EFFECT OF MYELOID PROTEIN TYROSINE PHOSPHATASE MONOCYTE CHEMOTACTANT PROTEIN-1 AS A GLUTAREDOXIN-1 OVEREXPRESSION INDUCES CIRCULAR WOUNDS WOUND HEALING RATE UNDER NORMOGLYCAEMIC AND HYPERGlyCAEMIC CONDITIONS, SUGGESTING THAT PTP1B INHIBITION AS A NOVEL THERAPY FOR TREATMENT OF NON-HEALING WOUNDS IN DIABETES AND CVD.

8 EFFECT OF MYELOID PROTEIN TYROSINE PHOSPHATASE 1B (PTP1B) INHIBITION ON DIABETIC WOUND HEALING

Abdul Othman*, Heather M Wilson, Milena Delibegovic. University of Aberdeen, Aberdeen, UK

Diabetes and its associated vascular complications e.g., cardiovascular disease and chronic wounds is a leading healthcare concern. Protein tyrosine phosphatase 1B (PTP1B) is a key regulator of whole-body glucose and energy metabolism. Our recent research suggests that myeloid-specific PTP1B deletion protects against atherosclerosis. We hypothesised that inhibiting myeloid-specific (macrophage) PTP1B would improve the efficacy of wound healing that is hampered by the diabetic environment.

In vivo, wound healing was assessed under physiological, normoglycemic conditions in control wildtype (PTP1Bfl/fl) and myeloid-PTP1B deficient (LysM PTP1B-/-) littermate. Experiments were conducted in streptozotocin-induced diabetic mice. Wound healing was quantified over a period of 10 days. Two circular wounds were made horizontally in the dorsal region. The wounds were assessed using tracing and ruler methods.

In vitro, wound healing was assessed using wound healing assays, under hyper-glycaemic conditions. The keratinocyte cell line (HaCaT) was cultured with bone marrow-derived macrophages (BMDM) from diabetic C57Bl6 mice. Wound healing was also assessed in presence/absence of the PTP1B inhibitor, MSI-1436.

Under physiological conditions, there was a significant improvement in wound healing in LysM PTP1B-/- mice 4 days post-surgery. Under diabetic conditions, LysM PTP1B-/- mice had a significantly faster wound closure compared to PTP1Bfl/fl, on day 8 post-surgery. Wound healing assays revealed more efficient wound closure in HaCaT cells co-cultured with BMDM from diabetic C57Bl6 mice, in the presence of MSI-1436. Thus, inhibiting myeloid-PTP1B improves wound healing rate under normoglycaemic and hyperglycaemic conditions, suggesting that PTP1B inhibition as a novel therapy for treatment of non-healing wounds in diabetes and CVD.

9 MONOCYTE CHEMOTACTANT PROTEIN-1 AS A BIOMARKER OF VASCULAR DYSFUNCTION IN PATIENTS WITH TYPE 2 DIABETES

1William MacDonald*, 2Francesco Casanova, 3Kim Gooding, 4Kuni Aizawa, 5Angela Shore, 1Faisal Khan. 1Division of Systems Medicine, University of Dundee School of Medicine, Dundee, UK; 2Diabetes and Vascular Medicine Research Centre, University of Exeter Medical School and NIHR Exeter Clinical Research Facility, Exeter, UK

Endothelial dysfunction has been shown to be strongly associated with cardiovascular disease (CVD) outcomes. CVD risk in diabetes shows heterogeneity and new biomarkers are required to stratify CVD risk in these patients. This study analysed the association of Monocyte Chemoattractant Protein-1 (MCP-1) with measures of vascular function in 509 patients with type 2 diabetes mellitus (T2DM). Endothelial function was measured using laser Doppler imaging (LDI) and peripheral arterial tonometry (PAT) (EndoPat). Arterial stiffness was measured using carotid to femoral pulse wave velocity (PWV) (SphygmoCor).

Firstly, the study showed the negative association of MCP-1 with endothelium-dependent vasodilator responses to acetylcholine (R²=0.240, p=5.02*10^-10) as measured by LDI. Secondly, the study showed the negative association of MCP-1 with reactive hyperaemia index (RHI) (R²=0.0716, p=0.0109) and Framingham RHI (R²=0.0987, p=0.0294) as measured by PAT. Thirdly, the study showed the positive association of MCP-1 with PWV (R²=0.387, p=0.0088). Framingham risk factors, diabetes duration, HbA1c and eGFR were controlled for. The study also showed the independent association of MCP-1 with CVD death (odds ratio (OR)=18.2, 95% confidence interval (CI) [1.46 - 631.0], p=0.0487) and all-cause mortality (OR=4.51, 95% CI [1.07 - 21.8], p=0.0462) in a three-year follow-up period. There was no significant improvement to area under receiver operating characteristic curve (AUROC) when MCP-1 was added into risk models.

This study shows MCP-1 to be a good candidate as a biomarker of vascular dysfunction in T2DM. Further research in larger cohorts with longer follow-up periods should be conducted to determine its usefulness in improvement of risk models.

10 GLUTAREDOXIN-1 OVEREXPRESSION INDUCES HYPERTENSIVE PREGNANCY AND MATERNAL CARDIAC FIBROSIS

Jennifer Ker*, Agathe Lermant, Colin E Murdoch. University of Dundee, Dundee, UK

Elevation of oxidative stress is explicitly linked to hypertensive pregnancies with high levels measurable in the maternal circulation. Hypertensive pregnancies lead to long-term risk of cardiac dysfunction, yet the underpinning molecular pathway are unknown. Oxidative stress modify proteins via oxidative post-