GA06

In vitro platform of failing iPSC-derived cardiomyocytes to study new therapeutic strategies targeting SR and mitochondria in heart failure

Arici M.[1], **D'Elia N.**[2], Metallo A. [1], Barile L[3], Rocchetti M.[1]

E-mail: nicole.delia01@universitadipavia.it

[1] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Milan, Italy

[2] Department of Biology and Biotechnology, University of Pavia, Pavia, Italy

[3] Cardiocentro Ticino Institute-EOC Regional Hospital, Bellinzona, Switzerland

Keywords: hiPSC-CMs; SERCA2a; VDAC; heart failure; istaroxime

Abstract:

Cardiomyocytes (CMs) must regulate the production and the storage of ATP and Ca^{2+} for their correct function; indeed, there is a close cooperation between the sarcoplasmic reticulum (SR) and mitochondria. In particular, Ca^{2+} sequestration in the SR occurs thanks to the ATPase activity of SERCA2a and, at the same time, Ca^{2+} is essential for ATP production at mitochondrial level. Impairment of this relationship seems to play a crucial role in cardiac remodeling associated to heart failure (HF). Recent studies suggest that restoring the correct intracellular Ca^{2+} homeostasis by stimulating SERCA2a or affecting the voltage-dipendent anion channel (VDAC) on mitochondria, could be a promising therapeutic approach for HF treatment.

My thesis' project aims to examine the interplay between SR and mitochondria in healthy and failing human induced pluripotent stem cell derived-cardiomyocytes (hiPSC-CMs). To generate a failing phenotype, hiPSC-CMs are chronically treated with isoproterenol (ISO), a well-known β-adrenergic agonist. The second aim is to analyze the protective effects of SERCA2a stimulation and/or VDAC modulation in preventing or limiting the development of the failing hiPSC-CMs phenotype. To this end, istaroxime derivatives acting as SERCA2a selective stimulators, and the VDAC modulator efsevin are used.

Overall, thanks to this study, an *in vitro* cardiac cellular platform of HF will be developed and a new therapeutic strategy limiting proarrhythmic Ca^{2+} accumulation in the cytosol is proposed for HF treatment.