Investigation of Ca^{2+}-dependent pathogenic mechanisms in Arrhythmogenic Cardiomyopathy associated to a PKP2 mutation

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Abstract

Background: Arrhythmogenic cardiomyopathy (ACM) is an inherited cardiac disease characterized by contractile deficit, myocardial remodeling and fibro-fatty infiltration. ACM is often related to mutations in genes encoding for proteins of the desmosomal complex such as plakophilin-2 (PKP2) encoded by *pkp2* gene. PKP2-mediated ACM impacts on cardiomyocytes (CMs), leading to electrical and contractile dysfunction, and on mesenchymal stromal cells (MSCs) that undergo fibro-adipose substitution. The latter may impair electrical conduction.

Aim of the project: The aim is to characterize the pathogenetic mechanism of the disease associated with the PKP2 mutation in CMs and MSCs.

Materials and methods: Human induced pluripotent stem cells differentiated into CMs (hiPSC-CMs) and 2D microtissue models of hiPSC-CMs and MSCs have been used. Mutant preparations (Mut) were compared to isogenic wild-type (WT) ones. Alterations in Ca^{2+}-handling have been first evaluated in CMs by using epifluorescence analysis and then abnormalities in contractility have been analyzed in microtissues by exploiting Muscle Motion, a software that allows to evaluate and quantify the cardiac contractile function.

Results and conclusions: Preliminary results indicates that the Ca^{2+} transients' amplitude was decreased in Mut CMs compared to WT. Furthermore, we will analyze contractility dysfunction comparing WT and Mut 2D microtissue. Also, we will investigate alterations in Ca^{2+} dynamics and electrical conduction as possible pathogenetic mechanisms related to PKP2-mediated ACM.