Extracellular vesicles at the heart of cell-cell communication

Impact paragraph

Heart failure (HF) is the leading cause of mortality and hospitalization among adults and elderly in the western world, affecting more than 37.7 million people worldwide [1]. HF severely impacts patient's quality of life with daily activities being limited, leading to a high need of healthcare services. Besides the increasing demands on healthcare systems, cardiovascular diseases are also a huge economic burden and it is estimated that, only in the United States, direct medical costs will increase from $318 billion to $749 billion between 2015 and 2035 [2].

Although in the past decades the clinical management of HF remarkably improved, patients are still being treated with drugs that target the symptoms and not the cause of disease, prolonging survival while prognosis remains poor. This indicates the urgency to find new therapeutic options that will prevent the development and/or cure HF, improving patient's life expectancy and quality of life. Despite the efforts of the research community to tackle the underlying molecular mechanism leading to HF, we still fall short in understanding the mechanisms leading to impairment of cardiac vascular remodeling.

Here, we demonstrate the importance of extracellular vesicles derived from cardiomyocytes and their enrichment in certain microRNAs as a model to identify new pathophysiological mechanisms in the failing heart, contributing to a better understanding of the complex networks of cellular processes leading to HF. In this thesis we validate the role of a specific ncRNA, miR-200c-3p, in pathological cardiac vascular remodeling, specifically in the context of intercellular signaling through extracellular vesicles.

This knowledge is relevant not only for scientific community, since we are able to better understand cardiac intercellular communication through miRNAs, but also for drug development as our findings, will potentially open new possibilities for tailored treatment strategies. To date, two clinical trials have been initiated using specific miRNA inhibitors, CDR132L and MRG-110, to prevent HF onset and induce angiogenesis (NCT04045405; NCT03603431). CDR132L is a synthetic antisense oligonucleotide, inhibitor of miR-132, injected intra-venously in patients with HF of ischemic origin. miR-132 was shown to induce pathological CM growth leading to

HF [3]. MRG-110 is a locked nucleic acid (LNA)-modified inhibitor of miR-93, a potent antiangiogenic ncRNA[4]. Thereafter, this thesis is a further step towards identifying new promising miRNA targets, opening to new opportunities to bring ncRNA biology from bench to bedside.

Moreover, vesicle content can be modified for therapeutic purposes with exogenous molecules. EV-secreting cells can be modulated by introducing pro-regenerative factors. Enriched vesicle released by these cells, when injected in injured mouse hearts, increase cardiac function [5]. Alternative studies explored the possibility of isolating EVs, from body fluids or cultured medium, and directly change the vesicular load before injecting them in the myocardium [6]. However, modifying the EV content or the EV-secreting cell, can disrupt the delivery vehicle bioactivity and properties, therefore, knowledge of EV biology is pivotal to use engineered vesicles as delivery cargoes for transfer of bioactive small molecules.

We preliminary showed an insight of the biology of EV release, uptake, location and concentration. EVs have already been used as therapeutic tools [7-9] in mouse models and our findings will improve the current knowledge of vesicular trafficking and open new venues to precisely target organs and cells and, therefore, enable progress for next-generation therapies for HF.

References

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