Deregulation of IGF2BP1-mRNP components during the differentiation of FSHD muscle cells.

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Facioscapulohumeral muscular dystrophy (FSHD) is caused by the misexpression of *DUX4*. Its homologue *DUX4c* is also induced in FSHD muscles. In contrast to DUX4, DUX4c is expressed in all myoblasts and is proposed to play a role in normal muscle regeneration. DUX proteins are transcription factors but their normal functions in muscle are not understood yet. In FSHD muscle fibers, myofibril disorganization and sarcomeric dysfunction are shown but are not explained until now by the DUX4 target genes.

During Y2H and co-IP screens, we identified 3 major classes of DUX4/4c binding partners: RNA-binding proteins (RBPs), cytoskeletal(-associated) proteins and exportins. The latter includes known nuclear exporters of mRNP (messenger ribonucleoparticles) components, arguing for a possible nuclear export of DUX4/4c with these components. Many DUX4/4c-associated RBPs reside in mRNP granules in association with IGF2BP1 (Insulin-like growth factor II mRNA-binding protein), an important cytoplasmic regulator of mRNA fate. IGF2BP1 regulates e.g. *β-Actin* mRNA in mRNP complexes to allow its translation to subcellular areas at a specific time. We showed IGF2BP1 expression early during differentiation of FSHD compared to healthy muscle cells. The IGF2BP1-associated proteins ILF3 and therelated isoform NF90 also showed mislocalization between nuclei and cytoplasm in healthy and FSHD muscle cells but only at specific times during differentiation. We observed partial co-localization of these RBP proteins with DUX4 or DUX4c and currently validated them as direct DUX4 interactors in the cytoplasm.

Recent reports showed that NF90 regulates skeletal muscle differentiation and can induce muscle atrophy. Our study suggests that deregulations of IGF2BP1-mRNP components could be part of the pathophysiological mechanisms of FSHD. Indeed, these deregulations might result from the DUX4 binding to these RBPs affecting specific mRNA fates during muscle differentiation.