Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 12

Title: New therapeutic targets for the treatment of myocardial fibrosis in heart failure patients

Department/ Laboratory
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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. This process is regulated by a number of factors which are over-expressed in HF patients such as cytokines (e.g. TGF-β and cardiotrophin-1), matricellular proteins (e.g. osteopontin) and oxidative stress (e.g. NADPH oxidases [NOX]-mediated). In particular, our group has recently shown that cardiotrophin-1 may play a relevant role in the development of myocardial fibrosis in these patients.[2] Similarly, we have also shown that osteopontin is involved in the process of collagen cross-linking.[3]

In this conceptual framework this project has 2 objectives: 1) To validate in vitro and in vivo the role of newly identified players in myocardial fibrosis like cardiotrophin-1 or

osteopontin; 2) To develop and test inhibitors for the most promising targets 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, González A, Querejeta R, Larman M, Rábago G, Díez J. Association of cardiotrophin-1 with myocardial fibrosis in hypertensive patients with heart failure. Hypertension 2014;63:483-489.

3- López B, González A, Lindner D, Westermann D, Ravassa S, Beaumont J, Gallego I, Zudaire A, Brugnolaro C, Querejeta R, Larman M, Tschöpe C, Díez J. Osteopontin-mediated myocardial fibrosis in heart failure. A role for lysyl oxidase? Cardiovasc Res 2013;99:111-120.

POSSIBILITY OF PhD

YES*

* (PhD grant required)