DOTTORATO DI RICERCA IN BIOLOGIA CELLULARE E DELLO SVILUPPO

40th CYCLE
Project proposal for a Sapienza PhD scholarship

Main research line

Title: Exploring sensory-motor neuron innervation of skeletal muscle affected in Duchenne Muscular Dystrophy (DMD)
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Summary

In Duchenne Muscular Dystrophy (DMD), the absence of Dp427 and one or more of its short isoforms has a significant impact not only on skeletal muscle. In the central nervous system, several molecular pathways are directly and/or indirectly affected by the lack of dystrophin, among which the inhibitory GABA signaling in specific brain regions. The spinal cord (SC), which is the portion of the central nervous system directly connected to the muscle via the double stream of sensory and motor neurons (MNs), is likely to endure the impact of dystrophin deficiency, along with signals associated with muscle atrophy. Nevertheless, the impact of DMD pathology on sensory neurons innervating skeletal muscles and their intraspinal connections with ventral MNs remains largely unexplored. A recent report suggests that proprioception, largely dependent on the activity of muscle spindles, might be impaired in DMD patients, although nociception and tactile sensitivity are preserved. Experimental evidence highlights anatomical and/or functional alterations in muscle spindles in both DMD patients and the mdx mouse model of the disease and modifications in intraspinal connections between sensory and MNs. GABA receptors play a major role in modulating the sensory-induced activation of MNs, and alterations in the abundance and composition of GABA receptors have been reported in mdx vs. wild type mice. Together, these abnormalities in the sensory-motor connections might compromise muscle reflexes, strength, and coordination, exacerbating motor imbalances and muscular deficits associated with the disease. This project seeks to elucidate the extent to which structural and functional interplay between skeletal muscles, sensory neurons, MNs, and intraspinal sensory-motor connections is affected in DMD. Utilizing the mdx mouse and its wild-type control, the study will employ various approaches and techniques, to perform a comprehensive analysis of morphological and functional alterations in sensory ganglia (neurons and satellite cells), MNs, and intraspinal connectivity. The hypothesis that muscle necrosis has repercussions on sensory and MNs, possibly through the activation of glial cells will be explored by treating mice with TRAM-34, a selective blocker of ion channels expressed in macrophages/microglia, ganglionic satellite cells and fibroblasts, which reduces muscle fibrosis and promotes an anti-inflammatory profile of muscle macrophages and spinal microglia. The ultimate objective is to provide insights into potential innovative therapeutic approaches focused not only on improving the muscular condition but also on enhancing

muscle-SC sensory-motor interaction.

Pertinent Publications of the proponent (last 5 years)

1. Botticelli E, Guerriero C, Fucile S, **De Stefano ME**, Matera C, Dallanoce C, De Amici M, Tata AM (2023) Activation of α7 nicotinic acetylcholine receptors via metabotropic dowstream signaling pathways may improve Schwann cell regeneration potential. *Cells* 12:1494. **doi**: 10.3390/cells12111494; **IF**: 7.666; **5-year IF**: 7.677
2. Rosito M, Sanchini C, Gosti G, Moreno M, De Panfilis S, Giubettini M, Debellis D, Catalano F, Peruzzi G, Marotta R, Indrieri A, De Leonibus E, **De Stefano ME**, Ragozzino D, Ruocco G, Di Angelantonio S, Bartolini (2023) Microglia reactivity entails microtubule remodeling from acentrosomal arrays. *Cell Rep* 42:112104. **doi**: 10.1016/j.celrep.2023.112104; **IF**: 9.995; **5-year IF**: 10.990
3. Morotti M, Garofalo S, Cocozza G, Antonangeli F, Bianconi V, Mozzetta C, De Stefano ME, Capitani R, Wulff H, Limatola C, Catalano M, F Grassi (2022) Muscle damage in dystrophic *mdx* mice is influenced by the activity of Ca^{2+}-activated $KCa_{3.1}$ channels. *Life* 12:538. **doi**: 10.3390/life12040538
4. **De Stefano ME**, Ferretti V, Mozzetta C (2021) Synaptic alterations as a neurodevelopmental trait of Duchenne muscular dystrophy. *Neurobiol Dis* 168:105718. **doi**: 10.1016/j.nbd.2022.105718
5. Briatore F, Pregno G, Di Angelantonio S, Frola E, **De Stefano ME**, Vaillend C, Sassoe-Pognetto M, Patrizi A (2020) Dystroglycan mediates clustering of essential GABAergic components in cerebellar Purkinje cells. *Front Mol Neurosci* **13**: 164. **doi**: 10.3389/fnmol.2020.00164
6. Persiconi I, Cosmi F, Guadagno NA, Lupo G **De Stefano ME** (2020) Dystrophin is required for the proper timing in retinal histogenesis: a thorough investigation on the *mdx* mouse model of Duchenne Muscular Dystrophy. *Front Neurosci* 14:760. **doi**:10.3389/fnins.2020.00760
7. Fragapane P, Cosmi F, De Stefano ME (2020) Cultured hippocampal neurons of dystrophic mdx mice respond differently from those of wild type mice to an acute treatment with corticosterone. Exp Cell Res 386:111715. **doi**:10.1016/j.yexcr.2019.111715

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