P7.05

***DUX4c* preservation: A key consideration in FSHD therapeutic strategies to safeguard muscle regeneration**

Clothilde Claus[1], Karimatou Bah[1], Moriya Slavin[2], Nir Kalisman[2], Alexandra Belayew[1], Frédérique Coppée[1]

[1] *University of Mons*
[2] *Hebrew University of Jerusalem*

Most therapeutic strategies in development for FSHD target the *DUX4* causal gene, aiming to inhibit expression of its encoded protein. *DUX4c*, a *DUX4* homologue with high sequence similarity, is expressed in healthy muscles and induced in FSHD. Several antisense tools targeting *DUX4* mRNA also effectively target *DUX4c* mRNA. Their encoded proteins are identical over 342 residues, including the double homeodomain. *DUX4* pathological expression leads to cell death, muscle atrophy, and disruption of RNA processes enabling synthesis of aberrant proteins. Additional DUX4 protein toxicity may result from competition with *DUX4c*, disturbing its normal functions. 1) *DUX4/4c* competition affects transcription of genes involved in WNT/beta-catenin pathway activation, with *DUX4c* counteracting *DUX4*-mediated toxicity in myoblasts (Ganassi et al., 2022). 2) *DUX4/4c* competition could affect common partners, as shown for C1qBP, a multi-compartmental protein involved in mitochondrial activity and cell differentiation. On FSHD muscle sections *DUX4* and C1qBP are co-detected in abnormal myocytes/fibers with features of regeneration, suggesting an ineffective process that could result from *DUX4* inhibition of normal *DUX4c*/C1qBP interaction. Novel *DUX4/4c* partners will be presented. In conclusion, we think a decrease in *DUX4c* levels, as a side effect of drugs targeting *DUX4*, is a challenge for FSHD treatment. Maintaining sufficient *DUX4c* amounts is crucial to allow its normal functions in patient muscles.

P7.06