IMEG Seminar Series

The road to global science

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Muscular Dystrophy UK

Satellite cell dysfunction in neuromuscular disease: DUX4 and PAX7 interactions in FSHD

January 25 th, 2021, 17:00~18:00

The seminar series is for all students and researchers in Kumamoto University. Check your email and find the Zoom ID and passcode.

Muscle health relies on satellite cells that enable postnatal muscle growth, maintenance and repair. However, satellite cell function is gradually compromised in many muscular dystrophies and congenital myopathies. A key issue is whether a pathogenic mutation directly affects satellite cell function. Our multimodal approach defines Satellite Cell-opathies: muscle disorders in which satellite cell dysfunction directly contributes to pathology (Ganassi et al., 2022). Primary Satellite Cell-opathies we define as conditions where mutations directly affect satellite cell function: generally characterised by congenital onset, with hypotonia and involvement of respiratory, trunk and facial muscles, but normal serum CK levels. Archetypes include mutations in PAX7 causing Progressive Congenital Myopathy with Scoliosis and MYOMAKER in Carey-Fineman-Ziter Syndrome. Secondary Satellite Cell-opathies have pathogenic mutations that directly affect both satellite cells and muscle fibres, and include disorders such as Muscular Dystrophy, Congenital Merosin-Deficient, 1a and facioscapulohumeral muscular dystrophy (FSHD), exhibiting a wider range in onset and pathology. Focussing on FSHD, involvement of satellite cells is indicated by low levels of muscle regeneration and suppression of the target genes of PAX7 (Banerji and Zammit, 2021). Mis-expression of the transcription factor DUX4 is associated with FSHD, and we found that DUX4 affects PAX7 protein stability. DUX4 also compromises myoblast viability, culminating in apoptosis. Such cytotoxicity is rescued by the DUX4 homolog DUX4c through molecular antagonism, revealing pathomechanisms converging on WNT/β-CATENIN signalling in FSHD. Finally, we report that DUX4 alters myoblast homeostasis, partially through perturbing mitochondrial performance, with altered mitochondrial respiration and ROS metabolism (Heher et al., 2021).

References

- Banerji, C.R.S. and Zammit, P.S. (2021). Pathomechanisms and biomarkers in facioscapulohumeral muscular dystrophy: roles of DUX4 and PAX7. EMBO Molecular Medicine 13: e13695. (doi: 10.15252/emmm.202013695).
- Ganassi, M., Muntoni, F. and Zammit, P.S. (2022). Defining and Identifying Satellite Cell-opathies within Muscular Dystrophies and Myopathies. Experimental Cell Research 411: 112906 (doi: 10.1016/j.yexcr.2021.112906).
- Heher, P., Ganassi, M., Weidinger, A., Engquist, E. N., Pruller, J., Nguyen, T.H., Tassin, A., Declèves, A.E., Mamchaoui, K., Grillari, J., Kozlov A.V. and Zammit, P.S. (2021). Interplay between mitochondria and reactive oxygen and nitrogen species in metabolic adaptation to hypoxia in facioscapulohumeral muscular dystrophy: potential therapeutic targets. bioRxiv (doi: 10.1101/2021.09.08.459509).

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