C INSULIN RESISTANCE IMPAIRS ANGIOGENIC PROGENITOR CELL FUNCTION AND DELAYS ENDOTHELIAL REPAIR FOLLOWING VASCULAR INJURY

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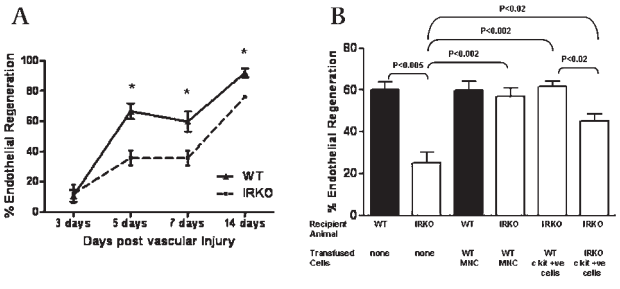
Introduction Insulin-resistance, the primary metabolic abnormality underpinning type-2-diabetes mellitus (T2DM) and obesity, is an important risk factor for the development of atherosclerotic cardiovascular disease. Circulating-angiogenic-progenitor-cells (APCs) participate in endothelial-repair following arterial injury. Type-2 diabetes is associated with fewer circulating APCs, APC dysfunction and impaired endothelial-repair. We set out to determine whether insulin-resistance *per se* adversely affects APCs and endothelial-regeneration.

Research Design and Methods We quantified APCs and assessed APC-mobilisation and function in mice hemizygous for knockout of the insulin receptor (IRKO) and wild-type (WT) littermate controls. Endothelial-regeneration following femoral artery wire-injury was also quantified at time intervals after denudation and following APC transfusion.

Results The metabolic phenotype of IRKO mice was consistent with compensated insulin resistance, with hyperinsulinaemia after a glucose challenge but a normal blood glucose response to a glucose tolerance test. IRKO mice had fewer circulating Sca-1+/Flk-1+ APCs than WT mice at baseline. Culture of mononuclear-cells demonstrated that IRKO mice had fewer APCs in peripheral-blood, but not in bone-marrow or spleen, suggestive of a mobilisation defect. Defective VEGF-stimulated APC mobilisation was confirmed in IRKO mice, consistent with reduced eNOS expression in bone marrow and impaired vascular eNOS activity. Paracrine-angiogenic-activity of APCs from IRKO mice was impaired compared to those from WT animals. Endothelial-regeneration of the femoral artery following denuding wire-injury was delayed in IRKO mice compared to WT (re-endothelialised area 35.8±4.8% vs 66.6±5.2% at day 5 following injury and 35.6±4.8% vs 59.8±6.6% at day 7; P<0.05) (Abstract C Figure 1A). Transfusion of mononuclear-cells from WT mice normalised the impaired endothelial-regeneration in IRKO mice (57±4% vs 25±5%; p<0.002). Transfusion of c-kit+ bone-marrow cells from WT mice also restored endothelial-regeneration in IRKO mice (62±2% vs 25±5%; p<0.002). However, transfusion of c-kit+ cells from IRKO mice was less effective at improving endothelial-repair (62±2% vs 45±4%; p<0.02) (Abstract C Figure 1B).

Conclusions Insulin-resistance impairs APC function and delays endothelial-regeneration following arterial injury. These findings support the hypothesis that insulin-resistance per se is sufficient to jeopardise endogenous vascular repair. Defective endothelial-repair may be normalised by transfusion of APCs from insulin-sensitive animals but not from insulin-resistant animals. These data may have important implications for the development of therapeutic strategies for insulin-resistance associated cardiovascular disease.



Abstract C Figure 1 (A) Time-dependent endothelial regeneration following vascular injury (n=5 mice per group; *denotes p<0.05). (B) Effects on endothelial regeneration 5 days after wire-injury of transfusion of spleen-derived MNCs or BM-derived c-kit (CD117)+ve cells from WT or IRKO mice (n=4 mice per group).

D UPTAKE OF ULTRASMALL SUPERPARAMAGNETIC PARTICLES OF IRON OXIDE PREDICTS GROWTH IN ABDOMINAL AORTIC ANEURYSMS: A PILOT STUDY

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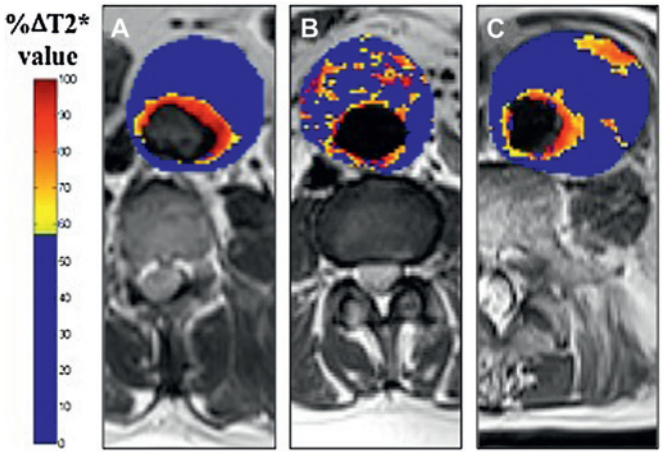
Background Prediction of abdominal aortic aneurysm (AAA) expansion and rupture is challenging and currently relies on serial measurements of maximum aneurysm diameter. Using ultrasmall superparamagnetic particles of iron oxide (USPIO) and MRI, we aimed to assess whether areas of cellular inflammation correlated with the rate of abdominal aortic aneurysm expansion.

Methods and Results An image acquisition and data analysis algorithm for the detection of focal USPIO accumulation in tissues was developed. Patients (n=29; 27 male; aged 70±5 years) with asymptomatic AAA (4.0–6.6 cm) were recruited from an outpatient surveillance programme and underwent 3T MRI before and 24–36 h after administration of USPIO. The change in T2* value on T2*-weighted imaging was used to detect accumulation of USPIO within the abdominal aortic aneurysm. Histology of aortic wall tissue samples confirmed co-localisation and uptake of USPIO in areas with macrophage infiltration. Patients were classified into one of three groups on the basis of imaging findings (Abstract D Figure 1). Group 1: peri-luminal USPIO uptake only. Group 2: USPIO uptake throughout the thrombus. Group 3: USPIO uptake in the aortic wall. Patients in group 3 with distinct mural uptake of USPIO had a threefold higher growth rate (n=13; 0.66 cm/yr; p=0.020) than those with no (Group 1; n=7; 0.22 cm/yr) or non-specific USPIO uptake (Group 2; n=9; 0.24 cm/yr) despite having similar aneurysm diameters (5.4±0.6, 5.1±0.5 and 5.0±0.5 cm respectively; p>0.05) and patient characteristics (p>0.05). In one patient with an inflammatory aneurysm, USPIO uptake and inflammation extended beyond the aortic wall into surrounding tissues.

Conclusion USPIO uptake in the aortic wall detects cellular inflammation in patients with AAA and appears to predict more rapidly progressive AAA expansion. This technique therefore holds major promise as a new method of risk-stratifying patients with AAA that extends beyond the simple anatomical measure of aneurysm diameter.



Abstract D Figure 1