Autism associated shank3 mutations alter skeletal muscle maturation: therapeutic strategies using 3D-bioprinted skeletal muscles

Maria Demestre
Anne-Kathrin Lutz, Tobias Boeckers, Samuel Sanchez
Institute of Bioengineering of Catalonia, Baldiri Reixac 10-11, Barcelona, SPAIN
mdemestre@ibecbarcelona.eu

Abstract
Heterozygous mutations of the gene encoding Shank3, a scaffold protein mainly present at the post synapse, are associated with syndromic forms of autism spectrum disorders (ASD). One of the earliest clinical symptoms of children born with Shank3 associated ASD is neonatal skeletal muscle hypotonia. However, mechanisms underlying this symptom are completely unknown. Here we used induced pluripotent stem cells derived from patients, a well-established Shank3 know-down murine model and muscle biopsies from Phelan Mc Dermid patients to analyse skeletal muscle defects associated with the loss of Shank3. First, we could see Shank3 localisation at the skeletal muscle sarcomere and also at the neuromuscular junctions[1]. Mutations in Shank3 induced ultrastructural alterations of the Z-disc bounding the sarcomere and at the neuromuscular of both our murine and human models. In addition, an impairment of the acetylcholine clustering in our motorneurone skeletal muscle co-cultures derived from induced pluripotent stem cells[2] was also observed. This could be reflected in functional defects in murine muscles giving insight of a very important role of Shank3 not only in the brain but also in the periphery. Providing thus, an open window for therapeutic strategies not only targeting the central nervous system but skeletal muscle. This could be in our hands modelled in 3D-bio-printed functional skeletal muscles[3].

REFERENCES

[1] Lutz AK, Pfaender S, Föhr KJ, Cammerer K, Zoller M, Higelin J, Ioannidis V, Schoen M, Orth M, Liebau S, Barbi G, Grabrucker AM, Delorme R, Bourgeron T, Verpelli C, Demestre M, Tobias M. Boeckers. Autism-associated SHANK3 mutations lead to impaired maturation of hiPSC derived motor units. Science Translational Medicine. 2020, 10;12(547)

[2] Demestre M, Orth M, Föhr KJ, Achberger K, Ludoplh Ac, Liebau S, Boeckers TM[#]. Formation and characterization of neuromuscular junctions between hiPSC derived motoneurons and myotubes. Stem Cell Resesrch. 2015 . 15 (2).(328)

[3] Mestre R, Patiño T, Barcelo X, Anand S, Pérez-Jiménez A, Sánchez S. Force modulation and adaptability in 3D-bioprinted Biological actuator based on skeletal muscle. Advanced Material Technologies. 2019. 4. (1800631)

FIGURES