The cardiac fetal gene program in heart failure

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Chapter 1

Introduction and Aims
Heart failure (HF) as a result of myocardial infarction (MI) and ischemic heart disease remains the most prominent health challenge of the developed world, with a five year survival rate of less than 50%. HF is defined as the complex end stage clinical syndrome that can result from numerous cardiac disorders, including myocardial infarction (MI), hypertension, cardiomyopathies, and valvular disease. HF is characterized by the acute or gradual loss of functional cardiomyocytes. The remaining cardiomyocytes ineffectively attempt to compensate for the loss of myocardium, initiating a cascade of processes which eventually lead to cardiac remodeling. Cardiac remodeling induces scar tissue formation, ventricular wall thickening, and eventually diminished cardiac muscle functionality. Current clinical therapeutic interventions are successful in slowing down the progression of HF. Such therapies include several forms of drug treatments (e.g. ACE inhibitors), lifestyle modifications, surgery and ultimately heart transplantation. Cardiac transplantation is to date the only therapeutic option for end-stage HF but due to the low number of organ donors only a few thousand patients a year have access to a transplantation program. Therefore, novel strategies aimed at identifying the pathophysiological pathways involved in HF development and progression may lead to novel therapeutic strategies to help patient prognosis.

Over the past decade multiple advances in myocardial cell homeostasis and stem cell biology have enhanced our understanding of cardiac development and maturation. These findings coupled to our knowledge of HF has led to the discovery that cardiac injury in the adult heart leads to a switch in gene expression which to some extend resembles the expression pattern observed in the fetal heart. This process has been described as cardiac fetal reprogramming, and is defined as the reversion from an adult gene expression profile to a fetal gene expression profile in the diseased myocardium. The exact reasons and mechanisms as to why the adult heart reverts back to a fetal-like expression pattern remains unknown. However, it has been suggested that this process is an adaptive response to cope with adverse remodeling in the heart. Furthermore, it is unknown if the expression of fetal gene profile protects the heart during HF or whether this adds further insult to the already weakened heart.

**Aims and outline of this thesis**

The primary aims of this thesis are:
1. To identify novel members of the cardiac fetal gene program.
2. To characterize the pathophysiology of identified novel cardiac fetal genes
3. To characterize the therapeutic potential of these novel cardiac fetal genes

In chapter 2 we describe the current knowledge regarding the cardiac fetal gene program, and how targeting this process might lead to novel therapeutic strategies to
improve patient outcome. In chapter 3 we sought out to identify novel members of the cardiac fetal gene program in HF, by looking at gene expression during murine cardiac development and ischemic HF. Furthermore, in chapter 3, we were also interested in characterizing the therapeutic potential of these novel cardiac fetal genes, in particular that of our top candidate gene OplaH, encoding for 5-oxoprolinase, and its substrate 5-oxoprolinase. OPLAH is a member of the γ-glutamyl cycle, responsible for the homeostasis of the major antioxidant glutathione, where it converts 5-oxoproline, a degradation product of glutathione (GSH) and an oxidative stress inducing agent, into glutamate. To study the effects of OPLAH depletion, and therefore 5-oxoproline induced oxidative stress, on the heart, in chapter 4 we developed an OplaH knockout mouse model. Of particular interest was to identify whether OPLAH ablation coupled to 5-oxoproline accumulation, resulting in oxidative stress, could lead to the development of HF with a preserved ejection fraction (HFpEF). Currently there is limited knowledge regarding the pathophysiology of HFpEF and therefore there are also limited therapeutic strategies targeting this form of HF. However, oxidative stress is suggested to play an important role in the pathophysiology of HFpEF.

Since OPLAH and 5-oxoproline are members of the γ-glutamyl cycle, in chapter 5 we were interested in developing a LC-MS method for the quantification of 5-oxoproline, glutamate, GSH and GSSG (oxidized GSH), key components of the γ-glutamyl cycle, in several biological samples of mice with HF and healthy controls. This might lead to new information regarding the involvement of the γ-glutamyl cycle in HF, and potentially novel biomarkers and therapeutic targets for HF. Finally, following the observations made in this thesis that OPLAH and 5-oxoproline, members of the γ-glutamyl cycle, are involved in HF, in chapter 6 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.

Finally, the relevance of this thesis for the field of cardiovascular research is discussed in the Discussion and future perspectives.