

# Vacuolar H<sup>+</sup>-ATPase as target to restore cardiac function in the diabetic heart

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### Valorization

#### *Social and clinical relevance*

Heart failure is the leading cause of morbidity and mortality worldwide, currently affecting at least 28 million humans. It raises global health concerns because of increasing economic and social impact given its high incidence and prevalence. Over the past decades, despite the significant development of treatment options and prevention strategies of heart failure, the rates of morbidity and mortality remain very high. Therefore, more effective treatment and prevention against the development of heart failure are urgently needed. Diabetes mellitus (DM), obesity, pulmonary hypertension, chronic obstructive pulmonary disease, atrial fibrillation, anemia, and chronic kidney disease are thought to increase risk for the progression of heart failure. In this thesis, we mainly focus on diabetes mellitus-induced cardiomyopathy (DCM).

Diabetes mellitus (DM), a chronic and progressive disease, is an increasing problem worldwide with 451 million cases in 2017 and an estimated amount of 5 million deaths each year. Part of the diabetes cases are related to type 1 diabetes, where  $\beta$ -cells in the pancreas are not able to produce (sufficient) insulin, whereas the largest contribution (> 90%) to the diabetes problem arises from type 2 diabetes mellitus (T2DM). The main cause of morbidity and mortality among patients with T2DM is diabetic cardiomyopathy (DCM). In its early stages, DCM includes a hidden subclinical period characterized by structural and functional abnormalities, including left ventricular hypertrophy, fibrosis, and cell signaling abnormalities. These pathophysiological changes of cardiac fibrosis and stiffness and associated subclinical diastolic dysfunction often evolve into heart failure with normal (preserved) ejection fraction (HFpEF) and eventual systolic dysfunction accompanied by heart failure with reduced ejection fraction (HFrEF). Additionally, as obesity increases the risk for both T2D and cardiovascular disease, it has been postulated that obesity-mediated alterations in myocardial lipid metabolism are critical to the pathophysiology of DCM. When there is a mismatch between myocardial FA uptake and subsequent oxidation in mitochondria, this alteration in myocardial lipid metabolism results in the pathological accumulation of lipid intermediates to cause myocardial lipotoxicity and insulin resistance. Both lipotoxicity and insulin resistance are usually well-documented as the major contributors to the development of DCM in many rodent models and T2D patients, and was linked to an increased CD36-mediated FA uptake in the heart. Therefore, strategies to counteract lipid-induced insulin resistance and contractile dysfunction by

decreasing CD36-mediated FA uptake have been suggested to be very beneficial against the development of DCM.

The studies in this thesis reveal that v-ATPase reassembly, which is achieved through a) increased glucose availability and b) addition of the specific AA (a mixture of arginine/leucine/lysine), is an attractive target process to protect the heart from lipid-induced insulin resistance and contractile dysfunction, and to possibly prevent the development of DCM (**Chapters 2, 3, and 4**). Our findings hold great promise for the clinical application in the future and thereby eventually may reduce the economic costs on the healthcare of these cardiac metabolic diseases.

### ***Potential target groups***

The current thesis mainly focus on preventing and treating the pathophysiology of insulin resistance and contractile dysfunction as a consequence of the diabetic heart. The contents of this thesis offer relevant knowledge as well as understandings for: (1) academic researchers working on a wide range of research field encompassing human/animal nutrition, cellular biochemistry and signaling, cardiac energy metabolism, as well as cardiac (patho)physiology, (2) the pharmaceutical industry working on the anti-diabetic drug development, (3) clinical cardiologist, (4) and diabetic patients. More importantly, many scientists working on chronic metabolic diseases (i.e., obesity, diabetes, and cardiovascular and liver/kidney diseases) also could benefit from our current novel findings.

### ***Innovation and potential application***

In this thesis, we identify that in the heart lipids (long-chain fatty acids), glucose, AA, and ketone bodies are added to the list of metabolites/nutrients regulating v-ATPase function, suggesting that v-ATPase integrates nutritional information. Yet, at present, the underlying upstream mechanism by which these nutrients (palmitate and ketone bodies) contributes to v-ATPase disassembly remains unknown. Continuing and expanding this study is highly essential if we aim to understand and further disclosure the underlying downstream mechanisms by which these nutrients regulate the assembly/disassembly cycles of v-ATPase in the heart. In this thesis, we provide strong evidence for the potential roles of v-ATPase on regulating energy metabolism in the control heart and the lipid-overloaded heart. The data presented in **Chapter 4** demonstrate that, similarly to lipid exposure, chronic exposure to ketone bodies also increases CD36-mediated FA uptake via v-ATPase disassembly, and then

results in a loss of insulin sensitivity, and finally of contractile function in cardiomyocytes. Therefore, deciphering the mechanism behind ketone bodies-induced insulin resistance could prove useful in furthering our understanding of insulin resistance and associated diseases (e.g., T2D) and identify other targets for therapeutic intervention. On the other hand, v-ATPase re-assembly by increased glucose availability and/or AA supplementation by itself already can be regarded as a promising target to restore lipid-induced insulin resistance and contractile dysfunction in the diabetic heart (**Chapter 2** and **Chapter 3**). Therefore, the information obtained in **Chapter 2** and **Chapter 3** reveals v-ATPase function as a key regulator of cardiac substrate preference and as a novel treatment approach for the diabetic heart.

**In summary**, v-ATPase is a promising and innovative target for treatment of T2D and DCM, even though a long road still awaits its final validation, drug development and clinical testing, before introducing a new medication into the medical market. It should be noted that v-ATPase being a therapeutic target to rebalance cardiac substrate utilization in T2D and DCM has been established in an *in vitro* model, so that the immediate next step should involve *in vivo* investigations in rodents subjected to high fat diets before clinical studies should be undertaken. The last chapter of this thesis (**Chapter 5**) describes that we have already initiated these *in vivo* studies.