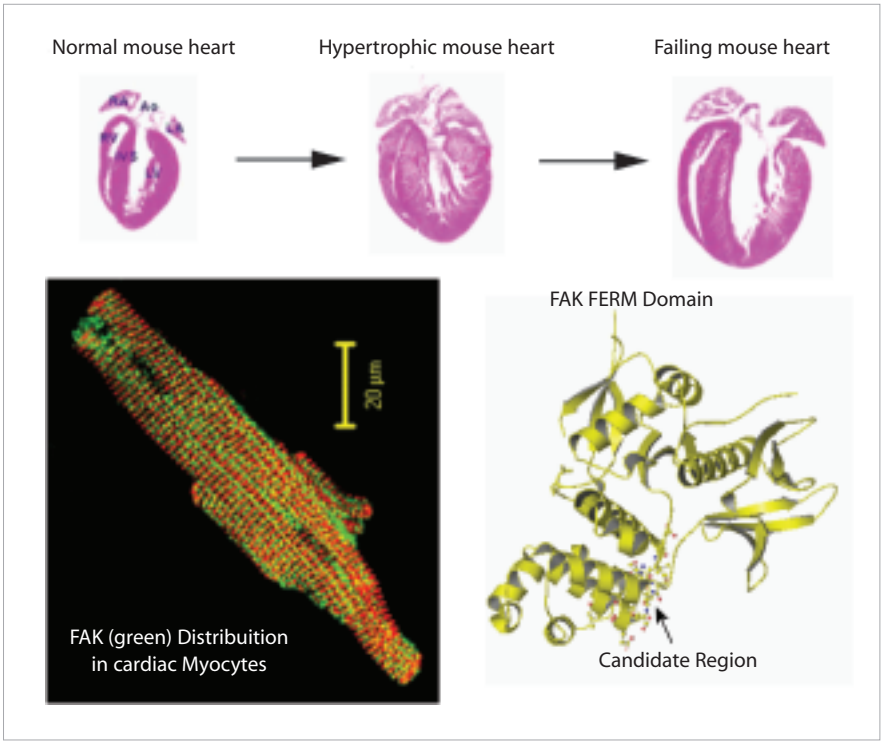
PATHOGENESIS OF CARDIAC HYPERTROPHY AND FAILURE: MECHANISMS ACTIVATED BY MECHANICAL STRESS

Kleber Gomes FRANCHINI

School of Medical Sciences / State University of Campinas (Unicamp)



Example of structural changes in mouse left ventricle progressing from hypertrophy to failure. Example of adult mouse cardiac myocyte double stained with phalloidin (actin) and anti-FAK antibody. Structure of FAK FERM N-terminal domain indicating a mapped region explored for its role in the control of FAK activity.

Cardiac hypertrophy often accompanies cardiac diseases and is thought to set the stage for heart failure in the clinical settings of hypertension, myocardial infarction and valve diseases. Myocardial hypertrophy and its progression into heart failure are mostly driven by elevated mechanical stress, which leads to hypertrophy and injury of cardiac myocytes. The overall goal of our research plan is to identify the signaling mechanisms that control for the phenotypic and functional alterations of cardiac myocytes in response to mechanical stress. Our recent studies have been focused on the contribution of FAK (*focal adhesion kinase*) to the transduction of mechanical stimuli into biochemical signals, and the regulation of gene transcription during the hypertrophic growth of cardiac myocytes and the left ventricle. The research efforts are expanded to the development of synthetic organic compounds targeted at FAK.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

By using different models (i.e. cell culture, pressure overload induced hypertrophy, and failure in rodents and samples of human diseased hearts), we have found that FAK is activated in cardiac myocytes in conditions associated with mechanical stress. By using distinct experimental strategies that included overexpression of inactive mutant of FAK, pharmacological inhibitors and RNA interference technology, we showed that FAK is necessary for the mechanical stress-induced hypertrophy of cultured cardiac myocytes. More recently, by using a strategy of *in vivo* RNA interference, we confirmed the important role played by FAK in the pathogenesis of left ventricle hypertrophy in mice with chronic pressure overload induced by aortic constriction. Treatment with small interfering RNA targeted at FAK not only prevented the hypertrophy but also the progression of hypertrophic hearts to failure. These data indicate FAK as a potential target for the development of therapeutic tools aimed to control hypertrophy and prevent heart failure.

Also, we have used biochemical and structural biology approaches to identify the molecular mechanisms responsible for FAK activation by mechanical stress in cardiac myocytes. The experimental approaches include the mapping of regions potentially involved in intra and inter-molecular interactions, site mutations and the design of peptides to probe the importance displayed by specific regions of FAK in the process of its activation in cardiac myocytes. Another issue explored by our studies refers to the control of FAK activity by the tyrosine phosphatase SHP2. In addition, we have been using a two-hybrid system for screening a cardiac myocyte cDNA library and a combination of immunoprecipitation, protein separation by 2D-electrophoresis and identification of the resolved protein spots by mass spectrometry fingerprinting in order to identify partners that interact with FAK in non-stretched and stretched cardiac myocytes.

MAIN PUBLICATIONS

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Kleber Gomes FRANCHINI

Faculdade de Ciências Médicas / Universidade Estadual de Campinas (Unicamp)
Departamento de Clínica Médica
Caixa Postal 6111 – Cidade Universitária
13084-971 – Campinas, SP – Brasil

+55-19-3521-8023
franchin@unicamp.br