Of mice and men in ACM

Summary

Arrhythmogenic cardiomyopathy (ACM) is a genetically inherited heart disease characterized by progressive fibro-fatty replacement of the myocardium leading to ventricular arrhythmias and sudden death in patients. Endurance exercise can initiate or exacerbate disease progression, making early and reliable diagnosis vital. Genetically, ACM is very heterogenous, with at least 16 linked genes, most of them related to the intercalated disc and especially the desmosome. Currently, there are no real curative treatments for ACM, stemming in part from the lack of insight into what molecular mechanisms drive the disease.

To answer this need, in **chapter 2** we describe two mouse models carrying the p.Q563* *Dsg2* nonsense mutation in hetero- (*Dsg2*$^{KI/WT}$) or homozygosity (*Dsg2*$^{KI/KI}$) as well as a human induced pluripotent stem cell cardiomyocyte (hiPSC-CM) model carrying the homologous p.Q558* DSG2 nonsense mutation found in an ACM patient. We found that the *Dsg2*$^{KI/WT}$ mice had a very attenuated phenotype without clear signs of ACM, however the *Dsg2*$^{KI/KI}$ mice had a strong ACM-like phenotype with fibrosis and possible wall thinning in the right ventricle. Structural and functional measures became worse with age and following an exercise regimen. Meanwhile for the *in vitro* models, multiple components of the intercalated disc were dysregulated for the mutant hiPSC-CMs compared to isogenic controls we created. Comparing the results of RNA sequencing on all three models, we found that there were multiple transcriptional overlaps between the models, pointing towards commonly perturbed pathways.

In **chapter 3** we follow this up with the characterization of two more models, consisting of a murine line and a hiPSC-CM model both carrying the heterozygous p.R79* PKP2 mutation. Here we found that, while neither model showed strong ACM hallmarks, in mice, the cardiac desmosomes were affected and the cardiomyocytes were more susceptible to conditions of increased stress.

In addition to the lack of therapies, diagnosis of ACM is cumbersome, based on a set of major and minor criteria in six different categories. To answer this need for improved screening tools, in **chapters 4 and 5** we elaborate on the role of miRNAs and other epigenetic regulators in cardiovascular disease, after which in **chapter 6** we discuss miR-185-5p as a potential new circulating miRNA-based ACM biomarker.

In conclusion, the murine and hiPSC-CM ACM models we have characterized will help to deepen our fundamental understanding of the disease and can serve as testbeds for novel therapies, while the biomarker we have identified holds potential for the diagnosis of ACM.