Molecular signaling triggered by mechanic stimulation in cardiac myocytes: adaptation to metabolic needs

Kleber G. Franchini

Departamento de Clínica Médica, Faculdade de Ciências Médicas, Universidade Estadual de Campinas, franchin@unicamp.br

Our studies are focused on the mechanical stress as a major pathogenetic factor for myocardial hypertrophy and failure. Although myocardial hypertrophy is initially a compensatory response to hemodynamic overload continuous impact of mechanical stress on myocardium, set the stage for the latter progression of heart failure which, despite of all best efforts, is currently untreatable. We have previously shown that FAK (Focal Adhesion Kinase) is a central element in the signaling pathways activated by mechanical stress in cardiac myocytes. Studies performed in distinct models (e.g. intact left ventricle, isolated rat heart and isolated neonatal rat ventricular myocytes) unraveled the importance of Fak to the regulation of early gene transcription in response to stretch was demonstrated in neonatal rat cardiac myocytes, indicating that this kinase may coordinate signaling pathways involved in the hypertrophic growth induced by mechanical stress. More recently, we showed that mice treated with a FAK RNAi were unable to develop cardiac hypertrophy induced by pressure overload, demonstrating the critical importance of FAK to the LV phenotypic response to mechanical stress. Several mechanisms have been suspected to be responsible for the progressive deterioration of the hypertrophic heart, including calcium metabolism disorder, neurohumoral maladaptive response, necrosis and apoptosis of cardiac myocytes. Compromised energetics has been increasingly invoked as the basis to explain myocardium dysfunctions in the hypertrophic myocardium. Chronic heart failure is associated with morphological abnormalities of mitochondria such as increased number, reduced size and compromised structural integrity. During hypertrophy, proliferation of mitochondria does not keep pace with the increasing energy demand of the heart. Recent evidence shows that decreased expression of mitochondrial transcription factors and mitochondrial proteins are involved in mechanisms causing the energy starvation in heart failure. We have shown recently that FAK activation plays a role in the signaling mechanisms regulating the mitochondrial biogenesis in cardiac myocytes in response to mechanical stress. Thus, our mainstream hypothesis is that FAK controls the expression and activation of PGC-1α? PPARα? NRF-1,2 pathway and ultimately determines the mitochondrial biogenesis in cardiac myocytes in response to mechanical stress.