DUX4 protein interactors are involved in the DNA damage response

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Abnormal expression of DUX4 in skeletal muscle cells is accompanied by increased oxidative stress, accumulation of DNA damages and ultimately cell death. The DUX4 transcriptomic impact is not sufficient to explain all the FSHD features and how muscle cell death occurs. In collaboration with Professor Kalisman lab, we determined the DUX4 interactors by affinity purification followed by mass spectrometry. We also investigated the protein partners of DUX4c, a DUX4 homologue with a high sequence identity and that is normally expressed in muscle cells. We identified that the major interactors of both DUX4 and DUX4c are C1qBP, PARP1, XRCC5 and XRCC6. Interactions might therefore most probably occur by the DUX4/4c identical homeodomains. We were surprised to find that all these 4 proteins are involved in the repair of DNA double-strand breaks which are considered to be the most toxic genomic lesions. Moreover, our preliminary data suggest that DUX4 impact the level/localization of several DNA damage response (DDR) proteins during muscle cell differentiation. Adequate DDR is essential for muscle regeneration. We speculate that DUX4c role during muscle regeneration is linked to DDR and that DUX4 competes with this function allowing for the accumulation of unrepaired DNA lesions leading to the death of regenerating muscle cells.