IJAE
Vol. 117, n. 2 (Supplement): 172, 2012
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Fibroblast-myofibroblast transition and extracellular matrix remodeling in vitro: implication for Notch-1 pathway in muscle tissue repair/regeneration

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Skeletal muscle regeneration is often incomplete due to the overgrowth of extracellular matrix and deposition of collagen which lead to significant fibrous scarring. However, little is known about the mechanisms which regulate fibroblast differentiation into matrix-producing myofibroblasts after injury. To clarify this, in the present study, we investigate the involvement of Notch-1 signalling in the differentiation of fibroblasts into myofibroblasts and explore its potential role in the regulation of muscle fibrosis. The results showed that the treatment with TGF-β decreased the expression levels of Notch-1 and its target gene, Hes-1, and concomitantly increased α-smooth muscle actin expression and decreased MMP-2 and MMP-9 activity in NIH 3T3 and skeletal muscle fibroblasts. Interestingly, stimulation with a known anti-fibrotic hormone, relaxin (RLX) in the presence of TGF-β, was able to significantly increase Notch-1 expression and strongly attenuate TGF-β-stimulated fibroblast differentiation. Moreover, the pharmacological inhibition of Notch-1 by DAPT, accelerated fibroblast differentiation and prevented the inhibitory effects of RLX on skeletal fibroblast-myofibroblast transition.

These findings suggest that Notch-1 signalling may play a significant role in myofibroblast differentiation during muscle fibrosis and represent a unique target that can be manipulated to prevent fibrosis and improve the functional recovery of the injured muscle.

Keywords: Muscle fibrosis, Notch-1 patway, skeletal fibroblasts, differentiation.