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suggest that optical excitation of PCDPTBT provides a new, minimally invasive, tool to influence Ca^{2+} reuptake through an indirect modulation of SERCA2a activity.

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Integrated conductive and biomimetic polymeric interfaces able to serve as micronanostructured patches for myocardial protection and regeneration

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Nowadays, cardiovascular diseases constitute the leading cause of death worldwide, and tissue engineered acellular cardiac scaffolds are increasingly emerging as a possible strategy to promote tissue protection and regeneration in the ischemic damaged heart. Here takes place INCIPIT, an ongoing European research project aimed at improving engineered 3-D patches designed to recruit local stem cells, control left ventricular remodelling, and to support the electrical functionality in the regenerative processes after myocardial infarction (MI). In this regard, it was extremely important to validate the biocompatibility of INCIPIT patches and verify their efficacy in recovering cardiac functionality after MI, both *in vitro* and *in vivo*. The *in situ* recruitment of cells able to reconstruct cardiac tissue is necessary owed to the low endogenous regeneration rate of myocardium. The performed migration assays demonstrated the ability of INCIPIT functionalized electroconductive patches to recruit mesenchymal stem cells and rat non-myocyte cardiac cells. Cytosolic calcium concentration measurements showed that INCIPIT scaffold could promote induced pluripotent stem cell- derived cardiomyocytes (iPSC-CMs) cell-cell interaction and synchronous beating. Furthermore, gene expression analysis highlighted the cardioinductive effect of INCIPIT patches on cardiac stem cells. On the basis of the obtained results, the novel INCIPIT functionalized electroconductive patches emerged as a promising strategy for cardiac tissue regeneration, providing knowledge to support the presently ongoing *in vivo* study in a small animal model and possible subsequent translation to clinical trials.

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Phosphoinositide 3-kinase gamma at the crossroad between autophagy and metabolic control in doxorubicin-induced cardiomyopathy

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Doxorubicin (DOX) is a highly effective chemotherapeutic drug, which use is hampered by dose- dependent cardiotoxicity occurring within one year from treatment completion. Effective cardioprotective strategies to prevent DOX toxicity are still missing mainly because of an incomplete understanding of the underlying molecular mechanisms. We previously described that phosphoinositide 3-kinase γ (PI3Kγ) promotes DOX-induced cardiomyopathy by inhibiting mitochondrial autophagy and that pharmacological or genetic inhibition PI3Kγ restores autophagic disposal of damaged mitochondria and promotes cardioprotection. Here we sought to investigate how and to what extent this mechanism affects cardiac metabolism. Wild-type (WT) and knock-in mice expressing a kinase-inactive PI3Kγ (PI3Kγ kinase-dead; KD) were treated i.p. with DOX weekly for 3 weeks (4 mg/Kg on day 0, 7 and 14, cumulative dose 12 mg/Kg). Activity of glycolytic enzymes, mitochondria respiration rate, ketone bodies and glutamine consumption were measured in whole hearts at 3 and 42 days after the first DOX injection. To investigate the involvement of autophagy, WT and KD mice were injected with DOX (4 mg/Kg) on day 0 and with bafilomycin (0.3 mg/Kg on day 0, 1 and 2). Mice were sacrificed at day 3 and hearts were used for metabolic analysis as above. Fatty Acid Oxidation capacity and Electron Transport Chain activity was compromised in WT + DOX mice, resulting in an increase of ROS formation. Mitochondria dysfunction was associated with upregulation of glycolysis activity and reduction of ATP production. These effects were prevented in KD + DOX mice, that showed an increase of ketone bodies consumption and intracellular content of glutamine. Inhibition of autophagy abolished cardioprotective effect in KD + DOX mice and, interestingly, abrogates glucose utilization in both WT + DOX and KD + DOX groups. Overall, these results demonstrate that DOX promotes a metabolic rewiring of cardiomyocytes towards increased glucose utilization and identifies PI3Kγ as a master regulator of this metabolic switch.

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Use of hiPSC-derived cardiomyocytes to rule out proarrhythmic effects of drugs: The case of hydroxychloroquine in COVID-19

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In the early phases of the COVID-19 pandemic, drug repurposing was widely used to identify compounds that could improve the prognosis of

symptomatic patients infected by SARS-CoV-2. Hydroxychloroquine (HCQ) was one of the first drugs used to treat COVID-19 patients due to its supposed capacity of inhibiting SARS-CoV-2 infection and replication *in vitro*. While its efficacy is debated, HCQ has been associated with QT interval prolongation and potentially Torsades de Pointes, especially in patients predisposed to developing drug- induced Long QT Syndrome (LQTS) as silent carriers of variants associated with congenital LQTS. If confirmed, these effects represent a limitation to the at-home use of HCQ for COVID-19 infection as adequate ECG monitoring may be challenging. We investigated the proarrhythmic profile of HCQ with Multi-Electrode Arrays after subchronic exposure of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) from two healthy donors, one asymptomatic and two symptomatic LQTS patients. We demonstrate that: I) HCQ induced a concentration-dependent Field Potential Duration (FPD) prolongation *in vitro* and triggered arrhythmias that halted the beating at high concentration. II) hiPSC-CMs from healthy or asymptomatic carriers tolerated higher concentrations of HCQ and showed lower susceptibility to HCQ-induced electrical abnormalities regardless of baseline FPD values. These findings agree with the clinical safety records of HCQ and demonstrated that hiPSC- CMs potentially discriminates symptomatic vs asymptomatic mutation carriers through pharmacological interventions. Disease-specific cohorts of hiPSC-CMs may be a valid preliminary addition to quickly assess drug safety in vulnerable populations, offering rapid preclinical results with valuable translational relevance for precision medicine.

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Cellular determinants of arrhythmic risk in hypertrophic cardiomyopathy

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Background

The most devastating consequence of HCM is sudden cardiac death (SCD) due to ventricular fibrillation. The positive correlation between the extent of late gadolinium enhancement and the arrhythmic risk in HCM suggests that ventricular arrhythmias originate from the fibrotic regions. However, recent data suggest that enhanced cellular automaticity (early- or delayed-afterdepolarizations, EADs or DADs-) may be clinically more relevant in promoting ventricular arrhythmias in patients.Purpose Aiming to better understand the cellular and molecular mechanisms of arrhythmogenesis in HCM and to establish a reliable arrhythmic risk stratification in patients, we performed a translational study in HCM patients who underwent surgical myectomy, by combining a clinical follow-up study with in vitro assessments of cellular arrhythmogenicity.

Methods

We retrospectively studied 61 HCM patients who underwent surgical myectomy. At the time of surgery, fresh ventricular tissue was collected and used to isolate single ventricular cardiomyocytes (CMs), which were used for patch-clamp and Ca^{2+} imaging experiments to assess the occurrence of EADs and DADs. Patients were followed up for a median time of 8 years and the occurrence of non-sustained ventricular tachycardia (NSVT) or life-threateningarrhythmic events (LAE) was monitored.

Results

EADs occurred in CMs from 36% of patients and were associated with prolonged action potential duration. DADs occurred in 24% of patients and were associated with abnormalities of intracellular Ca^{2+} handling. The occurrence of NSVT/ LAE in patients strongly correlated with the presence of DADs in cardiomyocytes.

Conclusions

The presence of pro-arrhythmic changes appears to be necessary for arrhythmia generation in HCM and seems to be related with specific alterations at ECG level, that might be used as clinical arrhythmia predictors in HCM patients. Fibrosis per se is not a major predictor of arrhythmias in HCM but may contribute to generate sustained arrhythmias in the presence of substantial cellular triggers (DADs).

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A novel multidisciplinary approach in an LMNA-mutated patient: the importance of considering the overall clinical picture for the early diagnosis

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The cardiac involvement of laminopathies is characterized by electrical disturbances and structural abnormalities which are similar to those of more common conditions, such as the ischemic heart disease. This overlap of clinical manifestations makes their diagnosis challenging and can lead to a potentially fatal delay of the treatment.

A 60-year-old man, without cardiovascular risk factors, was admitted to the emergency department because of syncope and hypotension. The electrocardiogram showed atrial fibrillation which was promptly pharmacologically cardioverted. In the following months a 24-h electrocardiogram Holter monitoring reported a high-grade atrioventricular block. A coronary angiography was performed in order to rule out the ischemic aetiology which demonstrated only an intermediate stenosis (50%) in the left anterior descending artery. Therefore, a dual-chamber pacemaker was implanted and the patient was discharged with the indication to perform a cardiac scintigraphy. However, during the exertion of the abovementioned exam he presented loss of consciousness due to the onset of sustained ventricular tachycardia, which was successfully treated with cardiopulmonary resuscitation maneuvers. The arrhythmia was considered to be of ischemic origin, thus the patient underwent percutaneous transluminal coronary angioplasty with drug-eluting stent implantation at the known coronary stenosis. At this point, the patient underwent the molecular analysis of 128 genes known to be associated with cardiomyopathies, despite not fully respecting the indications of the Heart Rhythm Society/European Heart Rhythm Association consensus statement. While awaiting the result of the genetic analysis, the patient received a remote monitoring device in order to minimize in-person evaluations during the COVID 19-related lockdown. The molecular analysis tested positive for a pathogenetic mutation of the lamin A/C gene, thus the pacemaker was upgraded to a CRT-defibrillator.