Contribution ID: **9** Type: **not specified**

A reliable cellular model-based platform for pharmacological preclinical studies on Tubular Aggregate Myopathy and SOCE-related muscle disorders

Wednesday, 11 May 2022 12:10 (20 minutes)

Tubular aggregates myopathy (TAM) is a hereditary ultra-rare muscle disorder, actually without a cure, characterized by progressive weakness, myalgia or myastenic features. Biopsies from patients with TAM show the presence of tubular aggregates (TAs) originated from sarcoplasmic reticulum (SR) (1). TAs formation is triggered by functional consequences due to disruption in the SR-T- tubule junction related to altered Ca2+ homeostasis. Indeed, TAM is caused by gain-of-function mutations in STIM1 or ORAI1, proteins responsible for Store-Operated-Calcium-Entry (SOCE), a pivotal mechanism in cellular calcium signaling and in maintaining cellular Ca2+ balance (2). The mechanisms underlying muscle weakness and TAs formation from altered Ca2+ homeostasis in skeletal muscle of affected individuals remain to be clarified. To date, most of the STIM1 and ORAI1 mutations has been functionally studied in heterologous expression systems with consequent limitations in terms of disease model reliability and translatability of drug efficacy in humans (2). Although the current availability of some animal models get a hopefully chance in this context (3,4), murine models only partially replicate muscle symptoms observed in TAM patients. In our laboratory we recently created, for the first time, a reliable cellular model usefull for TAM preclinical studies, consisting of myoblasts and myotubes deriving from TAM patients' biopsy carrying Leu96Val STIM1 mutation. By using a plethora of techniques ranging from cytofluorimetry and high content imaging to molecular biology, we demonstrated that STIM1 mutation causes an increase of resting Ca2+ concentration associated with an augmented SOCE activation and proved that differentiating Leu96Val STIM1 myoblasts persisted in a mononuclear state, resulting in a reduced number of multinucleated myotubes with distinct morphology and different geometry of mitochondrial network. Our study provides novel evidences about the correlation between SOCE activation, mitochondrial sufferance and defecting myogenesis in TAM finally highlighting that STIM1/ORAI1 proteins can be considered promising therapeutic targets (5). Importantly, SOCE dysfunction is also observed in various skeletal muscle wasting disorders such as muscular dystrophy, sarcopenia and cachexia (6). Thus, our future purpose will be to use the preclinical pharmacological platform settled in our laboratories for characterizing patient-derived cellular models in order to define related-disease endpoints and to test patient-specific drugs. As it is usually desired for neuromusculuar disorders (7,8), a such experimental approach could finally allow a reliable translation in the clinical management of SOCE-related muscular disorders.

1) Böhm J. et al., Acta Neuropathol. 2018
2) Morin G. et al., Hum Mutat 2020
3) Cordero-Sanchez C. et al., Dis. Model Mech.2020
4) Silva-Rojas, R. et al., Hum. Mol. Genet. 2019
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Session Classification: Sessione