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Mechanosensing defects and YAP signaling in LMNA-related congenital muscular dystrophy.

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Abstract

Mechanotransduction is critical for tissue development, homeostasis and diseases. YAP (Yes-Associated Protein) signaling has emerged as a particularly important regulator of the mechano-response. A defective mechanosensing response, including aberrant YAP signaling, has been recently reported in human myoblasts from patients suffering from LMNA related congenital dystrophy (L-CMD) (Bertrand et al., 2014). L-CMD is a severe early-onset form of muscular dystrophies caused by mutations in A-type lamins. My PhD project aims to further dissect mechanosensing defects of immortalized muscle precursor cells which carry the L-CMD causing ΔK32 mutation.

My results showed that ΔK32 mutant myoblasts had a defective translation of mechanical forces at cell-cell contact sides. ΔK32 mutant myoblasts failed to inactivate YAP in high cell-cell contact conditions, as attested by an increased transcriptional activity of YAP and a persistent nuclear localization. YAP overactivity in ΔK32 mutant myoblasts was not related to an impaired activation of the Hippo signaling pathway. Defective YAP signaling was associated with a disorganization of different subsets of the actin cytoskeleton, including the supranuclear actin, the basal actin and the actin fibers at cell-cell junction. The formation of mature cell-cell contacts in ΔK32 myoblats was defective, and the protein expressions of both M- and N-cadherins were significantly reduced in high cell-cell contact conditions. Moreover, ΔK32 mutant myoblasts showed an increased loss of cell-cell contact during migration, which caused a shift from a sheet-like to a single cell migration pattern. Finally, we reported an increased transcriptional activity of mechanosensitive Smad 1/5/8 signaling in ΔK32 mutant myoblasts. Taken together, these results suggest that mechanosensing defects in ΔK32 mutant myoblasts affect the ability of myoblast to form cell-cell contacts and to migrate collectively. These mechanosensing defects may contribute to the pathophysiology of L-CMD.