35 activation in the migratory capacity of HVSVMC via its downstream effector ROCK1/2. This suggests GPR35 might be a therapeutic target in the setting of vein graft failure and restenosis.