DUX4 and DUX4c directly interact with C1qBP in FSHD regenerating myofibers

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Pathological DUX4 expression in skeletal muscle cells interferes with various pathways and ultimately leads to their death. DUX4c shares identical homeodomains with DUX4 and is normally expressed in healthy muscle cells. In order to better understand the FSHD pathophysiology, we previously determined that C1qBP is one of the strongest DUX4 protein partner that directly interacts with its second homeodomain. We now determined in FSHD muscle sections, using in situ proximity ligation assays that DUX4/4c-C1qBP interactions occurred in myocytes/myofibers showing regeneration features. We then confirmed that both DUX4 and DUX4c are co-expressed with regeneration markers (dMHC or MYOD) in such myofibers. These findings are in agreement with our previous DUX4c gain and loss-of-function studies and suggest that C1qBP also has a role during human muscle cell differentiation. Little is known about the C1qBP function in muscle cells and how DUX4 could impact it, however, we observed atypical morphology of FSHD myofibers suggesting a fusion defect of the muscle progenitors. Our results imply that DUX4 may compete with normal DUX4c functions and its interaction with C1qBP in muscle cells during their regeneration. As several therapeutic strategies have been developed to target C1qBP dysfunctions in cancer and mitochondrial disorders, they could be useful for the rational design of FSHD polytherapy, as well as molecules that will improve a healthy muscle regeneration.