1.8 CELL-INDUCED MATRIX CONTRACTION AND REMODELLING – A CRITICAL TARGET IN DUPUYTREN'S CONTRACTURE

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Background: Dupuytren's disease is a common and disabling condition of the palmar fascia. Despite advances in surgical technique, recurrent contracture remains an unrelenting burden. Matrix metalloproteinase (MMP) activity has been shown to play a critical role in cell-mediated collagen contraction and tissue scarring in vivo.
Aim: To determine whether ilomastat, a broad-spectrum MMP inhibitor, suppresses contraction mediated by Dupuytren's fibroblasts in vitro.
Methods: Nodule and cord-derived fibroblasts were isolated by explant culture from five Dupuytren's patients, carpal ligament acted as the control. A Culture Force Monitor was employed as an in vitro kinetic model of fibroblast-mediated collagen lattice contraction. Fibroblast-seeded lattices were attached to a strain gauge and allowed to contract for 48 h: cell contraction was then disrupted by cytochalasin-D revealing a residual matrix tension (RMT). The maximum force of contraction and RMT were recorded (in dynes) in the presence of ilomastat, and compared with untreated cells or cells treated with a control peptide. MMP activity was assessed by zymography and ELISA.
Results: Nodule and cord-derived fibroblasts exhibited a greater force of contraction (160 ± 15; 150 ± 16 dyn, respectively) compared to control (70 ± 20; $P < 0.01$). Ilomastat significantly inhibited the development of mechanical tension by nodule, cord and carpal-ligament-derived fibroblasts (100 μM; optimal concentration). RMT was unaffected by ilomastat exposure. All fibroblasts secreted MMP-1,2 and expressed membrane-bound MMP-14. Ilomastat suppressed MMP-1,2 activity whilst MMP-14 was up-regulated.
Conclusion: These results demonstrate that ilomastat-mediated inhibition of MMP activity reduces the force of contraction developed by Dupuytren's fibroblasts in vitro and may prove to be effective in reducing progression and recurrence of contracture in Dupuytren's disease.

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1.9 PROTEOME ANALYSIS OF DUPUYTREN'S DISEASE DIFFERENTIATING BETWEEN DISEASE TISSUE PHENOTYPES (NODULE, CORD AND TRANSVERSE PALMAR FASCIA) AND CONTROL PALMAR FASCIA

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Background: Dupuytren's disease (DD) is the most common heritable disorder of connective tissue in Northern European Caucasians. Epidemiological studies provide compelling evidence that genetic alterations play an important role. Proteomics is the systematic analysis of protein identity, quantity, function and has potential in translation of genomics to clinically useful applications, in diagnostics, prognostics and therapeutics. Proteomics involves analyses variations in protein expression patterns (actual phenotypic expression of genetic variation).
Aim: Our previous gene expression in DD identified differentiating transcriptome profile between various DD tissue phenotypes and implicated several genes. The aim here was to generate proteomic expression profiles of DD nodule and cord versus Skoog's fibres and normal fascia samples.
Methods: Samples ($n = 12$) were harvested from three sites in the diseased patients, the nodules ($n = 3$), the cord ($n = 3$), and transverse palmar fascia or skoog's fibres from the same individual ($n = 3$), and compared to the palmar fascia samples ($n = 3$), from non-diseased individuals with no family history of DD. Protein extractions were performed on the tissue samples, using mechanical and chemical methods. The proteins were subsequently separated by 2-D gel electrophoresis and visualized using staining methods. In gel tryptic digests of the proteins were performed for peptide mass characterization via MALDI-TOF-MS (matrix-assisted laser desorption ionization time-of-flight mass spectrometry). This peptide mass fingerprint was used to search databases to identify the proteins involved in DD pathogenesis.
Conclusion: We identified key proteomic changes and quantified proteomic expression profiles in DD tissue versus control, but also provide data complementary to gene expression profiling. In conclusion, we define for the first time the proteome in both healthy and diseased palmar fascia. These findings will help in development of diagnostic platforms with therapeutic implications.

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