

Cytokines Modulated Myofibroblast Induction and Force Generation in Dupuytren's Fibroblasts; Lessons for Tissue Engineering?

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INTRODUCTION: Tissue engineering aims to get cells in vitro to lay down collagen and generate living functional 3D structures for implantation. The major challenge is getting fibroblasts to lay down functional collagen in vitro. We studied a natural condition where fibroblasts secrete excess collagen and shorten the matrix by remodelling it (Dupuytren's disease). Some of the collagen layed down is organised and has the structure of tendon (cord) but the active state is the nodule. The cells responsible for the fibrotic contractures seen in Dupuytren's disease are the myofibroblasts, expressing α -smooth muscle actin (α -SMA), correlating with increased deposition of extracellular matrix (ECM) components¹ and contractile force generation, contracting the ECM². Cytokines are potential targets for myofibroblast modulation, as they control expression of myofibroblast marker α -SMA³. We have examined the effect of cytokines, TGF- β 1 and PDGF-BB, on force generation and matrix remodeling.

METHODS:

Dupuytren's nodule and flexor retinaculum fibroblasts were cultured in 2D for myofibroblast induction and in 3D collagen type I constructs under isometric tension with and without the stimulation of cytokines, to test the effect of force generation in a culture force monitor (CFM)⁴.

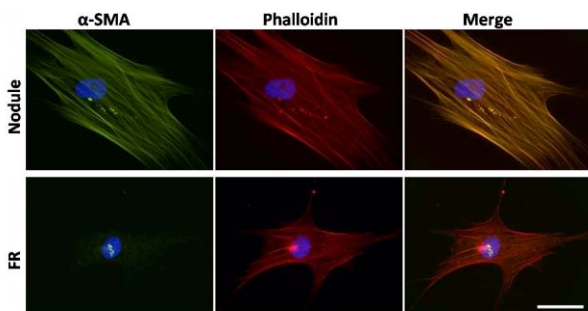


Fig. 1: α -SMA localisation to stress fibres in Dupuytren's nodule (myofibroblast) and flexor retinaculum cells

RESULTS:

Differences in force generation and myofibroblast induction were significant, and were modulated by cytokine stimulation. 12.5 ng/ml TGF- β 1 resulted in highest force generation and myofibroblast induction, however at higher concentrations there was a feedback inhibition. Stimulation with PDGF-BB resulted in lower force generation, correlation with decreased myofibroblast induction.

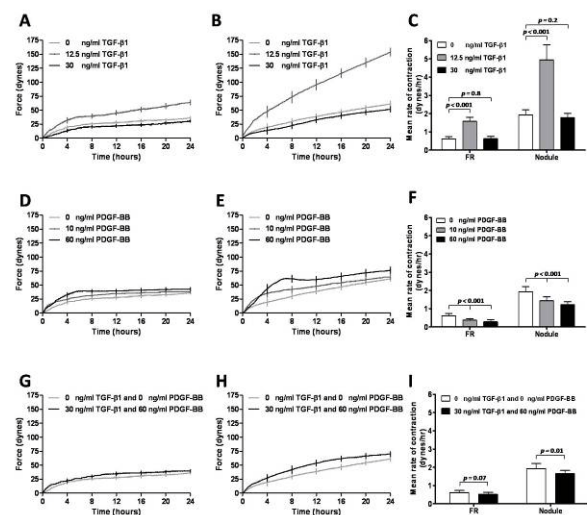


Fig. 2: Isometric contraction of collagen gels by Dupuytren nodule (B,E,H) and flexor retinaculum (A,D,G) cells after cytokine stimulation

DISCUSSION & CONCLUSIONS: Our findings suggest there is a correlation between cytokine concentration and matrix remodelling and force generation in 3D. This data can be used to modulate fibroblasts for tissue engineering applications.

REFERENCES: ¹ Marenzana et al., 2006 ² Rayan and Tomasek, 1994 ³ Hinz, 2007 ⁴ Eastwood, 1996

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