Extracellular vesicles at the heart of cell-cell communication

Understanding into depth the molecular mechanisms underlying pathological cardiac remodelling leading to heart failure (HF), is an important step to reach tailored therapy for cardiovascular diseases.

The general "one-size-fits-all" approach uses conventional pharmacology, such as β-blockers, diuretics and ACE-inhibitors, to attenuate the symptoms, but it does not consider the primary source of the problem[1, 2]. Hence, patients will experience relatively improved life quality and expectancy but the prognosis is still moderate, remarking the importance of novel therapeutic approaches.

MiRNAs are very powerful small molecules, apt to regulate gene expression and change cell faith. Identification of the miRNAs that are involved in pathological conditions, will allow us to modulate and therapeutically target these non-coding molecules and potentially induce cardiac molecular and cellular adjustments, avoiding development towards HF. To this end, we performed an extensive literature review **(chapter 2)** on how, different non-coding RNAs (ncRNAs), such as lncRNAs, circRNAs and miRNAs, play a role in pathophysiological hypertrophy. Many non-coding RNAs were found to be differentially expressed in response to cardiac stress and played a part in being regulators of pathological cell growth, interfering with specific target genes. Although CMs are large cells and make most of the heart volume, they endure only ~30% of all the cardiac cells[3]. MiRNAs were found to be differentially expressed not only in CMs, but also in different cell types that have received considerably less attention in the pathogenesis of HF. Interaction among different cells is fundamental for the development and function of multicellular organisms, also allowing for adaptation to external (pathological) stimuli. Cells can communicate among each other by, either adhering to one another through adherens junctions and/or adhesion molecules such as selectins, integrins and members of the Ig family, or they can secrete signal molecules that act as local mediators and influence the immediate environment surrounding by affecting non-contacting neighbouring cells. Short-range communication is often not sufficient to effectively respond to specific stimuli[4]. Therefore, in **chapter 3** we looked how long-range communication, mediated by EVs, has the capacity to alter specific molecular mechanisms and lead to the development of cardiac disease. This provided insight on

the importance of identifying the content of EVs that are derived from specific cell types and subsequently understand how it can change under pathological conditions. These findings underline how the utter changes the heart goes through when subjected to pathological conditions, not only involve the cardiac muscle cells, but rather is an intertwined reaction from different cardiac cell types.