SEMINARIO / SEMINAR

***Titolo / Title*:**
Using mitochondrial Ca^{2+} uptake as a therapeutic target for ALS

***Quando / When*:**
23 Settembre, ore 16:30 / 23rd of September 2021 at 16:30 CET

***Dove / Where*:**
Online (Microsoft Teams)
https://teams.microsoft.com/l/meetup-join/19%3a0b724a844f004f47bbf9e6bfc4ccc1b8%40thread.tacv2/1632142414275?context=%7b%22Tid%22%3a%2241f8b7d0-9a21-415c-9c69-a67984f3d0de%22%2c%22Oid%22%3a%22f0a66cde-1f23-46ea-a18a-4b29cf7a6f9d%22%7d

***Relatore / Speaker*:**
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***Abstract*:** Amyotrophic lateral sclerosis (ALS) is a fatal, adult-onset neurodegenerative disease characterized by progressive motor neuron (MN) loss, muscle denervation, and eventually, paralysis. Currently, no effective treatments are available to stop or reverse ALS disease progression and the precise molecular mechanisms that underlie ALS pathogenesis remain elusive. Prior studies revealed decreased mitochondrial respiratory chain activity, altered mitochondrial ultrastructure, and mitochondrial dysfunction in both MN and skeletal muscle (SM) in ALS patients and mouse models. The first sign of ALS pathology occurs at the neuromuscular junction (NMJ), where presynaptic MN axons connect with postsynaptic SM end plates. To date, whether signals resulting in the initial NMJ damage are from MN or SM remain unclear. In this project, we aim to determine the tissue-specific causative role of mitochondrial Ca^{2+} uptake in SM and MN in disease onset and progression, and the therapeutic efficacy of reducing mitochondrial Ca^{2+} uptake on NMJ and SM function in ALS mice. We hypothesize that mitochondrial Ca^{2+} mishandling in both SM and MN actively contribute to ALS disease pathogenesis and that attenuating mitochondrial Ca^{2+} uptake mitigates mitochondrial damage and preserves NMJ/muscle function. To test this hypothesis, we will use transgenic mice with inducible, SM or MN-specific expression of a dominant negative form of the mitochondrial Ca^{2+} uniporter to specifically and selectively reduce mitochondrial Ca^{2+} uptake in SM and MN in hSOD1G93A mice and C9-500 (C9orf72) mice, two mouse models associated with the most prevalent genetic causes for ALS. The central hypothesis will be tested in two Specific Aims. Aim 1 will determine the role of mitochondrial Ca^{2+} uptake in SM or MN in survival, motor function, NMJ function and in vivo muscle performance in hSOD1G93A and C9-500 mice. Aim 2 will assess the impact of tissue-specific inhibition of mitochondrial Ca^{2+} uptake in SM or MN on NMJ and muscle structure, MN survival, muscle intrinsic contractile properties, mitochondrial structure and mitochondrial bioenergetics in SM of hSOD1G93A and C9-500 mice. This project will: 1) provide a systematic, longitudinal characterization of SM and NMJ function from a cellular level to whole animal level at different stages of disease progression in hSOD1G93A and C9-500 mice; 2) determine the degrees to which defects in mitochondrial Ca^{2+} uptake in SM or MN contribute to altered NMJ structure/function, disease onset and progression in hSOD1G93A and C9-500 mice; 3) provide the first detailed dissection on the relative role of mitochondrial Ca^{2+} uptake in SM and MN in ALS phenotype using the same genetic models and determine the origin of the signals that result in NMJ destruction (from SM or MN or both); 4) provide mechanistic evidence for whether mitochondrial Ca^{2+} mishandling is a trigger or a target for disease progression in ALS mice, regardless of the causing mutations (mitochondrial related or non-mitochondrial related); and most importantly, 5) test the validity of a potential new therapeutic target (mitochondrial Ca^{2+} uptake, or the mitochondrial Ca^{2+} uniporter, MCU) for the treatment of ALS.