The cardiac fetal gene program in heart failure
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Chapter 8

Summary
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Heart failure (HF) as a result of myocardial infarction (MI) and ischaemic heart disease remains the most prominent health challenge of the developed world, with a five year survival rate of less than 50%. Although, many breakthroughs have been made, the fundamental mechanisms responsible for the development and progression of HF have not yet been fully elucidated. In recent years it has been observed that cardiac injury in the adult heart leads to a switch in gene expression which to some extent resembles the expression pattern observed in the fetal heart. This process has been described as cardiac fetal reprogramming, and is defined as the suppression of adult and re-expression of fetal genes in the diseased myocardium. The exact reasons and mechanisms as to why the adult heart reverts back to a fetal-like expression pattern and the consequences here of remain unknown.

In chapter 2, we reviewed the current knowledge regarding cardiac fetal reprogramming in HF, by looking at the expression profiles during cardiac development and disease, with a particular focus on cardiac metabolism, contractile machinery, electrophysiology, and neurohormonal expression. The findings discussed in chapter 2, suggest that cardiac fetal reprogramming is an integral part of the pathophysiology of HF. Although there is plethora of evidence regarding cardiac fetal reprogramming and its importance during HF, there still remains much to be uncovered regarding this process and its involvement in the development and/or progression of HF.

With this thesis we tried to further characterize cardiac fetal reprogramming in HF, and how a better understanding of this process can lead to novel therapeutic strategies for patients with HF. In chapter 3, we identified several novel genes of the cardiac fetal gene program, by looking expression at different stages of cardiac development and disease in mice. Of the identified genes, OPLAH encoding 5-oxoprolinase a member of the γ-Glutamyl cycle, was found to be the most cardiac specific. Further investigation revealed that OPLAH possessed a cardio-protective function by scavenging 5-oxoproline, an oxidative stress inducing metabolite formed by degradation of glutathione. In turn, we also demonstrate that 5-oxoproline is a novel biomarker for patients with HF. Together these findings suggest OPLAH, a novel member of the cardiac fetal gene program, to be an ideal target for therapeutic intervention in HF.

To further study the importance of OPLAH in the heart, in chapter 4, we describe the development of an Oplah full body knock-out (KO) mouse and the effects ischemia/reperfusion (IR) injury has on these mice. At baseline, KO mice were found to have a cardiac and renal phenotype resembling the clinical manifestation of HF with preserved ejection fraction (HFP EF). To date, there is limited knowledge regarding the pathophysiology of HFP EF, and more importantly there are no known treatment
options for patients with this disease. Therefore, developing a murine model for HFpEF by means of OPLAH ablation, leading to increased oxidative stress from 5-oxoproline accumulation, may eventually lead to a better understanding of the disease and possible new therapeutic strategies to treat the disease. By stressing these KO mice by inducing HF, we found these mice to be more susceptible to cardiac injury. Finally, we also demonstrate that 5-oxoproline is elevated in the plasma of HFpEF patients and associates with more concentric remodeling, a hallmark of HFpEF. Although, highly interesting, it still remains uncertain to what extend OPLAH and 5-oxoproline are involved in the onset of clinical HFpEF. Additionally, it still remains unclear as to what extend circulating 5-oxoproline is specific for HFpEF, or whether it is a marker for HF in general.

In chapter 3 and chapter 4 we utilized a LC-MS method that enabled us to measure 5-oxoproline and glutamate. However to obtain a better understand of the involvement of the γ-glutamyl cycle in heart failure, in chapter 5, we sought out to develop a LC-MS method for the quantification of 5-oxoproline, glutamate, GSH and GSSG (oxidized GSH), key components of the γ-glutamyl cycle, in biological samples. Utilizing the developed methodology, we assessed the effects on the γ-glutamyl cycle following the induction of HF in mice. Specifically in the heart we found increases in 5-oxoproline together with a decrease in the GSH/GSSG ratio in mice exposed to HF, further strengthening the notion that 5-oxoproline is an oxidative stress inducing agent. In addition to being elevated in the heart, 5-oxoproline levels were found to be increased in the kidney, liver, plasma and urine of all mice exposed to HF. However, the GSH/GSSG ratios in the kidney and liver of these animals remained stable, suggesting that these tissues have a higher buffering capacity for oxidative stress. Interestingly, we found 5-oxoproline levels in urine to be elevated following cardiac injury, suggesting that, like plasma, urine 5-oxoproline levels could serve as a possible HF biomarker.

OPLAH is a member of the γ-Glutamyl cycle, and following the observations made in this thesis, we were interested in further characterizing this cycle in HF and uncover whether other members of this cycle could also serve as possible therapeutic targets for patients with HF. To this end, in chapter 6 we reviewed the current knowledge regarding the γ-Glutamyl cycle and its association to oxidative stress and HF. Several studies focused on the γ-Glutamyl cycle have uncovered that certain enzymes involved in this cycle have cardio-protective properties, including GCL, GPx, and OPLAH. However, clinical strategies for targeting these steps have not been explored, which is in large part due to the lack of drugs or small molecules that specifically target these enzyme. The research focused on dissecting the involvement of the γ-Glutamyl cycle and GSH in HF has not only resulted in the
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Identification of novel therapeutic targets for this disease, but has also lead to the characterization of several novel oxidative stress associated HF biomarkers. These findings further address the importance GSH and the γ-Glutamyl cycle have in the development and progression of HF.

In summary, we show that, by further characterizing the cardiac fetal gene program, novel targets for therapeutic intervention in HF can be identified. We demonstrate that OPLAH, a novel cardiac fetal gene, has a cardio-protective effect in HF and that the ablation of this gene results in the development of HFpEF in mice. Furthermore, we characterize the substrate of OPLAH, 5-oxoproline, as being a novel HF biomarker. Together these findings identify OPLAH and 5-oxoproline as novel pathophysiological pathway in HF, and targeting the expression and/or activity of OPLAH may lead to new therapeutic options of HF patients.