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SEMINAR PROGRAMME 2018

Tuesday, 15 May 2018 | 12:00 noon | ICGEB Seminar Room, W building | Padriciano, 99, Trieste, ITALY

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Mutations in LMNA gene, encoding the nuclear lamina proteins LaminA/C, cause a group of diseases called laminopathies that, at the heart level, manifests with dilated cardiomyopathy (DCM) typically associated with various conduction system defects. LaminA/C proteins regulate many biological processes, from maintenance of nuclear structure to mechanosensing, chromatin organization and transcription. However, studies so far have mainly focused on fibroblasts, while the pathophysiological mechanisms underlying defective LaminA/C in cardiomyocytes (CMs) and their consequences in myocardial diseases remain undefined. With the advent of induced pluripotent stem cells (iPSC), generation of human disease-specific cardiomyocytes (CMs) in vitro has become feasible and allows the creation of cellular models, in which molecular mechanisms of disease may be investigated. In our study, we generated CMs from iPSCs of patients carrying the K219T mutation, which gives rise to DCM. Using this cellular model, we performed a comprehensive analysis of the functional properties by electrophysiological techniques both, at the single cells levels and in a multi-cellular setting.Results from patch-clamp highlighted major functional changes in LMNA-CMs compared to CNTR (i.e. maximal upstroke velocity, action potential amplitude and overshoot), accompanied by a reduction of the peak sodium currents and a diminished conduction velocity. Molecular studies targeting the sodium channel protein Nav1.5 and its encoding gene, SCN5A, indicated a significant reduction of both transcript and protein in LMNA-CMs; this event was associated with an increased binding to SCN5A gene promoter of LaminA/C, together with the H3K27me3 and H3K9me3 repressive marks, and with a preferential localization of SCN5A gene at the nuclear periphery in mutant cells.
Altogether, our findings support an epigenetic regulatory circuit driven by LaminA/C underlying the reduction of sodium currents and the consequent slower conduction velocity, which potentially justify for the conduction defects typically observed in patients with LMNA-cardiomyopathy.

"iPSC-based models for cardiac diseases: focus on LMNA-dependent Cardiomyopathy"

Host: M. Giacca

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