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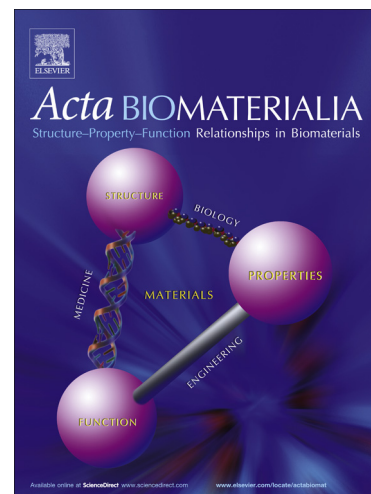
Regulation of fibrotic changes by the synergistic effects of cytokines, dimensionality and matrix: towards the development of an in vitro human dermal hypertrophic scar model

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Regulation of fibrotic changes by the synergistic effects of cytokines, dimensionality and matrix: towards the development of an *in vitro* human dermal hypertrophic scar model

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Abstract

Current therapeutic strategies to reduce scarring in full thickness skin defect offer limited success due to poor understanding of scar tissue formation and the underlying signaling pathways. There is an urgent need to develop human cell based *in vitro* scar tissue models as animal testing is associated with ethical and logistic complications and inter-species variations. Pro-inflammatory cytokines play critical role in regulating scar development through complex interplay and interaction with the ECM and corresponding signaling pathways. In this context, we assessed the responses of cultured fibroblasts with respect to their differentiation into myofibroblasts using optimised cytokines (TGF- β 1, IL-6 and IL-8) for scar formation in 2D (tissue culture plate, collagen type I coated plate) vs 3D collagen type I gel based constructs. We attempted to deduce the role of dimensionality of cell culture matrix in modulating differentiation, function and phenotype of cultured fibroblasts. Validation of the developed model showed similarity to etiology and pathophysiology of *in vivo* hypertrophic scar with respect to several features: 1) transition of fibroblasts to myofibroblasts with convincing expression of α -SMA stress fibers; 2) contraction; 3) excessive collagen and fibronectin secretion; 4) expression of fibrotic ECM proteins (SPARC and Tenascin); 5) low MMP secretion. Most importantly, we elucidated the involvement of TGF- β /SMAD and Wnt/ β -catenin pathways in developing *in vitro* dermal scar. Hence, this relatively simple *in vitro* human scar tissue equivalent may serve as an alternative for testing and designing of novel therapeutics and help in extending our understanding of the complex interplay of cytokines and related dermal scar specific signaling.

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