Genetics Day Poster Submission

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Title: MITIGATING ONSET OF CONGENITAL MYOPATHY WITH EXERCISE

Abstract: Tubular aggregate myopathy (TAM) is an inherited skeletal muscle disease associated with progressive muscle weakness, cramps, and myalgia and has been linked to gain-of-function mutations in the proteins involved in store-operated Ca2+ entry (SOCE). Primarily, mutations in the sarcoplasmic reticulum (SR) Ca2+ sensor STIM1 and the ORAI1 Ca2+ channel have been implicated in TAM. The extensive presence of tubular aggregates (TAs) which appear as regular arrays of highly ordered and densely packed SR vesicles in muscle biopsies from TAM patients represents a key histopathological hallmark of this disease. In this study, we assessed the therapeutic potential of voluntary wheel running (VWR) exercise to mitigate onset of TAM in a mouse model containing a known TAM-causing mutation observed clinically. Eight-month-old ORAI1G100S/+ mice presented with functional deficits in both slow and fast-contracting muscles and displayed reduced SOCE function, elevated store Ca2+ content, and robust TA presence. VWR exercise improved slow-contracting soleus muscle function, reduced store Ca2+ content to baseline levels in fast-contracting flexor digitorum brevis muscle, and reduced TAs in fast-contracting extensor digitorum longus muscle. Whole muscle proteomic analysis revealed that solei from ORAI1G100S/+ mice downregulated mitochondrial respiratory machinery and that VWR exercise increased expression of proteins involved in mitochondrial respiration while also upregulating proteins involved in cellular detoxification of byproducts of mitochondrial respiration such as ROS. Together, exercise improved slow twitch muscle function, reduced the presence of TAs in fast twitch muscle, and normalized the proteome of ORAI1G100S/+ mice consistent with adapted proteostasis and mitochondrial function.