Transcription factors, microRNAs and extracellular vesicles at the crossroad of right and left heart failure

CHAPTER 9

"Impact Paragraph"

Ethics, Economy and Society

Cardiovascular diseases (CVDs) are the number one cause of mortality worldwide. In 2019 alone, CVDs were accountable for 17.9 million deaths (WHO data, 2021)[1] predominantly due to heart failure and stroke. Nevertheless, it is estimated that this number will rise to 23 million by 2030 (WHO data)[2]. Furthermore, the concept that CVDs only affect high-income countries and the elderly population is wrong, as 75% of deaths caused by CVD occur in low and middle-income countries, and 38% of premature deaths (under 70 years old) in non-communicable diseases are caused by CVDs (WHO data, 2021)[1].

With the advances in medical care, life expectancy is increasing, and a person lives on average 80 years[3]. However, this does not translate into healthy life expectancy as, in fact, with increased life expectancy, the life quality dramatically decreases, and the last years of an individual are marked by severe disability, and dementia, among others[4]. Therefore, better treatments are essential to improve the survival rate of each patient and the quality of life by decreasing the comorbidities associated with CVDs. Overall, this thesis may be a small step toward a healthier society. Therefore, firstly, it focused on RVF patients by highlighting the divergences between right and left heart failure and how ventricle-specific treatment might be needed when treating HF, particularly in RVF patients. Secondly, it contributed more data that might directly impact the life quality and expectancy of patients with aortic stenosis (a pathology that belongs to the CVDs group) by predicting if patients could benefit from aortic valve replacement surgery. Finally, by creating new models of HF, we will gain knowledge of new cardiac pathophysiological mechanisms, and ultimately, this will help discover new treatments for HF patients.

CVDs without an efficient treatment can have a massive impact on health care systems by draining large quantities of money from the society and governmental organizations that support it. Within the European Union, overall CVD costs up to €210 billion per year (EHN 2017), being that €111 billion are spent on health care costs, 54 billion are due to productivity losses, and 45 billion on informal care[5]. A better treatment will directly reflect on the health care system, directly decrease the costs associated with patient therapy, and indirectly improve its community's economic status. The results obtained within this thesis will contribute to finding an adequate and more efficient treatment against CVDs, directly and indirectly improving the economic and social state of individuals, communities, and nations.

Moreover, the work reported within this thesis was performed through a double degree agreement and in collaboration between two countries, The Netherlands and Portugal, joining efforts and combining different expertise to increase the network within labs and opening doors for future collaborations working towards a common goal. Besides helping to increase the soft power of both countries, it contributes to cultivating values of openness, pluralism, empathy, freedom, and diplomacy among the European Union.

Peers, Scientific Community and Pharmaceutical Industry

The survival rate of a patient with heart failure is 45.5% at 5 years, but this value drastically decreases to 12.7% at 15 years[6]. Also, a study from Coimbra, Portugal, reported that the long-term survival rate (at 3 years) of individuals with pulmonary hypertension (PH) from different classes such as idiopathic, hereditable, or drug-related PH is only 55%, indicating that

3 years after diagnosis almost half of the patients will die[7]. Both pathologies show frightening survival rates and still lack efficient treatment.

Beyond the comorbidities and the high mortality rate, patients suffering from CVDs are more prone to other diseases. For example, in 2020, the COVID 19 pandemic had a drastic impact on people with CVDs; therefore, these patients constitute a group risk, lowering their chances of survival. Therefore, it is imperative to decrease the number of risk groups and the number of individuals that belong to these groups. In this direction, the work developed within this thesis allowed us to increase our understanding of RV vs LV pathological remodeling. Precisely, we found that potential targets of LV failure due to pressure overload are not suitable for RV failure, as is the case of Hand2. Also, we were able to amplify our knowledge of epigenome transference between cells, namely miRs, during cardiac injury.

The content of this thesis affects a broad spectrum of areas within the CVD field, including the following topics: disease-associated information on RV failure; pulmonary hypertension; heart failure; cardiac reverse remodeling biomarkers to basic fields, including differences between left and right ventricle response to injury and cardiac intercellular communication between different types of cells both in physiological situations.

Up to date, there is no treatment for heart failure and the ultimate goal of my research is to find potential therapeutic targets to improve the efficacy and efficiency of current treatments. Each year the use of miRs as therapeutic agents becomes closer to clinical practice, as it is already happening with Miravirsen, an antagomiR targeting miR-122, crucial in preventing the multiplication of hepatitis C virus in the liver[8,9]. Miravirsen is currently in clinical phase II, and it is expected to be used routinely in clinical practice in the next few years[9], thus influencing the pharmaceutical sector.

However, the results reported here can be applied to other fields. For example, extracellular vesicles (EVs) are a common ground for several types of cancers, neurological diseases, and diabetes, among other pathologies. Furthermore, while EVs have been accepted as potential biomarkers[10,11], recent research has been focused on EVs as new drug-delivery tools[12]. The attractive features of EVs include large bioavailability and exceptional biocompatibility paired with a low immunogenic response assuming a “safe-to-use” platform[13]. Interestingly, EVs can also cross the blood-brain barrier, usually a hindrance to drug delivery, and in this way allow drug access to brain tissues[14]. To further increase target efficacy and stability, EVs can also be engineered and modified regarding their structure, composition, and content[15,16] creating a promising future for EVs as delivery tools in multiple contexts.

Finally, knowledge is only valuable to the world if it is shared. During the last years, the findings reported in this thesis were disseminated by attending international meetings from the European Society of Cardiology and others, where I had the opportunity to expose our data in posters and oral presentations. Furthermore, the scientific data was used to elaborate four papers, including original articles and reviews, submitted to journals in the cardiovascular field, facilitating knowledge spreading throughout all scientific community and academia.

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