Denervation-induced skeletal muscle fibrosis is mediated by CTGF/CCN2 independently of TGF-β

Muscular fibrosis is caused by excessive accumulation of extracellular matrix (ECM) that replaces functional tissue, and it is a feature of several myopathies and neuropathies. Knowledge of the biology and regulation of pro-fibrotic factors is critical for the development of new therapeutic strategies. Upon unilateral sciatic nerve transection, we observed accumulation of ECM proteins such as collagen and fibronectin in the denervated hindlimb, together with increased levels of the profibrotic factors transforming growth factor type β (TGF-β) and connective tissue growth factor (CTGF/CCN2). In mice hemizygous for CTGF/CCN2 or in mice treated with a blocking antibody against CTGF/CCN2, we observed reduced accumulation of ECM proteins after denervation as compared to control mice, with no changes in fibro/adipogenic progenitors (FAPs), suggesting a direct role of CTGF/CCN2 on denervation-induced fibrosis. During time course experiments, we observed that ECM proteins and CTGF/CCN2 levels are increased early after denervation (2–4 days), while TGF-β signaling shows a delayed kinetics of appearance (1–2 weeks). Furthermore, blockade of TGF-β signaling does not decrease fibronectin or CTGF levels after 4 days of denervation. These results suggest that in our model CTGF/CCN2 is not up-regulated by canonical TGF-β signaling early after denervation and that other factors are likely involved in the early fibrotic response following skeletal muscle denervation.