

Ca²⁺-Dependent Signaling Pathways Through Calcineurin and Ca²⁺/Calmodulin-Dependent Protein Kinase in Development of Cardiac Hypertrophy

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Summary. Cardiac hypertrophy is induced by a variety of cardiovascular diseases such as hypertension, valvular diseases, myocardial infarction, cardiomyopathy, and endocrine disorders. Although cardiac hypertrophy may be initially a beneficial response that normalizes wall stress and maintains normal cardiac function, prolonged hypertrophy becomes a leading cause of heart failure and sudden death. A number of studies have elucidated molecules responsible to the development of cardiac hypertrophy, including protein kinase C (PKC), protein kinase A (PKA), Raf-1 kinase, mitogen-activated protein (MAP) kinase family, and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) family, Ras, and Rho family. It has been reported that Ca²⁺ regulates a number of cellular processes including cardiac hypertrophy. Since most hypertrophic signaling pathways are associated with an increase in intracellular Ca²⁺, Ca²⁺-dependent signaling pathways may be critical targets for therapies designed to prevent the progression of cardiac hypertrophy. Recently, a Ca²⁺/calmodulin-dependent protein kinase, and a Ca²⁺/calmodulin-dependent protein phosphatase, calcineurin, have attracted much attention as critical molecules that induce cardiac hypertrophy. In this review, we summarize the Ca²⁺-dependent signaling pathways through Ca²⁺/calmodulin-dependent protein kinase and calcineurin in cardiac hypertrophy.

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INTRODUCTION

Cardiac hypertrophy is recognized as an adaptive increase in heart size characterized by a growth of cardiomyocyte rather than an increase in cell number. Cardiac hypertrophy is induced by a variety of cardiovascular diseases such as hypertension, valvular diseases, myocardial infarction, cardiomyopathy, and endocrine disorders (1,2). It has been well known that a variety of stimuli including mechanical stress, ischemia, and neurohumoral factors can activate multiple intracellular signaling pathways, leading to the development of cardiac hypertrophy (3). Although cardiac hypertrophy may be initially a beneficial response that normalizes wall stress and maintains normal cardiac function, epidemiological studies demonstrated that cardiac hypertrophy is a major risk factor of heart diseases and becomes a leading cause of heart failure and sudden death (4). Therefore, it is important to understand the precise mechanisms and mediators of cardiac hypertrophy and to prevent it. Recently, a Ca^{2+} /calmodulin-dependent protein kinase (CaMK), and a Ca^{2+} /calmodulin-dependent protein phosphatase, calcineurin, have attracted much attention as critical molecules that induce cardiac hypertrophy. Furthermore, the molecules related to CaMK and calcineurin, which include endogenous inhibitors of cardiac hypertrophy, have been also elucidated. This article focuses on the Ca^{2+} -dependent signaling pathways through calcineurin and CaMK in cardiac hypertrophy.

Ca^{2+} /CALMODULIN

It has been known that Ca^{2+} regulates a number of cellular processes including cardiac hypertrophy (5). In response to external stimuli, cells increase their cytosolic Ca^{2+} levels (5). Because chelating of extracellular or intracellular Ca^{2+} abolishes hypertrophic responses by hypertrophic stimulators in cardiac myocytes, the increase in intracellular Ca^{2+} level and the activation of Ca^{2+} -dependent signaling pathway may be involved in cardiac hypertrophy (6–8). The elevation of cytosolic Ca^{2+} levels is accomplished by Ca^{2+} influx from external space and/or Ca^{2+} release from internal stores such as sarcoplasmic reticulum (SR) (5). L-type Ca^{2+} channels, T-type Ca^{2+} channels, $\text{Na}^+/\text{Ca}^{2+}$ exchanger, sarcolemmal Ca^{2+} -ATPase, SR Ca^{2+} -ATPase (SERCA), and ryanodine receptor are involved in Ca^{2+} transport in cardiac myocytes. Ca^{2+} influx through L-type Ca^{2+} channels induces a large Ca^{2+} release from SR through ryanodine receptor, which is called Ca^{2+} -induced Ca^{2+} release (CICR) (9,10). By using a Ca^{2+} -binding fluorescent dye (fluo3) and patch clamp technique, it has been shown that mechanical stress also induces Ca^{2+} influx through stretch-sensitive ion channels, leading to induction of CICR (11). The increase in intracellular Ca^{2+} levels usually evokes cellular events through its binding to Ca^{2+} binding proteins such as troponin C, calmodulin, calsequestrin, and calreticulin. Calmodulin has been well known as a major Ca^{2+} binding protein in all eukaryotic cells (12). It has been reported that the growth of cardiac myocytes is specifically regulated by calmodulin concentrations and that overexpression of calmodulin