The phosphatidylinositol-3 kinase (PI3K)-Akt signaling axis mediates cellular growth responses in multiple organisms and cell types. In endothelial cells, it is activated by many angiogenic growth factors and regulates downstream target molecules that are involved in blood vessel growth and homeostasis. In the heart, this signaling cascade is an important positive regulator of post-natal cardiac growth, and it is activated in diseases that increase heart weight relative to body weight. Heart failure is a final common consequence of various heart diseases, and is a leading cause of mortality worldwide. Hypertrophy of cardiac muscle cells is a common feature of failing myocardium. Cardiac myocyte hypertrophy is initially an adaptive response to increased external load that occurs in pathological situations because it can normalize the increase in wall stress induced by mechanical overload. However, increased cardiac mass can also lead to diluted cardiomyopathy (heart failure) through poorly understood mechanisms. Thus, stress-induced or ‘pathological’ cardiac hypertrophy appears to be detrimental for the heart, at least in the chronic phase. On the other hand, normal post-natal growth of the heart or exercise-induced cardiac growth also occurs through hypertrophy of individual cardiac muscle cells. These forms of so called ‘physiological’ cardiac hypertrophy are not associated with contractile dysfunction and are morphologically and molecularly distinct from stress-induced hypertrophy. These observations raise two important questions: (i) what are the mechanisms by which sustained overload results in heart failure? and (ii) what determines the difference between ‘physiological’ versus ‘pathological’ cardiac hypertrophy? We hypothesize that these aspects of heart growth and function can be influenced by the relative balance between the extents of cardiac myocyte hypertrophy and angiogenesis within this organ.
To better understand the mechanisms that control heart growth and function, we developed a conditional transgenic system that expresses an activated Akt1 gene in the heart and sequentially develops adaptive cardiac hypertrophy with preserved contractility in the acute phase and dilated cardiomyopathy in the chronic phase. Coronary angiogenesis was enhanced during the acute phase of adaptive cardiac growth but reduced as hearts underwent pathological remodeling. Enhanced angiogenesis in the acute phase was associated with induction of myocardial VEGF and angiopoietin-2 expression. These findings led us to speculate that impaired coronary angiogenesis could contribute to the contractile dysfunction that occurs following prolonged Akt-mediated heart growth. To test this hypothesis, we utilized a decoy VEGF receptor to attenuate angiogenesis during cardiac growth. Inhibition of coronary angiogenesis during the early ‘physiological’ growth phase resulted in reduced capillary density, contractile dysfunction and conversion from ‘physiological’ to ‘pathological’ hypertrophy. In contrast, the decoy VEGF receptor had no effect on heart function or capillary density in control hearts. Presumably, in the absence of cardiac growth, normal contractile capacity can be maintained without the need for ongoing VEGF-dependent angiogenesis. Recently, we corroborated these findings by experiments that showed that treatment with decoy VEGF receptor will promote heart failure in a model of pressure overload hypertrophy.

These data show that both heart size and cardiac function are angiogenesis-dependent, and disruption of coordinated tissue growth and angiogenesis in the heart contributes to the progression from adaptive cardiac hypertrophy to heart failure. These findings also suggest that therapeutic strategies involving the manipulation of angiogenesis may have unexpected consequences on the heart. Specifically, anti-angiogenesis therapy for various diseases including cancer could inhibit coronary angiogenesis and have adverse effects on the hearts of patients with cardiac hypertrophy that are at risk for heart failure.

References: