**Title:** Insulin-like Growth Factor Binding Protein (IGFBP)-6: A mediator of myofibroblast differentiation in Dupuytren’s Disease?

**Hypothesis:**
Down-regulation of IGFBP6, encoding Insulin-like growth factor binding protein-6, leads to decreased IGFBP-6 levels, in turn increasing IGF-II availability in DD, to promote differentiation of myofibroblasts and the deposition of collagen into the ECM.

**Methods:**
Primary cells derived from Dupuytren’s Disease (DD) cord tissue or phenotypically normal palmar fascia from DD patients (PF) are being assessed for proliferation (WST-1 assays) and myofibroblast differentiation and contractility (Stressed Fibroblast Populated Collagen Lattice assay, sFPCL) with or without the addition of exogenous recombinant IGFBP-6 alone or in combination with transforming growth factor (TGF)-β. α-smooth muscle actin levels are assessed by immunoblotting to confirm myofibroblast differentiation. Chromatin Immunoprecipitation (ChIP) assays are used to assess TGFβ-induced β-catenin /TCF/LEF transcription complex binding to the IGFBP6 promoter. T tests and ANOVA analyses are performed using SPSS.

**RESULTS:**
Microarray analyses indicate a decrease in IGFBP6 mRNA expression in DD cord tissue relative to patient-matched palmar fascia. TGF-β treatment of primary DD cells induced an increase in cytoplasmic β-catenin levels and repression of IGFBP6 mRNA levels. PF cells were less sensitive than patient-matched DD cells to TGF-β-induced repression of IGFBP6 transcription. ChIP assays to confirm TGF-β-induced β-catenin /TCF/LEF transcription complex binding to the IGFBP6 promoter are underway. Preliminary data indicate that exogenous IGFBP-6 treatment has no discernable effect on DD or PF cell proliferation, however exogenous addition of IGFBP-6 inhibits TGF-β-induced contractility of DD and PF cells in sFPCLs. The effects of exogenous IGFBP-6 on DD and PF cell COL1A1 and IGF2 mRNA expression are currently being assessed using Real Time PCR.

**Conclusions:**
TGF-β induces β-catenin accumulation in DD and PF cells and induces the repression of IGFBP6 expression, potentially through β-catenin /TCF/LEF transcription complex interactions with the IGFBP6 promoter. As the primary function of IGFBP-6 is to sequester IGF-II, repression of IGFBP-6 may increase IGF-II availability in DD. As combinatorial interactions between TGF-β and IGF-II have been shown to result in myofibroblast differentiation and increased collagen production in other systems, it is plausible that decreased IGFBP6 expression is specifically targeted to DD to facilitate myofibroblast differentiation and collagen deposition in this disease.