Elevated TGF β2 serum levels in Emery-Dreifuss muscular dystrophy: implications for myocyte and tenocyte differentiation and fibrogenic processes.

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Abstract

Among rare diseases caused by mutations in LMNA gene, Emery-Dreifuss Muscular Dystrophy type 2 and Limb-Girdle muscular Dystrophy 1B are characterized by muscle weakness and wasting, joint contractures, cardiomyopathy with conduction system disorders. Circulating biomarkers for these pathologies have not been identified. Here, we analyzed the secretome of a cohort of patients affected by these muscular laminopathies in the attempt to identify a common signature. Multiplex cytokine assay showed that transforming growth factor beta 2 (TGF β2) and interleukin 17 serum levels are consistently elevated in the vast majority of examined patients, while interleukin 6 and basic fibroblast growth factor are altered in subgroups of patients. Levels of TGF β2 are also increased in fibroblast and myoblast cultures established from patient biopsies as well as in serum from mice bearing the H222P Lmna mutation causing Emery-Dreifuss muscular dystrophy in humans. Both patient serum and fibroblast conditioned media activated a TGF β2-dependent fibrogenic program in normal human myoblasts and tenocytes and inhibited myoblast differentiation. Consistent with these results, a TGF β2 neutralizing antibody avoided fibrogenic marker activation and myogenesis impairment. Cell intrinsic TGF β2-dependent mechanisms were also determined in laminopathic cells, where TGF β2 activated AKT/mTOR phosphorylation. These data show that TGF β2 contributes to the pathogenesis of Emery-Dreifuss Muscular Dystrophy type 2 and Limb-Girdle muscular Dystrophy 1B and can be considered a potential biomarker of those diseases. Further, the evidence of TGF β2 pathogenetic effects in tenocytes provides the first mechanistic insight into occurrence of joint contractures in muscular laminopathies.
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