Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 13

Title: New players in the development of myocardial fibrosis in chronic heart failure. Potential therapeutic applications of the PCP/PCPE-1-LOX axis.

Department/ Laboratory Laboratory of Heart Failure, Program of Cardiovascular Diseases, Center for Applied Medical Research (CIMA)

Director 1 Begoña López Salazar
Contact: blopez@unav.es

Codirector: Arantxa González Miqueo
Contact: amiqueo@unav.es

Summary

Heart failure (HF) is a complex syndrome representing one of the leading causes of mortality and hospitalizations in Western countries including Spain. Importantly, even with the optimal pharmacological treatment, the prognosis is very bad, with a survival rate below 40% 5 years after diagnosis, suggesting that the agents currently available are not effective enough. Therefore it is essential to identify new targets involved in the onset and progression of this disease (1). One of the main histopathological alterations underlying the development of HF is myocardial fibrosis, which increases left ventricular stiffness contributing to the impairment of cardiac function. This fibrosis is the result of an excessive deposition of collagen fibers due to an imbalance between its synthesis and its degradation.

Our group has recently shown that the enzymatic systems involved in collagen fiber formation, the procollagen carboxy-terminal proteinase (PCP) and its enhancer PCPE-1 (3) and lysyl oxidase (2), play a relevant role in the development of myocardial fibrosis and the impairment in cardiac function in HF patients. Therefore, they emerge as potential new therapeutic targets for the treatment of myocardial fibrosis.

In this conceptual framework this project has 2 objectives: 1) To characterize in depth the role of the PCP/PCPE and LOX systems in the development and progression of myocardial fibrosis in different experimental models of HF; 2) To develop and test inhibitors for the most promising target by using interference RNA, peptides, chemical inhibitors (screening of libraries of small molecules) or aptamers depending on the target.

References

1- González A, Ravassa S, Beaumont J, López B, Díez J. New targets to treat structural remodeling of the myocardium. J Am Coll Cardiol 2011;58:1833-1843.

2- López B, Querejeta R, González A, Larman M, Díez J. Collagen cross-linking but not collagen amount associates with elevated filling pressures in hypertensive patients with stage C heart failure. Potential role of lysyl oxidase. Hypertension 2012;60:677-683.

3- Beaumont J, López B, Hermida N, Schröen B, San José G, Heymans S, Valencia F, Gómez-Doblas JJ, de Teresa E, Díez J, González A. MicroRNA-122 down-regulation may play a role in severe myocardial fibrosis in human aortic stenosis through TGF-β1 up-regulation. Clin Sci 2014;126:497-506.

POSSIBILITY OF PhD

YES*

* (PhD grant required)