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CTGF/CCN2 a profibrotic factor to target in neuromuscular diseases

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Muscular fibrosis is an excessive accumulation of extracellular matrix (ECM) replacing functional tissue, characteristic of several myopathies and neuropathies. The knowledge of pro-fibrotic factors biology and regulation is critical to develop new therapeutic strategies. Upon unilateral sciatic section, we observe in denervated hindlimb accumulation of ECM proteins such as collagen and fibronectin together with an increase of profibrotic factors TGFβ and CTGF/CCN2. We use hemizygous mice for CTGF/CCN2 and treatments with a blocking antibody against CTGF/CCN2 and we observe reduced denervation-induced fibrosis when compared to control mice suggesting a direct role for CTGF/CCN2 on denervation-induced fibrosis. In time course experiments, we observe that ECM proteins and CTGF/ levels are increased early after denervation (2-4 days), while TGFβ signalling present a delayed kinetics of appearance (1-2 weeks). Furthermore, blockage of TGFβ signalling does not decrease fibronectin or CTGF levels 4 days after denervation. These results suggest that in our model CTGF/CCN2 is not up-regulated by canonical TGFβ signalling early after denervation and other factors might be involved in the fibrotic response very soon after skeletal muscle denervation.

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