Metabolic rewiring of the failing heart

Impact

Research

Cardiovascular disease (CVD) represents a major cause of mortality, accounting for 45% of all deaths within Europe in 2019.[1] Costs associated with CVD for the European Union are estimated to sum up to more than 200€ billion per year, constituting a considerable socioeconomic burden, which is only expected to increase in the future.[1] In a similar fashion, due to increased ageing of the population, the prevalence of heart failure is expected to increase as well.[2] Around 50% of all heart failure patients suffer from heart failure with preserved ejection fraction (HFpEF), which is characterized by impaired relaxation or filling of the left ventricle, leading to diastolic dysfunction. The prognosis of HFpEF is poor and HFpEF patients suffer from a variety of symptoms, such as exercise intolerance, dyspnoea and fatigue, leading to frequent hospital (re)admissions and a significantly reduced quality of life. HFpEF patients and people at risk for HFpEF often also have comorbidities such as chronic kidney disease, hypertension, hyperlipidaemia, type 2 diabetes, and obesity.[3] These metabolic comorbidities compile the metabolic syndrome and are accompanied by chronic low-grade inflammation and an altered systemic metabolism.[4] Cardiometabolic alterations are increasingly recognized as contributing factors in HFpEF development, but the details of this process are not quite clear yet. Fundamental research is therefore needed to unravel the exact nature of both the intra- and extracardiac metabolic disturbances and to design adequate treatment strategies for HFpEF.

Our main objective for this thesis was to strengthen our understanding of cardiometabolic alterations in cardiac pathophysiology with an emphasis on HFpEF. We successfully added to the current knowledge and demonstrated that mitochondrial oxidative metabolism and fatty acid metabolism are highly affected and possibly mismatched processes in HFpEF. Additionally, as evidenced by metabolic modulation of cardiac fibroblasts, we documented that cellular metabolism and phenotypical remodeling can be regarded as bidirectional processes impacting each other, providing new avenues of investigation for treatment strategies.

Relevance

In this thesis, we used both novel and underutilized analytical techniques to investigate the underlying processes in the pathophysiology of cardiac diseases, which can be of interest to other researchers separately from the results and conclusions we derived.

In **chapter 3**, we presented a novel approach for cardiome-directed network analysis of RNA-Sequencing datasets. This methodology can be directly utilized for the analysis of other cardiac disease-based datasets but can also be modified and used for other pathologies or tissues to identify relevant processes and transcripts.

A rather underutilized technique in cardiovascular research is mass spectrometry imaging (MSI), which we applied in **chapter 4** and **5**. We demonstrated that MALDI-MSI can reveal distinct metabolite patterns both in preclinical models of HFpEF and myocardial infarction, and

can therefore aid in the detection of different classes of biomolecules in other cardiac disease models as well. It will be interesting to explore if MSI can also be applied to cardiac biopsies from patients suffering from cardiac disease.
Furthermore, as we demonstrated in **chapter 5**, it can be worthwhile to take results from other research specialties into consideration. The principle of metabolic rewiring as a determinant of cellular function and phenotype is more commonly considered in cancer and immunology research. We demonstrated, as a proof of principle, that this mechanism is also relevant in cardiac research and appears applicable in cardiac fibroblasts.

Target groups and activities

To make our results accessible to the wider scientific and medical community, parts of this thesis have been submitted and published online in international, peer-reviewed journals, some of which in open-access format. The yet unpublished chapters will be submitted similarly in the upcoming time. The conducted research has also been presented at (inter)national meetings and conferences.
Although at this stage the results of this thesis are not directly translatable into new treatment strategies, they are essential as steppingstones, providing new mechanistic concepts and opportunities to investigate and devise therapies for HFpEF treatment and prevention. Our results substantiate the assumption that “lifestyle diseases” such as diabetes and obesity, directly impact the heart and contribute to the development of HFpEF. Metabolic interventions should therefore be considered as complementary therapy for HFpEF treatment and prevention. The altered substrate availability in obesity and diabetes also invites considerations into possible effects of nutrition, in general, and specific dietary supplements, in particular, on cardiac disease development. The HFpEF-afflicted heart is commonly regarded as metabolically inflexible, partially due to insulin resistance, and thereby likely unable to deal with excess fuel availability. This will result in cardiac lipotoxicity, oxidative stress and local inflammation, all mechanisms that will impact cardiac function.[5] Close collaboration between preclinical and clinical researchers, including cardiologists and endocrinologists, can contribute towards the development of successful treatments which will reduce HFpEF morbidity and mortality and benefit patients, ultimately the most important target group.
Improving scientific communication to generate interest for cardiovascular research in the general public, is increasingly recognized as an important endeavour and can benefit researchers as well, generating visibility and public support. In an effort to connect with the public and communicate our research, aspects of heart failure research from our group have been presented to heart failure patients, their relatives, as well as people generally interested in heart failure research during a hospital experience day among others.

References

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