Long-Awaited Molecular Mechanism of Facioscapulohumeral Dystrophy Revealed

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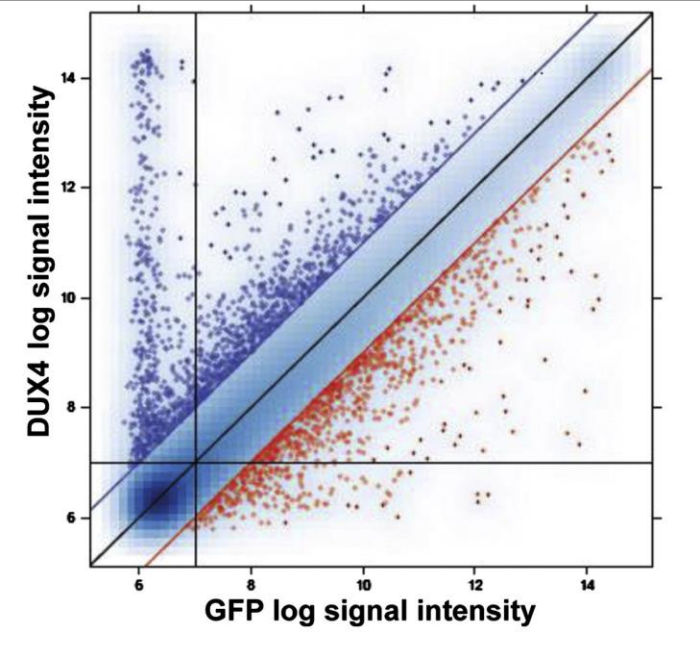
Facioscapulohumeral dystrophy, or FSHD, is the third most common form of muscular dystrophy with an estimated incidence of 1 in 14,000 births. It causes progressive weakness and wasting in skeletal muscles, particularly muscles of the face, shoulders, and arms. The age of FSHD onset is highly variable, but typically occurs between the second and third decades of life and there is a wide range in the severity of this autosomal dominant disease.

Approximately ten years ago, it was discovered that *DUX4* gene copies exhibit reduced epigenetic repression in individuals with FSHD compared to healthy controls. However, it was extremely difficult to find molecular evidence of DUX4 mRNA or protein in FSHD muscle; therefore, the link between genotype and phenotype remained elusive. In 2010, a team lead by Dr. Stephen Tapscott of the Human Biology Division found that DUX4 is normally highly expressed in the testes of healthy individuals but not in healthy skeletal muscle, whereas very low amounts of DUX4 could be detected in the skeletal muscle of individuals with FSHD. Finally, in last month's issue of*Developmental Cell*, postdoctoral fellows Drs. Linda Geng and Zizhen Yao, along with other members of the Tapscott Lab and outside collaborators, discovered the fundamental mechanism linking *DUX4*to the pathophysiology of FSHD. In short, the authors demonstrated that DUX4 is a transcription activator that stimulates aberrant gene expression in FSHD muscle.

Geng *et al.* showed that DUX4 stimulates a massive upregulation of genes in healthy primary muscle cells, including β-defensin 3, retrotransposons, genes involved in RNA transcription and processing, and genes involved in stem cell and germ cell function (e.g., gamete/spermatogenesis). This was the first indication that DUX4 is a transcription activator. When the authors then examined transcripts from FSHD muscle cells, they readily detected transcripts from DUX4 target genes that were not present in healthy muscle. Many of these gene products may contribute to the pathophysiology of FSHD in diverse ways that remain to be established. For example, the authors showed that β-defensin 3 can inhibit genes involved in the differentiation of muscle tissue, whereas the misexpression of testis proteins in FSHD skeletal muscle may cause pathology by stimulating an adaptive (auto) immune response. This study has also provided a remarkable number of putative

biomarkers and therapeutic targets for FSHD, all of which underscore the importance of understanding the disease mechanism.

Geng LN, Yao Z, Snider L, Fong AP, Cech JN, Young JM, van der Maarel SM, Ruzzo WL, Gentleman RC, Tawil R, Tapscott SJ. 2012. DUX4 activates germline genes, retroelements, and immune mediators: implications for facioscapulohumeral dystrophy.*Developmental Cell* 22:38-51.



Modified from manuscript

A pairwise comparison of the number and intensity of transcripts that are upregulated (blue dots) or downregulated (red dots) in healthy primary muscle cells upon expression of DUX4 with reference to a negative control (GFP).