MicroRNAs as therapeutic targets in heart diseases

VALORIZATION

Contribution to society and innovation

According with the most recent report of the World Health Organization (WHO), cardiovascular disease (CVD) still represents the biggest cause of death worldwide [1]. In particular, during the last 15 years, ischemic heart disease, followed by stroke, occupied the leading positions of the global top 10 causes of death. Together they account for 15.2 million out of the 56.9 million deaths worldwide in 2016.

Interestingly, even if CVD appears to be an established health problem in the High/Upper-middle-income countries, it shows an incidence spike in the Low/lower-middles-income countries. This effect is ascribable to the globalization of westernized life style conjointly with a more limited access to CVD treatments [2].

Among the different heart diseases, ischemic heart disease is a major cause of heart failure (HF). Moreover, regardless the causing reasons, a diagnosis of HF results in patient death for up to 50% in a time frame of 5 years [3, 4]. Recent observations report that HF incidence appears to be stable in High/Upper-middle-income countries, yet in more recent years its prevalence showed an increase due to improvement on stabilizing treatment and ageing of population [5]. Unfortunately, increased hospitalization and health care costs are predicted to grow more in future decades. For these reasons, truly curative therapies that can effectively lead to a better health state of HF patients is a pivotal goal of cardiovascular research.

In this context, the findings reported in this thesis add a new piece of knowledge to better understand the molecular response to cardiac injury. Moreover, by focusing on the involvement of miRNAs, our work proposes new possibilities of therapeutic targets for cardiac therapies.

Target groups and implementation

The involvement of miRNAs in heart diseases shows a potential benefit for HF patients. In particular, it opens new therapeutic strategies to treat cardiac remodeling. Even though we recognize that further investigations are still needed, with our work we suggest patient target groups that may have beneficial effect from the results provided in this thesis.

Specifically, the described role of the cluster miRNA-106b~25 in the regulation of cardiomyocyte hyperplasia and hypertrophy is giving new insight on the control of anti-cell-cycling and pro-hypertrophic factors responsible for the switch of these phenotypes from pre- to postnatal life. In line, its reported regenerative action draws a clear link to a potential application on patients afflicted from a new acute myocardial infarction (AMI) or any injury causing a widespread loss of cardiomyocytes and the consequent compensatory hypertrophic response of the surviving myocardium. In addition, if the regenerative therapy would show clinical benefit, this patient target group can be potentially extended to

patients that have experienced older myocardial injuries that have now been converted to stable scars.

With regards to miRNA-148a, its modulation between conditions of concentric and eccentric hypertrophic remodeling could offer benefit to delay or block the dilation of the heart. Patients affected by high blood pressure or dilated cardiomyopathy may take advantage by a therapy able to reduce or stop the disease progression.

As we said, further investigations have to clarify the concrete potential application of our findings on therapeutic strategies aimed to cure cardiac patients inducing cardiac function conservation or rescue. Still in the preclinical phase, the validation of our findings in larger animal models is a mandatory step. Studies using porcine models represent the ideal option due to their anatomical and physiological similarities to humans. There are several types of porcine models with cardiac pathologies, nowadays widely used by research groups from all over the world. For example, the transient occlusion of the left anterior descending artery (LAD) through the inflation-deflation of an angioplasty catheter can better mimic the ischemia-reperfusion condition to which AMI patients are subjected as a consequence of the reperfusion treatment they receive in coronary care units [6].

At this preclinical level, it will also be important to develop the delivery route of therapies together with the vehicle used to carry miRNAs to the heart. For both these points, recent works of Catalucci's group suggests an interesting approach [7, 8]. Treating patients with an aerosol of bio-inspired nanoparticles loaded with miRNAs could avoid invasive procedure of administration and increase the safety of the treatment. In fact, as already discussed in the chapter 2, the use of some AAV serotypes represents a powerful tool that we cannot completely control yet.

A second and mandatory feature of drug development that needs precise investigation is the non-toxicity of the treatment, usually represented by dose-escalation studies in two species, for example one rodent and one non-rodent species such as non-human primates. This point is linked with the two mentioned before in terms of level of miRNA overexpression and timing of the therapy. Being able to discriminate the effects on the short- and long-term of the treatment will give a solid basis to move to clinical studies.

Finally, the three phases of the clinical trial are the more challenging and historically more failure-prone parts of the entire research & development path. At this level the acquired knowledge of molecular reasoning, pharmacodynamics properties and safety of the proposed therapy should help us to better identify the sample of patients to include in our study. Fundamental in this part is the definition of the expected results/objectives depending on the phase of the trial. This careful planning will increase the chance of an efficient interpretation of the resulting experimental outputs and hopefully will offer successful therapeutic achievements also in terms of the cost-benefit ratio of the costs of the new therapeutic modality and patient benefit.

Activities and dissemination

The findings reported in this thesis are the result of the work of an international network composed by motivated and committed scientists collaborating from different international scientific centers. These data have been presented and discussed in international conferences from the European Society of Cardiology, the American Heart Association, EMBO organization, Keystone meetings, as well as more specialized conferences on noncoding RNA. Moreover, the scientific outputs have been submitted and published on international peer-reviewed journals with a proactive approach of sharing our findings to the entire scientific community.

References

1. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death, W.H.O. *The top 10 causes of death*. 24 May 2018.
2. Agyemang, C. and B.J. van den Born, *Limited access to CVD medicines in low-income and middle-income countries: poverty is at the heart of the matter.* Lancet Glob Health, 2018. **6**(3): p. e234-e235.
3. Greenberg, B., *Gene therapy for heart failure.* Trends Cardiovasc Med, 2017. **27**(3): p. 216-222.
4. Ammar, K.A., et al., *Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community.* Circulation, 2007. **115**(12): p. 1563-70.
5. Savarese, G. and L.H. Lund, *Global Public Health Burden of Heart Failure.* Card Fail Rev, 2017. **3**(1): p. 7-11.
6. Wei, K., et al., *Epicardial FSTL1 reconstitution regenerates the adult mammalian heart.* Nature, 2015. **525**(7570): p. 479-85.
7. Miragoli, M., et al., *Inhalation of peptide-loaded nanoparticles improves heart failure.* Sci Transl Med, 2018. **10**(424).
8. Di Mauro, V., et al., *Bioinspired negatively charged calcium phosphate nanocarriers for cardiac delivery of MicroRNAs.* Nanomedicine (Lond), 2016. **11**(8): p. 891-906.