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**EFFECTS OF PROINFLAMMATORY CYTOKINES ON
MTRICELLULAR PROTEIN EXPRESSION IN HUMAN
CARDIAC FIBROBLASTS**

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Rationale Cardiac fibroblasts (CF) are integrally involved in the myocardial remodelling process and are highly responsive to proinflammatory cytokines such as interleukin-1 (IL-1) and tumour necrosis factor α (TNF α), whose levels are elevated early after myocardial infarction (MI). Here we determined the effect of IL-1 and TNF α on expression of matricellular proteins, a group of extracellular matrix-modulating proteins, in CF cultured from different patient donors.

Methods and Results Effects of IL-1 α on mRNA expression of several matricellular proteins were analysed by real-time RT-PCR array. IL-1 α (10 ng/ml, 6-h) increased tenascin C (TNC) expression by 10-fold and decreased connective tissue growth factor (CTGF/CCN2) expression by 80% (n=3). IL-1 α did not alter expression of thrombospondins 1, 2 or 3 or SPARC/osteonectin, and SPP1/osteopontin expression was not detectable. Quantitative real-time RT-PCR showed the effects of IL-1 α on TNC and CTGF mRNA expression were both rapid and prolonged, being evident within 2-h and maintained for at least 24-h (p<0.01, n=3). In comparison, TNF α (10 ng/ml, 6-h) had only a modest 2.6-fold stimulatory effect on TNC mRNA expression (p<0.01, n=4), but did not significantly affect CTGF expression. A panel of pharmacological inhibitors of relevant signalling pathways (ERK, JNK, p38, PI3K/Akt, NF-kB) were then used to determine the pathways responsible for altered CT GF and TNC gene expression.

Conclusions In human CF, IL-1 α potently increased TNC expression and decreased CTGF expression. Understanding the effects of proinflammatory cytokines on CF function in the context of ECM remodelling may identify novel therapeutic targets for ameliorating adverse myocardial remodelling post-MI.