inhibition of Notch in these mice accelerates and exacerbates cardiac hypertrophy. In addition, the cardiac response in 1K1C model, as measured by the expression level of cardiac hypertrophy genes is 2–4 times more elevated in mice lacking Notch1 than in wild-type counterparts. Quantitative analysis of cardiac gene expression and α-actinin/NIC immunostaining revealed that cultured Notch1-deficient cardiac myocytes express 4–10-fold more cardiac-specific genes, are generally larger and display a more elaborate myofibrillar apparatus than wild-type counterparts. Our results suggest that Notch modulates cardiac response to stress by controlling cardiac gene expression program.

Keywords: Cardiac hypertrophy; Signalling; Gene expression

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Ventricular dysfunction after pressure overload is associated to impaired CD4 CD8 recruitment in diabetic mice

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Cardiac hypertrophy and diabetes mellitus (DM) are independent risk factors for the development of heart failure. We induced left ventricular (LV) pressure overload by transverse aortic constriction (TAC) in wild-type mice (WT) and in mice homozygous for a mutation in leptin receptor (db/db) showing type II DM phenotype. Seven days after TAC WT but not db/db mice showed a significant increase in LV mass calculated by LV weight to body weight (BW) ratio despite a similar pressure gradient (51.7 mm Hg in WT vs. 52 mm Hg in db/db NS). TAC did not change LV end diastolic (ED) and end systolic (ES) diameter (D) in WT (2.80 mm vs. 2.87 mm and 1.17 mm vs. 1.21 mm after TAC) whereas db/db showed a significant increase (2.9 mm vs. 3.7 mm $p<0.05$ and 1.39 vs. 1.82 mm $p<0.05$). Beta adrenergic receptor (βAR) kinase 1 expression was significantly augmented in WT after TAC, but not in db/db, suggesting that other mechanisms rather than βAR dysfunction are responsible for the early LV dilatation. It is known that in WT CD8+ T cells contribute to collateral development after hind limb ischemia recruiting CD4+ T cells through IL-16 production. Moreover, disruption of coordinated tissue growth and angiogenesis in the heart contribute to the progression from adaptive cardiac hypertrophy to heart failure. In the present study we found a marked increase in CD4+, CD8+ T cells and interleukin-16 (IL-16) in WT hearts. CD4+CD8+ T cells recruitment and IL-16 production were significantly blunted in db/db suggesting that the consequent impaired angiogenic response after TAC could be responsible for the early LV dilatation.

Keywords: Cardiac hypertrophy; Diabetes mellitus; Heart failure

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Some mitochondrial events in pressure overload induced cardiac hypertrophy—from gene to function

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In this study, using abdominal aortic constriction (AAC) model in rat, we confirmed that mitochondria (Mito) play a crucial role in the process of signal translation from mechanical overload to biological signaling causing cardiac hypertrophy. The process of cardiac hypertrophy can be divided into 3 stages: initial stage, remolding state and steady stage. In the initial stage, the expressions of two Mito genes, cytochrome b (cyt b) and Mito-creatine kinase in the hearts at the third day after ACC were firstly found to be increased. These early genic response is adaptive and can cause ordinal functional reinforcement of Mito to fit the increased energy demand. The instantaneous increase of cardiac CoQ_9 content (about 20% increased) supports this assumption. But the change does not improve the unfavorable condition of energy demand, remodeling state is followed. In this stage, the Mito proliferation, as shown by the increase of myocardial Mito DNA copy numbers (16% increased at the 28th day after ACC), is obvious. But accompanying with the change of Mito DNA numbers the Mito superoxide anion and hydrogen peroxide levels increased by 83% and by 394% because the dysfunction of respiratory chain due to shortage of cyt b causes the high reduced state and leaks more electron to generate superoxide. At the steady stage all the Mito events are quite down, and new balance is established. From these data we clarified a Mito related mechanism of pressure overload induced cardiac hypertrophy.

Keywords: Mitochondrial events; Pressure overload; Cardiac hypertrophy

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Myocyte hypertrophy in response to phenylephrine is inhibited by blockade of nuclear import of muscle LIM protein

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Prolonged hemodynamic overload results in cardiac hypertrophy with detrimental changes in myocardial gene expression and morphology. Myocyte hypertrophy is thought to be mediated through mechanosensors. Muscle LIM protein (MLP) is a mechanosensor and a nucleocytoplasmic shuttle protein in cardiac myocytes. It enters the nucleus through its nuclear localization signal (NLS), thereby activating gene expression. Using subcellular fractionation and immunocytochemistry, we have determined some of the factors that regulate the subcellular distribution of MLP in cultured rat neonatal cardiac myocytes. To assess whether changes in contractility