ABSTRACT

Myocardial infarction is one of the most common causes of human mortality word wide. It is caused by the occlusion of one of the coronary arteries. During this process cardiomyocytes die and are usually replaced by fibrotic tissue, which does not demonstrate contractility. Therefore, there is an obvious need for novel therapy to regenerate the post-infarcted heart, for example applying cellular therapies.

Our hope for effective treatment of damaged myocardium might be novel therapies based on stem cell application. Different types of stem cells have been used so far, e.g. myogenic stem cells, also known as myoblasts. This type of stem cells have many advantages, but their major obstacles have been associated with insufficient electrophysiological synchronization with recipient organ cardiomyocytes. The reason for this phenomenon is the lack of expression of the connexin 43 protein responsible for gap junctions formation.

So, the main goal of this dissertation was to develop a stem cell protocol therapy by using cells with genetic modification (provided by transient transfection of plasmid containing coding sequence for connexin-43) which might solve a problem associated with the occurence of additional simulations in post-infarcted heart (arrhythmia).

The results obtained have shown that genetically modified myoblasts (transfected with plasmid pCiNeo-CX3 containing gene encoding connexin-43) demonstrated significantly increased transcription of this introduced gene as well as translated CX43 protein. Moreover, it was observed that the introduced genetic modification decreased the occurrence of spontaenous and induced ventricular arrhythmias when compared to native myoblasts intervention in post-infarcted heart in rat model, (observed at four weeks after cells delivery).

Analysis of gene expression and their respective protein products structuring ion channels showed that connexin-43 overexpressing myoblasts revealed pre-vailing antiarrhythmic character, positively impacting the length of duration of the action potentials in the myocardium (in respect to calcium ions). Ncx1 and cacna1c proteins were statistically significantly reduced in MI+MbCX43 group of rats comparing to MI+MbWT intervention, and this was demonstrated studying the anti-arrhythmic effect of administered cells (MbCX43). In addition, we have observed a statistically significant increase in expression of

the Serca2a protein when compared with control MI+MbWT and MI+0.9%NaCl interventions. This can be perceived as the additional proof of therapeutic character of MbCX43 cells since an increase in expression of Serca2a can be a potentially considered as the validating biomarker of successful prevention of myocardial remodeling after MI.

Additonally, it has been documented the presence of genetically modified human myoblasts in post-infarction myocardium of rats with characteristic alignment in paralel to recipient organ cardiomyocytes which must possibly inducted formation of functional connexons among both cell types.