STIM1 over-activation generates a multi-systemic phenotype affecting the skeletal muscle, spleen, eye, skin, bones and immune system in mice

Introduction

- Tubular aggregate myopathy (TAM): Clinics: muscle cramps, weakness and myalgia. Histology: tubular aggregates on Gomori staining
- Stormorken syndrome (STRMK): TAM + short stature + asplenia + dyslexia + ichthyosis + miosis + thrombocytopenia

Objectives

Generation of the first mammalian model of TAM/Stormorken syndrome ➔ Knock-in mice for the most recurrent mutation in STIM1: R304W

Ca2+

Stim1R304W/+ mice as a mammalian model of TAM/STRMK by focusing on:

a. Ca2+

b. Stature
c. Muscle
d. Platelets
e. Immune system

Muscle: Histology

Muscle: Force

Platelets

Immune system

Perspectives

1. Determine the molecular effects of overactivated SOCE in muscle fibers and other tissues
2. Test the efficacy of therapeutic approaches

Conclusions

- TAM and Stormorken syndrome are associated with gain-of-function mutations in STIM1 and ORAI1 [1]
- Pathogenic effect: excessive Ca2+ entry within the cells

Platelets

Stim1R304W/+ mice did not present tubular aggregates
Stim1R304W/+ mice presented dystrophic features on muscle histology: central nuclei (♂), regenerating fibers (♀), cell infiltration (♂), fibrosis (♀) and presence of fibers with high Ca2+ content (♀).

Platelets

Stim1R304W/+ mice exhibited additional features not yet reported in patients
- Potentially of medical importance

References