Abstract Preview

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<tr><td colspan="2">ESC CONGRESS 2019</td></tr>
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Title : Zebrafish models for arrhythmogenic cardiomyopathy type 8: a starting platform for exercise stress test and drug treatment

Topic : 36.3.5 - Basic Science - Cardiac Diseases: Cardiomyopathies

Acronym : Searching for disease modifiers in arrhythmogenic cardiomyopathy: focus on exercise and sexual hormones to chase novel targets to prevent sudden death

Category : Bench

Option : No Options

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Background
Arrhythmogenic Cardiomyopathy (AC) is an inherited heart disease characterized by progressive substitution of the myocardium with fibro-fatty tissue, leading to electrical instability and high risk of sudden death, particularly in young subjects and athletes. In recent years, our laboratory has produced zebrafish (zf) mutant lines modelling AC type 8, an AC form linked to mutations in the junctional protein Desmoplakin (Dsp). Mutations in the DSP gene have been identified in both dominant and recessive AC cases, characterized by left-dominant and biventricular forms of the disease. Sports medicine has highlighted that they are the most dangerous forms, being less easily identifiable by ECG.

Purpose
Taking advantage of our zf Dsp mutant lines, we aim to fully characterize the pathological phenotype, analyze the perturbation of cell communication pathways, evaluate the role of the physical exercise, and test the efficacy of candidate drugs.

Methods
Among our zf lines we have identified double mutant animals, bearing both zf dspa and dspb mutations in heterozygous condition, as the best model able to recapitulate the human AC phenotype. This model underwent physical stress tests in the presence/absence of candidate drug treatment. Phenotyping included heart rhythm measurement, gene expression analysis using Real Time PCR and signaling pathway transgenes, immune-histochemistry, whole-mount in situ hybridization, standard histology and ultrastructural TEM analysis.

Results
Preliminary results from mutant phenotyping indicate alterations in heart rate, sudden cardiac death, structural alterations of the myocardium associated with junctional disorganization and, in parallel, dysregulation of Wnt,

Hippo and TGFbeta pathways. Specifically, Dsp mutant animals can range from an 8% decrease to a 14% increase of heart rhythm compared to the physiological range (120-140 beats per minute in zf larvae). At the adult stage, about 1% of the fish mutant population dies suddenly. The histological examination shows a 50% reduction of the myocardial cell mass, in parallel with a 50% decrease of Dsp signal, detected by TEM, associated with the so-called "pale desmosome" phenotype. Signaling dysregulation includes an 80% loss of Wnt/Beta-catenin, a 300% increase of TGFbeta and a 500% increase of Hippo/YAP-TAZ signaling in the cardiac tissue. Physical stress tests and pathway-directed drug treatment have clarified that these factors can modulate the pathological phenotype, as preliminarily evidenced by the rescue of Wnt signal decrease to normal levels through SB216763 treatment of Dsp-deficient individuals at rest.

Conclusion

Preliminary evidences corroborate the zf organism as a suitable model for AC cellular and molecular phenotyping, exploitable for the dissection of the genetic events leading to the onset and progression of the disease, and applicable to the analysis of chemical and mechanical modulators of AC-associated features.