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Cardiac Fibrosis in Heart Failure: modRNA as New Molecular Therapy

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Background: Cardiac fibrosis is associated with heart failure (HF), which is the number 1 cause of death globally. Although cardiac fibrosis is a physiologic organ response to tissue injury and is necessary for healing, excessive fibrosis disrupts normal cardiac architecture and results in impaired ventricular function leading to sudden death and progressive heart failure.

Methods: Different animal models of HF were used to have a more extended comprehension of treatment for replacement fibrosis, such as myocardial infarct or reactive fibrosis such as pressure overload, PLN R14del transgenic mice or collagen antibody-induced arthritis (CAIA) RA mice.

Results: Hearts from HF mice displayed hypertrophy, fibrosis and reduced left ventricular fractional shortening compared to control. Cardiomyocytes from HF mice showed reduced cytosolic [Ca^{2+}] transient amplitudes that were linked to reductions in sarcoplasmic reticulum (SR) Ca^{2+} store measured with Ca^{2+} imaging. Ca^{2+} handling proteins displayed oxidation-dependent posttranslational modifications that together with an increase in superoxide dismutase expression indicate a cell environment with oxidative stress. Modified mRNA represents a very promising therapy for acquired cardiomyopathy enabling cardiac gene expression manipulation in a rapid and target specific manner without genomic integration and systemic toxicity.

Conclusions: This study gives insights on important molecular mechanisms underlying the pathophysiology of cardiac fibrosis. Indeed molecular therapy based on chemically modified mRNA could be used as therapeutic plan in order to prevent cardiac molecular and physiological changes that impair cardiac function during HF.

Biography:

Dr. Gianluigi Pironti is an Assistant Professor at Karolinska Institutet, Integrated Cardio Metabolic Center (ICMC). He is leading research projects aimed to develop new therapies for cardiovascular diseases models (MI, TAC or transgenic mice) using stem cell, modified mRNA, tissue engineered heart patches introduced by Prof. Kenneth Chien, a pioneer in this field.

Dr. Pironti obtained his PhD at University of Naples Federico II (Naples, Italy) in 2012 with program in clinical pathophysiology and experimental medicine.

From 2012 until 2015 he was a post doc fellow in the laboratory of Prof. Howard Rockman at Duke University (NC/US) studying mechanism of G Protein Coupled Receptors (GPCRs) signalling in normal and failing hearts involving exosomes.

During the years spent in US he had the opportunity to work with Nobel Laureate Prof. Robert Lefkowitz, who inspired him to move and work closer to the source of Nobel prizes, at Karolinska Institutet. There, at department of Pharmacology and Physiology, he initially focused his research on cardiomyocytes' calcium signalling and contractility in pathological and physiological condition.

Dr. Pironti has more than ten years of experience in the field of translational medicine for heart failure, attested by numerous publications on peer reviewed journals, with great experience in microsurgery on animal models and characterization of physiological parameters invasively (cardiac catheterization) and non-invasively (echocardiography). He is also coordinating and conducting projects for joint collaboration with industry partners (Astra Zeneca).