Role of DUX4 and Pax3/7 interferences in Facioscapulohumeral muscular dystrophy (FSHD) pathogenesis

Darko Bosnakovski[1,2], Erik Toso[2] , Heather A. Lee[2], Abhijit Dandapat[2] and Michael Kyba[2]

[1]*University Goce Delčev - Štip, Faculty of Medical Sciences, Krste Misirkov b.b., 2000 Štip, R. Macedonia*

[2]*Lillehei Heart Institute, Department of Pediatrics, University of Minnesota, Minneapolis, MN, 55014*

DUX4 is a double homeodomain gene embedded within D4Z4 macrosatellite repeats on chromosome 4. Evidences emerged that DUX4 is the key factor in the underlining molecular mechanism of Facioscapulohumeral muscular dystrophy (FSHD). DUX4 is detected specifically in myoblast from FSHD patients and not in healthy donors. Myogenic cells derived from FSHD ES or IPS cells expresses DUX4 at every stage of differentiation, from early mesoderm to myotubes. DUX4 induced in high doses is toxic for most cell types including cells from myogenic lineage. Both N- and C-terminal domains are necessary for cytotoxic effect. DUX4 expressed in low levels in myoblasts mis-regulates expression of the myogenic regulatory factors (MRFs) and impairs myogenic differentiation. We found that only homeodomains alone are sufficient for altering MRF expression and inhibiting differentiation of myoblasts. Striking, among a number of proteins with highly related homeodomains, Pax3 and Pax7 uniquely display phenotypic competition with DUX4. Pax3 and Pax7 a key myogenic transcription factors in determination and maintaining satellite cells. Even genes with homeodomains of greater sequence identity to DUX4 do not exhibit interference effect. When the homeodomains of

DUX4 are replaced by those of Pax7, the hybrid protein behaves as DUX4, indicating that the Pax7/DUX4 mutual interference is likely mediated specifically by their respective homeodomains.