Editorial

Novel regulatory pathways modulating cardiac contractile function: fibroblast to myocardial crosstalk via extracellular vesicles and non-coding RNAs

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Adequate cardiac function results from proper synchronous activation of the cardiac chambers, leading to alternating systolic and diastolic phases. Electrical activation of the cardiac chambers is mainly controlled by cardiac conduction system. The main pacemaker of the heart is the slow-conducting sinoatrial node, which triggers and progressively spreads the electrical impulse towards the atrioventricular node through the atrial chambers. A time-delay in the atrioventricular node is followed by rapid activation of the His bundle and left and right bundle brunches to finalize on the peripheral Purkinje fiber network (1). Such a synchronous and coordinated activation of the atrial and ventricular chambers allows proper contraction of the cardiac chambers and thus blood propelling towards the entire organism.

Cardiac contractility is regulated by an exquisite interplay of thick and thin filaments that are regularly activated by calcium waves. Calcium regulation is mediated by a complex mechanism driving extracellular calcium into the myocyte by the L-type calcium channel ($Ca_v1.2$) and cyclically storing into the sarcoplasmic reticulum by the SR calcium pump (SERCA) and releasing through the ryanodine receptor (RyR). Additional control of the intracellular calcium levels is exerted at the plasma membrane by the sodium channels ($Na_v1.5$) and the sodium calcium exchanger (Ncx) [for recent reviews see (2,3)].

Cardiac insults such as myocardial infarction frequently results in moderate to massive myocardial injury, upon which the heart responds firstly replacing the damage tissue with fibroblasts and/or myofibroblasts and secondly enhancing the myocardial mass by cardiomyocyte hypertrophy. Such initial adaptation might become maladaptive if the heart is unable to cope with the required physiological demands, leading to calcium handling abnormalities [for recent reviews see (4,5)]. Over the last decade investigation have aimed to minimize such functional disorders while limited information was obtained on the regulatory mechanisms driving these events.

It has been classically considered that the main regulatory mechanism of gene expression is the transcriptional regulation of protein coding RNAs. Over the last decade we have witnessed with large surprise that non-coding RNAs are at least 10-fold more abundant than protein-coding genes and that they display a wide range of functional regulatory capacities. In addition, they are capable of been transmitted from cell to cell by extracellular vesicles (6,7) and even between distinct organisms (8), the latter is still debated (9). At least two large families of non-coding RNAs have been described to date, i.e., long (lncRNAs; >200 nt in length) and small (sncRNAs; <200 nt in length) non-coding RNAs. Among them, microRNAs, a subclass of small non-coding RNAs, are the most well-studied. Within the cardiovascular context, tissue-restricted, circulating plasma and exosome contained microRNAs in different biofluids have been reported as biomarkers of distinct pathological conditions such as heart failure, myocardial infarction and congestive heart failure (10,11). Exosome-mediated delivery of microRNAs can provide both beneficial/protective (12,13) and damaging (14,15) effects to the heart. While

ample information is available about the identification of candidate microRNAs as biomarkers, their reproducibility is still largely debated as well as their plausible cellular origin. In this context, an intriguing question is which are the cells that are delivering these extracellular vesicles to the circulation and which is their area of influence.

The study of Oh *et al.* (16) describes that upon cardiac injury fibroblast secreted exosomes containing miR-146a can influence SERCA function in the maladapted hypertrophic heart. microRNAs display tissue and developmental-specific expression in multiple developmental and diseases status. Several microRNAs have been reported to mediate cardiac electrophysiological modulation such as miR-219 and miR-192 to *Scn5a* (encoding $Na_v1.5$) and miR-21 to *Cacna1c* (encoding $Ca_v1.2$) (17-19) while the regulation of *Atp2a2* (encoding SERCA) by microRNAs remains largely unexplored. Interestingly, miR-146a has been widely described as biomarker of multiple pathological conditions, including cardiac pathology. Furthermore, miR-146a is frequently reported as an exosome-enriched microRNA in distinct cell types, including mesenchymal stem cells (20) and macrophages (21). miR-146a has also been reported as biomarker of cardiomyopathy (22) and heart failure (23), while its exogenous administration provides cardioprotective effects in distinct pathophysiological conditions (24,25), but to date modulation of molecular components regulating cardiac function have not been investigated. In this context, an important novelty reported by Oh *et al.* (16) is in fact putting into place the novel role of miR-146a modulating calcium handling. Such a modulatory mechanism is indirect, by regulation of post-translational SUMOylation. SUMOylation prevents degradation of the targeted proteins, providing therefore a larger half-life and thus their functional time window (26). SUMOylation has been previously reported targeting distinct components that modulate the electrophysiological properties of the adult heart, such as potassium channels, as well as SERCA in distinct homeotic and pathophysiological conditions such as myocardial infarction/reperfusion, heart failure as well as others settings of cardiac dysfunction (27-30). Therefore, intervening SUMOylation has been proposed as a plausible therapeutic intervention. In this context, Oh *et al.* (16) nicely demonstrate that modulating the functional capacities of a single microRNA, miR-146a, SUMOylation of SERCA can been altered resulting in enhanced capacities of calcium handling during cardiac physiopathological conditions.

Thus, the data presented in this paper provide seminal evidences in two fronts, on the one hand, the extracellular vesicle mediated cross-talk between fibroblasts and cardiomyocytes upon injury and on the other hand the microRNA-mediated post-translational modification of protein function via modulation of SUMOylation. Therefore, as pointed out by the authors, SUMO1 is identified as a new therapeutic target molecule for heart failure. These evidences open up the possibility of search for novel microRNAs that alone or in combination with miR-146a might further enhance the functional recovery of SERCA in cardiac maladaptive dysfunction and secondly, enlighten the possibility of modulating other cardiac contractile and/or electrophysiological disorders, by altering SUMOylation if the corresponding proteins are susceptible of suffering similar post-translational modifications, e.g., SUMOylation of potassium channels (30) underlying the onset of long-QT syndrome.

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