Figure 1

Methods To assess endothelial regeneration, insulin receptor (IR)^{+/-} mice with or without transgenic over-expression of IGFBP-1 (IGFBP1tg) underwent femoral artery endothelial denuding wire-injury. After five days, the area of regenerated endothelium was quantified in *en face* sections of injured artery. Endothelial regeneration was also assessed *ex-vivo* in human tissues by seeding segments of endothelium-denuded human saphenous vein with a sub-confluent density of human coronary artery endothelial cells, which were pre-incubated with or without IGFBP-1. Adherent cells were quantified using con-focal microscopy. The effects of IGFBP-1 on the functional properties of endothelial cells *in vitro* were examined using cell migration assays.

Results Endothelial regeneration following wire injury was blunted in IR^{+/-} mice, however regeneration was significantly improved in this model of insulin resistance by IGFBP-1 overexpression (n=5–10 per group). (Figure 1a) In human umbilical vein endothelial cells (HUVEC), insulin resistance was mimicked by the pro-inflammatory cytokine tumour necrosis factor- α , which significantly inhibited migration in a scratch wound assay (n=9). (Figure. 1b) Co-incubation with IGFBP-1 restored the migratory capacity of HUVEC to control levels. There was a trend to enhanced migration of Human Coronary Artery Endothelial Cells (HCAEC) in response to IGFBP-1 in a Boyden chamber assay (P=0.07). IGFBP-1 significantly enhanced endothelial cell adhesion on a human saphenous vein matrix (n=5, p<0.001). (Figure. 2)

Conclusions IGFBP-1 over-expression enhances endothelial repair in the insulin resistant setting. In endothelial cells, IGFBP-1 restores cell migration in a pro-inflammatory setting and improves cell adhesion. Ongoing studies are in progress to examine the underlying mechanisms. Collectively, these data raise the possibility that

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ENHANCING VASCULAR ENDOTHELIAL REPAIR IN THE SETTING OF INSULIN RESISTANCE: EFFECTS OF INSULIN-LIKE GROWTH FACTOR BINDING PROTEIN-1

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Introduction Insulin resistance predisposes to cardiovascular disease by inducing endothelial dysfunction. Our laboratory has shown that insulin resistance impairs the capacity for endothelial repair. Additionally, we have discovered that a circulating protein, insulin-like growth factor binding protein-1 (IGFBP-1), is potentially protective in the vasculature by stimulating nitric oxide production and enhancing insulin sensitivity. In cross-sectional studies, low IGFBP-1 levels are associated with diabetes and cardiovascular disease. In this project, we investigated whether IGFBP-1 can enhance vascular endothelial repair in insulin resistant mice *in vivo* and examined potential mechanisms in human endothelial cells and endothelial progenitor cells *in vitro*.

Figure 2

manipulating IGFBP-1 could be a strategy to enhance endothelial repair in patients with insulin resistance.