In skeletal muscle calcium is a key second messenger regulating contraction and the sarcoplasmic reticulum (SR) is the intracellular organelle involved in its regulation. The ryanodine receptor Ca2+ channel (RyR1) present on the terminal cisternae of the SR, is closely apposed to and is directly activated by, the dihydropyridine receptor an L-type Ca2+ channel functioning as voltage sensor. Upon depolarization, the voltage sensor undergoes a conformational change promoting the opening of the RyR1, leading to Ca2+ release from the SR; this elevation of the myoplasmic [Ca2+] is necessary for, and leads to, muscle contraction and this process is called excitation-contraction coupling (Fig. 1).

More than 700 RYR1 variants have been identified in patients worldwide, making this gene the primary target of neuromuscular disorders and accounting for over 30% of mutations found in patients with congenital myopathies. Both dominant and recessive RYR1 mutations occur and usually associate with different phenotypes. Dominant mutations are causative of malignant hyperthermia/rhabdomyolysis/exertional heat intolerance and central core disease and functionally impact the channel’s biophysical properties. Patients bearing recessive mutations are generally more severely affected, characteristically also display involvement of extraocular muscles and are diagnosed as having multi-minicore disease/centronuclear myopathy. The latter mutations have no major effect on the channel properties, but their presence is accompanied by profound biochemical changes in patients’ muscles, including a significant reduction of the RyR1 protein content and high levels of expression of class II histone de-acetylases. The reduced RyR1 levels in the SR membrane cause a decrease of calcium release during excitation contraction coupling, leading to weak muscles.

Our laboratory focuses on determining the functional effect of RYR1 mutations with the long-term goal of developing a pharmacological strategy to improve muscle function in patients. To do so we use two main experimental models: patient-derived biological material and transgenic mouse models knocked in for mutations identified in patients. Muscle biopsies are evaluated biochemically and physiologically. Our results have demonstrated that muscle biopsies from patients carrying recessive RYR1 mutations show abnormally low RyR1 protein content, alteration of gene methylation and an increase in the content of chromatin modifying enzymes including class II histone de-acetylases and DNA methyl transferases. A mouse model we knocked in for a mis-sense mutation in one allele and a frameshift mutation in the other allele (DKI mouse, Fig. 2) exhibits severe muscle impairment, reduced levels of calcium release and disorganization of the muscle ultrastructure. Additionally, extraocular muscles from the transgenic mice have impaired excitation contraction coupling, as well as almost no EO-MyHC, the eye-muscle specific myosin heavy chain isoform. These results are consistent with the weak eye muscles of patients carrying recessive RYR1 mutations.

We are also interested in other aspects of skeletal muscle and in particular in identifying and validating the function of newly identified SR proteins. We have characterized a number of novel proteins including JP-45, junctate, SRP-27 and SRP-35; the latter is a membrane bound retinol-dehydrogenase converting retinol (Vitamin A) to all trans-retinaldehyde. Our results show that SRP-35 is involved in glucose metabolism, facilitating glucose uptake into skeletal muscle. We are currently investigating directly the role of Vitamin A in skeletal muscle physiology.

Taken together the results of our studies will have important implications especially since they will promote the development of pharmacological therapies to improve the quality of life of patients with disorders leading to a decreased levels of RyR1 and may shed new information regarding the link between metabolic disorders and skeletal muscle glucose metabolism.
Selected Publications


