Deciphering DUX4 (Year II): Is Transient Expression of the DUX4 Gene Sufficient to Cause Muscular Dystrophy?

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Facioscapulohumeral muscular dystrophy (FSHD) is a genetic, progressive myopathy and the second most common muscular dystrophy. Progression of the disease primarily begins in the facial, shoulder, and upper arm muscles, and can go on to cause respiratory and cardiac issues. Aberrant expression of the DUX4 gene in muscle cells is widely accepted to be the primary cause of the FSHD phenotype. A challenge arises in FSHD research as the DUX4 protein itself is almost undetectable in the muscle cells of FSHD patients. For this reason, it is hypothesized that instead of being expressed continuously in muscle cells, which has severely cytotoxic effects, DUX4 is expressed transiently and at very low levels. This hypothesis, however, has yet to be fully demonstrated in an experimental model of the disease. I developed and optimized a transient cell assay of DUX4 in vitro, using the human myoblast cell line LHCN #3 iDUX4, to investigate whether low level, transient expression of DUX4 was sufficient to sustain increased expression of target genes associated with the FSHD genotype, while avoiding immediate cell death, and how expression of the DUX4 pathway affected long term cell viability. Low level transient DUX4 expression significantly increased the expression of a number of DUX4 target genes for a prolonged period, causing proportional cytotoxicity and injury to cells. This research represents an important step toward clarifying the mechanism behind FSHD and eventually developing effective FSHD therapies.

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