



MASTER'S DEGREE IN BIOMEDICAL RESEARCH

Research Project Proposal

Academic year 2023-2024

Project Nº 53

Title: CRISPRCas screening analyses for the study of the epigenetic regulation of fibrosis in myocardial infarction

Department/ Laboratory:

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Summary :

Cardiovascular diseases constitute the greatest health risk in Western countries. In Europe alone, cardiac events, primarily myocardial infarction (MI), take the lives of 4million people each year. The main problem of MI disease is the irreversible loss of the cardiac tissue after the infarct, which is replaced by a stiff non-contractile collagen scar. This remodeling process occurs as consequence of the activation/differentiation of cardiac fibroblasts (CF), which are the main mediators of collagen deposit. CF can sense the stiffness of the scar and respond through mechanotransductory pathways that promote their activation/differentiation. Importantly, epigenetic regulators like histone modifiers and chromatin remodelling-complexes are known to play a critical role in these mechanosensing processes, but mechanisms remain unknown.

The main objective of this Project is to identify the molecular mechanisms involved in the epigenetic regulation of CF activation/differentiation in response to mechanical stimulation.

Pro-fibrotic epigenetic-factors will be identified by ex vivo FACs-based CRISPR-screenings in primaryCF by targeting histone-modifiers and major subfamilies of chromatin remodeling-complexes. Cells will be cultured in 2D/3D systems of polyacrilamde/collagen gels of different stiffness that emulate the healthy and infarcted heart. After initial screening and validation, the role of the selected genes will be investigated to confirm their pro-fibrotic role and elucidate the molecular mechanisms underlying their activation/differentiation. To this end, functional in vitro assays, as well as NGS techniques, will be performed. Finally, putative reversal of the fibrotic CF phenotype will be assessed by (sg)CRISPR-RNA or drug-targeting. This effect could next be assayed in a murine model of MI.

The results obtained from these studies will be of great relevance, not only to better understand the mechanisms of fibrosis in the heart, but also to develop future anti-fibrotic therapies.

(* Possibility of PhD (grant required)).

yes	<input checked="" type="checkbox"/>
no	<input type="checkbox"/>

Does the project include the possibility of supervised animal manipulation to complete the training for animal manipulator? Yes