Transcription factors DUX4 and DUX4c associate with mRNP granules in the cytoplasm of fusing myoblasts: a new function in translation regulation?

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DoUble HomeoboX 4 (DUX4) is a transcription activator and induces a large gene deregulation cascade causing the major pathological features of FSHD. Its homologue, DUX4c expressed in healthy muscles is also induced in FSHD and contributes to the pathology. In a recently published search for DUX4/4c protein partners we have unexpectedly identified many cytoplasmic or nucleo-cytoplasmic proteins involved in myofibril organization and mRNA translation control. The functionality of such interactions is suggested by the cytoplasmic location of otherwise nuclear DUX4/4c when myoblasts fuse. Moreover we have already validated a number of partners by co-immunoprecipitation, co-immunofluorescence or in situ Proximal Ligation Assay.

Terminal muscle differentiation is associated with a general transcription inhibition and the required structure proteins (actin, tubulin…) are synthesized by increased translation of pre-existing mRNAs associated with ribonucleoparticles (RNPs). An interactome built with validated or identified DUX4/4c partners showed 12 of these belonged to mRNP-granules associated with IGF2 mRNA binding proteins (IGF2BPs, also named IMPs or ZBP). These mRNPs contain untranslated mRNAs, transport them along microtubules to subcellular areas (like elongating cell tips) where their translation is required at specific times.

Our previous studies mostly involved overexpressed DUX4/4c proteins. By the use of new specific antibodies we could observe endogenous DUX4c association with mRNP granules on long stretches extending from the nuclei in young primary myotubes, and co-localisation with newly synthesized Troponin T stacks near clusters of myonuclei. Endogenous DUX4 co-localized in elongating myoblasts with beta-crystallin B chain, a chaperone required for newly synthesized desmin folding.

In conclusion, besides transcription, DUX4/4c appear involved in translational control of mRNAs producing structure proteins required for muscle terminal differentiation.