Role for phosphatidylinositol 4-kinase IIIβ in cardiac metabolic diseases

Valorization

Social and clinical relevance

Heart failure is one of the leading causes of morbidity and mortality worldwide, currently affecting more than 28 million patients, and is a major global healthcare problem because of its high prevalence and economic costs which are continuously increasing. Despite the significant development of treatment and prevention, mortality and morbidity are still high. Therefore, more effective treatment and prevention are urgently needed. Diabetes mellitus, hypertension, obesity, chronic obstructive pulmonary disease, anemia and chronic kidney disease are thought to increase the risk of developing heart failure. In this thesis, we mainly focus on diabetes mellitus-induced cardiomyopathy and hypertension-associated cardiac hypertrophy.

Diabetes mellitus has become a global health threat in the past three decades. About 422 million people worldwide have diabetes, and more than 90% of diabetic patients have type 2 diabetes mellitus (T2DM). T2DM is characterized by high blood glucose levels caused by insulin resistance and insulin secretory dysfunction of pancreatic β-cells. The main cause of morbidity and mortality among patients with T2DM is diabetic cardiomyopathy. Moreover, it is mainly cardiac insulin resistance that leads to cardiac dysfunction. Hence, prevention of cardiac insulin resistance could also prevent diabetic cardiomyopathy.

An estimated 1.13 billion people worldwide have hypertension, and the prevalence is expected to increase further. Forty percent of the hypertensive patients suffer from left ventricular hypertrophy. In uncontrolled hypertension, it is believed that pressure overload initiates the inevitable cardiac hypertrophy and dysfunction which is a main reason of mortality among patients who have cardiovascular diseases.

The successful results obtained in this thesis highlight a novel cardioprotective target phosphatidylinositol-4-kinase-IIIβ (PI4KIIIβ) which can be applied to preserve insulin sensitivity and hopefully prevent diabetic cardiomyopathy (**Chapter 4**), but also to prevent cardiac hypertrophy-induced contractile dysfunction (**Chapter 5**). Our findings hold great promise for future clinical application and thereby may reduce healthcare costs for these cardiac metabolic diseases.

Innovation and potential application

In this thesis, we identify a downstream kinase of protein kinase D1 (PKD1), PI4KIIIβ, as a key player in contraction-induced GLUT4 translocation. Furthermore, this thesis provides new evidence that a metabolic shift towards an increased myocardial utilization of long chain fatty acids is associated with diabetic cardiomyopathy, whereas a metabolic shift towards increased

glucose utilization is associated with cardiac hypertrophy-induced contractile dysfunction. The main outcome of the experimental studies outlined in this thesis is that metabolic interventions involving PI4KIIIβ are able to prevent these cardiac diseases. Given that PI4KIIIβ regulates contraction-induced GLUT4 translocation via its product phosphatidylinositol 4-phosphate (PI4P), PI4P could be a potential drug to prevent insulin resistance in the diabetic heart. Moreover, cardiac insulin resistance is closely connected with skeletal muscle and liver insulin resistance. Hence, PI4P application may also turn out as a possible strategy against whole-body insulin resistance. In addition, MI14 and other PI4KIIIβ inhibitors could be potential compounds to prevent cardiac hypertrophy-induced contractile dysfunction. Yet, it may need a long time before these inhibitors could be clinically tested and eventually being introduced to the market. Therefore, the immediate next step would involve *in vivo* investigations to provide further evidence that PI4KIIIβ is a suitable target against cardiac metabolic diseases.