Al collegio docenti del Dottorato in Medicina Molecolare

Dr.ssa Elena Battirossi

Ciclo XXXVII

Tutor. Prof. Marco Linari, Prof. Pasquale Bianco

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INTRODUCTION

Actin plays crucial roles in cellular processes, like the dynamic remodeling of the cytoskeleton. Non-Muscle Actinopathies (NMAs) are disorders caused by heterozygous mutations in the genes encoding for the β- and γ- isoforms of cytoskeletal actin, whose underlying mechanisms remain to be defined. The aim of my project is to develop an analytical toolkit for detailed nanomechanical characterization of neuronal progenitor cells (NPCs) and neuronal cells (NCs), to establish a correlation between the different structural-mechanical-functional parameters of NMAs patient-derived cells.

METHODOLOGY

A Dual Laser Optical Tweezers is applied to characterize the viscoelastic properties of the membrane-cytoskeleton system of neurons wild-type (WT) and expressing the β-actin mutation R196H associated with malformations of cortical development. Ramp-and-hold pulls to generate a tether are imposed on the membrane of NPCs and NCs.

Patient-derived fibroblasts have been reprogrammed in induced pluripotent stem cells and differentiated into NPCs at the Institute for Clinical Genetics, Dresden. The NPCs sent to our laboratory are subsequently used as an experimental model, at passage 4, or differentiated into mature NCs and used, after 8 days, for the mechanical tests.

RESULTS

Tether formation-elongation is characterized by multiphase force response that were simulated using a 2^{nd} order Maxwell model that provides the estimates of both undamped-damped elastic coefficients and the friction coefficients of the tether. In both WT and R196H NCs the undamped elastic coefficient is not significantly affected by the maturation process. During maturation, friction and damped elastic coefficients show significant reductions in WT NCs, while in mutant NCs all the coefficients in NPCs are already reduced to the NCs values. The work provides the mechanical evidence that R196H mutation induces a faster differentiation of the NPC toward the mature, connection-rich morphology of the NC.

Courses attendance: “Complementary skills for PhD”, University of Siena:

- Ricerche bibliografiche e open access & science - Silvia Aurigi e Cristina Mencarelli (19/05/2022)
- Spin off e Start up della ricerca: Il modello di business e i regolamenti - Niccolò Fiorini (31/05/2022)
- Spin off e Start up della ricerca: L'ecosistema di innovazione a supporto delle start up - Francesco Maria Senatore (07/06/2022)
- Comunicare in ricerca - Elena Meli (20/06/2022)
- Fare ricerca per l’inclusione sociale – Alessandra Romano (27/06/2022)
- Lavoro editoriale per l'editoria scolastica e universitaria (scienze e lettere) - Alessandro Mongatti (1/07/2022)
- The role of standardization in innovation processes – Prof. Carlo Carobbi e Prof. Gianluca Murgia (7-8/09/2022)
- Possibili percorsi formativi post PhD - Gennaro Prota - Aida Ribera Navarro (15/09/2022)
- How to exploit your research idea: a quick introduction to EU project design and management – Donata Franzi (22-23/09/2022)

Lectures and seminars attendance:

- “*IPAM 3Rs-3days webinar cycle Replacement, Reduction, Refinement*”, Italian Platform on Alternative Methods, online seminars, 07-14-21/02/2022
- “*Functional dynamics of chromatin topology in human cardiogenesis and disease*”, NeuroWebinar, Prof. Alessandro Bertero, Molecular Biotechnology Center, University of Turin, 18/02/2022
- “*Exploring the Super-relaxed State of Myosin in Myofibrils from Fast-twitch, Slow-twitch and Cardiac muscle”,* Prof. Michael Geeves, School of Biosciences University of Kent,Canterbury (UK), Firenze, 07/04/2022
- “*PLN- R14del, a controversial cardiomyopathy – Observations from patient-derived cardiomyoctes and transgenic mice*”, Prof. Antonio Zaza, Dipartimento di Biotecnologie e Bioscienze, Università degli Studi Milano-Bicocca, Firenze, 12/10/2022

Abstract submitted for conference participation:

- ECF 2022: “*European Cytoskeletal Forum-The Cytoskeleton and Cell Behaviour”*, Hannover, Germany, 16-17-18-19/05/2022: “*Cytoskeleton-membrane dynamics of Neuron Progenitor Cells (NPC) studied with Dual Laser Optical Tweezers (DLOT)”*
- YRP 2022: “*Annual meeting of Young Researchers in Physiology”,* The Italian Society of Physiology (SIF), Bertinoro (FC), Italy, 13-14-15/06/202: “*Cytoskeleton-membrane dynamics of Neuron Progenitor Cells (NPC) studied with Dual Laser Optical Tweezers (DLOT)”*

- BPS 2023: "*Biophysical Society 67th Annual Meeting*", San Diego, USA, 18-19-20-21-22/02/2023: "*Assessment of the cytoskeletal impact of beta-actin mutations leading to non-muscle actinopathies by means of Dual Laser Optical Tweezers (DLOT)"*