Cardiobiology

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Regulation of protein turnover and energy metabolism in cardiac disease

Heart failure is a syndrome in which the heart is unable to adequately perfuse the body's organs with blood. It adversely affects the wellbeing of patients as it may cause muscle weakness and atrophy, dyspnoe, as well as organ damage and dysfunction. To be able to function as a pump that provides oxygen and nutrients to our whole body, the heart itself consumes large amounts of energy. A tight regulation of the use of all available resources, including cellular proteins, becomes particularly critical in disease states where metabolism must increase to maintain cardiac performance. In fact, a fundamental mechanism that underlies heart failure is the failure to metabolically adapt. Our laboratory investigates cellular mechanisms and signaling pathways that regulate cardiac protein turnover and energy metabolism.

Functions of mTORC1 and mTORC2 in the heart

We analyzed the function of the intracellular metabolic regulator mammalian target of rapamycin (mTOR), which has distinct functions depending on whether it is part of mTOR complex (mTORC)1 or mTORC2. Using tissue-specific inducible knockout approaches, we have been able to show that mTORC1 is required for basal cardiac function and that it becomes even more important in physiological or pathological cardiac stress induced by voluntary wheel running or aortic constriction. In mTORC1-deficient mice, pathological pressure overload caused dilated cardiomyopathy without a prior phase of adaptive hypertrophy due to a lack of adaptive cardiomyocyte growth via blunted protein synthesis capacity, and associated with reduced mitochondrial content, a shift in metabolic substrate use and increased apoptosis and autophagy. In contrast, rictor-deficient hearts (rictor is a specific component of mTORC2) are normal during growth or adulthood under basal conditions. We found that pressure overload significantly increases rictor protein along with PKCβII and PKCδ phosphorylation in control mice, but not in cardiac rictor knockout mice. Pressure-overload causes hypertrophy with maintained function in controls, but leads to systolic dysfunction of rictor-deficient hearts without having any effects on cardiac weight, hypertrophy markers or fibrosis. These data suggest that mTORC2 regulates metabolism and contractility of the heart via PKCII and PKCδ (Fig. 1, Xu, 2015; Shende, 2016).

Cardio-protective mechanisms of neuregulin1β

Neuregulin1β (Nrg1β) has beneficial effects in a range of cardiac disease models and ongoing clinical trials are investigating its therapeutic value in heart failure. The mechanisms that underlie the cardio-protective actions of Nrg1β are poorly understood. We investigated whether Nrg1β modulates cardiomyocyte metabolism and whether mTOR is implicated in its cardio-protective effects. We found that Nrg1β stimulates glucose uptake in cardiac myocytes via ErbB2/ErbB4 heterodimers and by activating PI3Kα, Akt and AS160 in a similar manner as insulin and insulin-like growth factor-I (Fig. 2, Pentassuglia, 2016). In our ongoing studies, we are assessing to what extent IRS-1 is implicated and whether the identified mechanism can be exploited under pathological conditions *in vivo*.

Obesity and diastolic dysfunction

Approximately 50% of heart failure patients have a preserved ejection fraction, which means that the fraction of total blood present after completion of the filling phase that is pumped out of the heart into the circulation is maintained. HFpEF has been associated with impaired filling of the heart during diastole. As both the systolic and diastolic parts of the cardiac cycle depend on the availability of high amounts of ATP, we are relating specific metabolic adaptations to contraction and relaxation efficiencies of the heart. To this end we established hypertension and diet-induced-obesity models that we follow using echocardiography prior to terminal invasive hemodynamic (pressure-volume loop) analysis, followed by molecular and microscopic analysis. We use both genders as well as ovariectomized mice for these studies while hoping to provide a fundamental basis for stratified strategies to prevent or treat cardiac dysfunction in both genders.

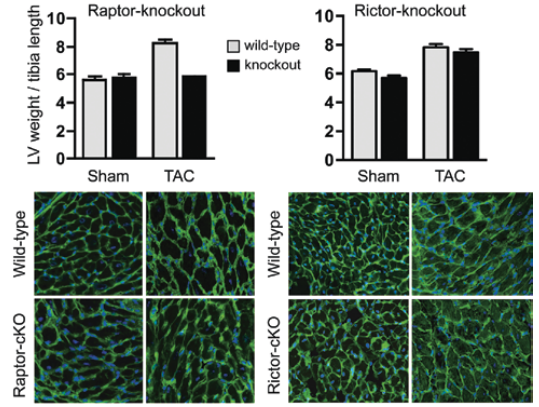

Fig. 1: Effects of cardiac raptor-deficiency (mTORC1 inactivation, left) and rictor-deficiency (mTORC2 inactivation) on left ventricular (LV) weight (top) and cardiomyocyte cross-sectional area (bottom, wheat germ agglutinin staining) in mice that were either sham-operated or exposed to transverse aortic constriction (TAC).

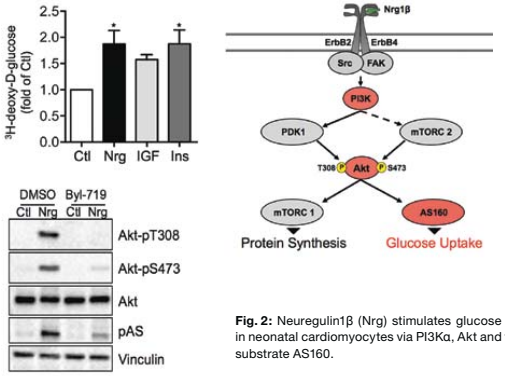

Fig. 2: Neuregulin1β (Nrg) stimulates glucose uptake in neonatal cardiomyocytes via PI3Kα, Akt and the Akt substrate AS160.

Selected Publications

Shende P, Xu L, Morandi C, Pentassuglia L, Heim P, Lebboukh S, Berthonneche C, Pedrazzini T, Kaufmann BA, Hall MN, *et al.* (2016) Cardiac mTOR complex 2 preserves ventricular function in pressure-overload hypertrophy. Cardiovasc Res 109, 103–114

Pentassuglia L, Heim P, Lebboukh S, Morandi C, Xu L, Brink, M. (2016) Neuregulin-1β promotes glucose uptake via PI3K/Akt in neonatal rat cardiomyocytes. Am J Physiol Endocrinol Metab 310, E782–794

Xu L, Brink M. (2016) mTOR, cardiomyocytes and inflammation in cardiac hypertrophy. Biochim Biophys Acta 1863. 1894–1903

Xu L, Shende P, Morandi C, Pentassuglia L, Heim P, Lebboukh S, Kaufmann BA, Berthonneche C, Pedrazzini T, Hall MN, *et al.* (2015) Regulators and effectors of mTORC2 in the heart. J Mol Cell Cardiol 86, S42–S43

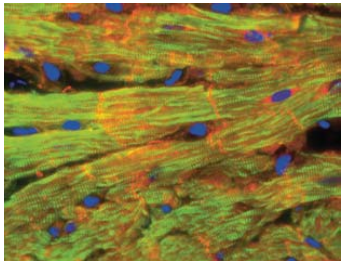

Fig. 3: Cardiac localization of the glucose transporter GLUT4 (red) and Troponin T (green). The nuclei are visualized with DAPI (blue).