C1QBP INHIBITS DUX4-DEPENDENT GENE ACTIVATION AND CAN BE TARGETED WITH 4MU

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FSHD is linked to the misexpression of the *DUX4* gene contained within the D4Z4 repeat array on chromosome 4. The gene encodes the DUX4 protein, a cytotoxic transcription factor that presumably causes the symptoms of the disease. However, individuals have been identified who express DUX4 in their muscle biopsies, but who remain asymptomatic, suggesting that there are other factors that modify FSHD penetrance or severity. We hypothesized that an FSHD-modifying factor would physically interact with DUX4, and we took a proteomic approach to identify DUX4-interacting proteins. We identified the multifunctional C1QBP protein as one such factor. C1QBP is known to regulate several processes that DUX4 affects, including gene expression, oxidative stress, apoptosis, and pre-mRNA splicing. We used siC1QBP knockdown assays to determine if C1QBP affects DUX4 activity. While C1QBP had little effect on DUX4 activity in myotubes, we found that it inhibits the kinetics of DUX4-target gene activation during myogenic differentiation. This identifies C1QBP as a regulator of DUX4 activity and a potential target for FSHD therapeutics. Importantly, C1QBP is regulated by binding to the signaling molecule hyaluronic acid (HA). Decreasing HA by treating cells with 4-methylumbelliferone (4MU), an inhibitor of HA synthesis, resulted in a sharp decline in DUX4 activity and also greatly reduced its cytotoxicity. We have found that DUX4-induced cytotoxicity is associated with severe mislocalizaton of C1QBP, which is prevented by 4MU. This defect is not a downstream result of DUX4-induced oxidative stress, as it could not be prevented by treating cells with an antioxidant, nor could it be recapitulated by exposing cells to oxidants. This identifies C1QBP as a target for the treatment of FSHD, and in particular indicates that 4MU, already an approved drug in Europe and currently under investigation for other indications, may be an effective C1QBP-targeting FSHD therapeutic compound.

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