**Glomerular IGFBP1 is down regulated in diabetic nephropathy and is important for podocyte function.**

**Introduction:** Insulin-like growth factor binding proteins (IGFBPs), a group of 6 secreted proteins, are involved in modulating the IGF system, by prolonging the half-life of IGF-I and –II, as well as regulating their passage into tissues and receptor binding. In addition, it has been shown that IGFBPs effect cell growth, differentiation and survival, independent of IGF. Dysfunction in the IGF axis is associated with many renal conditions, including diabetic nephropathy. Our research, and that of others, has previously shown that IGF-I and IGF-II signalling modulates podocyte biology. Evidence also suggests IGFBPs are linked to the pathogenesis of albuminuric renal disease, as polymorphisms in the IGFBP-1 gene have been associated with renal disease in type 2 diabetic patients.

**Objectives:** This project aimed to study the role of IGFBP production within the glomerulus in diabetic and non-diabetic environments and to investigate the signalling and functional responses of podocytes to IGFBP stimulation.

**Methods:** An IGFBP mRNA screen was performed in nephroseq, alongside QRT-PCR analysis of kidney tissue from type 1 diabetic mice, to determine any changes in glomerular IGFBPs in diabetic nephropathy (DN). Conditionally immortalised human podocytes were studied *in vitro.* IGFBPs were detected in concentrated cell culture supernatants by western blotting. Podocyte responses to IGFBPs were determined by western blotting, cell viability assays, migration assays, adhesion assays and Electrical Cell-Substrate Impedance Sensing (ECIS).

**Results:** Data obtained through nephroseq revealed a significant down-regulation of IGFBP-1 mRNA in glomeruli of human DN patients and of db/db (type 2 diabetic) mice. We have also found a significant reduction in IGFBP-1 mRNA in STZ-diabetic mice, compared to controls. Current data suggests that IGFBP-1 stimulated podocytes have altered FAK signalling pathways. This response appears to be nephrin and integrin dependent. IGFBP-1 stimulation increased podocyte survival, adhesion to collagen IV and migration.

**Conclusion:** Our work confirms that IGFBPs are produced by, and can also signal to, glomerular cells, directly influencing a number of key podocyte processes. Diabetic glomeruli exhibit IGFBP-1 down-regulation, and so increasing glomerular IGFBP-1 levels may be beneficial as a method of DN treatment.

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