Subcellular Redistribution of Focal Adhesion Kinase and Its Related Nonkinase in Hypertrophic Myocardium

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Abstract—Focal adhesion kinase (FAK) and focal adhesion kinase-related nonkinase (FRNK) are likely involved in mechanical signaling during hypertension. We investigated expression, subcellular distribution, and phosphorylation of FAK, as well as FRNK in left ventricles of spontaneously hypertensive heart failure rats. Compared with normotensive controls, FAK and FRNK increased in left ventricles of hypertensive rats. Increased FAK and FRNK were mainly present in membrane cytoskeleton and nuclear fractions. Confocal microscopy demonstrated that FAK and FRNK translocated to nuclei and intercalated disks in cardiac myocytes from hypertensive rats. Serine and tyrosine phosphorylation of FAK increased dramatically in hypertensive rats. FAK phosphorylated at tyrosine 397 was present in membranes and intercalated disks, but not in nuclei. FAK was also phosphorylated on serine 722 but not on serine 910. In contrast, FRNK was phosphorylated on serine 217, the equivalent site of FAK serine 910, but not serine on 30, the homologous site of FAK serine 722. Serine phosphorylated FAK and FRNK accumulated in membranes and nuclei but not in intercalated disks. Nuclear translocation of FAK and FRNK may play important roles in regulating mechanical signal transduction in cardiac myocytes. (Hypertension. 2003;41:1317-1323.)

Key Words: hypertrophy ■ heart failure ■ kinase ■ cell signaling

Our studies on lean female spontaneously hypertensive heart failure (SHHF) rats have shown that myocyte cross-sectional growth responsible for ventricular wall thickening reaches a maximum at ~4 months of age and remains stable thereafter. Myocyte lengthening, which underlies ventricular chamber dilatation, begins at 6 months of age and continues progressively with aging until the rats develop congestive heart failure (CHF) at 22 to 24 months of age. The switch from cross-sectional growth to myocyte lengthening ~6 months in SHHF rats suggests that maladaptive remodeling and abnormal growth of cardiac myocytes begins long before overt cardiac decompensation. Therefore, the key to decipher the molecular mechanisms involved in the transition of concentric cardiac hypertrophy to maladaptive remodeling is to determine the signaling molecules that control series sarcomere assembly in cardiac myocytes.

Focal adhesion kinase (FAK) is activated in cardiac myocytes and fibroblasts by in vitro treatment with a variety of hypertrophic stimuli. The C-terminus of FAK is expressed as a separate protein known as focal adhesion kinase-related nonkinase (FRNK) in certain cell types. FRNK inhibits FAK tyrosine phosphorylation and endothelin-induced cardiac myocyte hypertrophy. Recent studies have also shown that FAK is phosphorylated and activated during cardiac hypertrophy after acute pressure overload. The phosphorylation and activation of FAK appears to be transient and returns to normal levels after 1 week of overload. Thus, the potential role of FAK and FRNK in continuous remodeling of cardiac myocytes caused by chronic hypertension remains to be defined. FAK and FRNK may play a key role in cytoskeletal remodeling and maladaptive shape change of cardiac myocytes in SHHF rats.

Serine phosphorylation of FAK and FRNK follows FAK tyrosine phosphorylation. FAK become prominently phosphorylated on serine residues in a mitosis-specific fashion. Serines 722 and 910 are 2 major serine phosphorylation sites of FAK in interphase cells. The exact roles of these serine phosphorylation in mechanical signal transduction and cardiac hypertrophy remain to be investigated.

In the present study, we examined expression and relationship between subcellular localization and phosphorylation of FAK and of FRNK in the left ventricles (LVs) of SHHF rats. Our results indicate that FAK is increased and translocated to membrane cytoskeleton, intercalated disks, and nuclei during cardiac hypertrophy in SHHF rats. The nuclear translocation of integrin-mediated signaling molecules may play an important role in regulating mechanical signal transduction to the nucleus in cardiac myocytes during chronic hypertension.

Methods

Animals

Fifteen 6-month old lean female SHHF rats were purchased from Charles River (Indianapolis, Ind). Fifteen age-matched female
Wistar-Kyoto rats (WKY) from Harlan (Indianapolis, Ind) were used as normotensive controls. Five animals from each group were used to perform immunolabeling, cell fractioning, and nuclear protein extraction respectively. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals (NIH publication No. 93-23, revised 1985). All animal protocols were approved by the University of South Dakota Animal Care and Use Committee and followed institutional guidelines.

Antibodies
Rabbit polyclonal antibody against the N-terminus of FAK (A-17) and its blocking peptide, mouse monoclonal (H-1) and rabbit polyclonal (C-20) antibodies against the C-terminus of FAK, and mouse monoclonal antibody against histone H1 were obtained from Santa Cruz Biotechnology. A mouse monoclonal antibody against FAK kinase domain was purchased from Transduction Laboratories.

Phosphorylation site-specific antibodies against FAK phosphotyrosine at 397 (FAK-pTyr397), phosphoserine at 722 (FAK-pSer722), phosphoserine at 910 (FAK-pSer910), and their blocking peptides were acquired from Biosource International. Serine 910 of FAK corresponds to serine 217 of FRNK. FAK-pSer910 antibody specific to phosphorylated serine of FAK at 910 also reacts with phosphorylated serine of FRNK at 217 (FRNK-pSer217). Agarose-conjugated mouse monoclonal anti-FAK antibody was purchased from Upstate Biotechnology. Mouse monoclonal antibodies against actin, N-cadherin, and phosphotyrosine were purchased from Sigma. Alexa Fluor 488 or 568 conjugated goat anti-rabbit IgG or goat anti-mouse IgG antibodies for immunolabeling were obtained from Molecular Probes. Horseradish peroxidase-linked donkey anti-rabbit IgG antibody and goat anti-mouse IgG antibody for Western blots were from Amersham Pharmacia Biotech.

Myocyte Isolation, Immunolabeling, and Confocal Microscopy
Cardiac myocytes were enzymatically isolated as published previously. Immunolabeling and confocal microscopy of isolated myocytes were performed as described previously.

Antigen Retrieval
An antigen retrieval technique was performed for FAK-pTyr397 labeling as published. Briefly, after myocytes adhered to slides, the slides were put into sodium citrate buffer (pH 6.0), heated (≈90°C) for 30 minutes by microwave, and then processed for immunolabeling.

Cell Fractioning, Nuclear Protein Extraction, Gel Electrophoresis, and Western Blots
LV tissues were homogenized and separated into Triton X-100 soluble supernatant (TSS) and Triton X-100 insoluble fractions (TIF). The TSS was further separated into cytoplasmic (CF) and membrane skeleton fractions (MSFs) as described. The extraction of nuclear protein (NP) was performed as described. An equal amount of total protein, determined with the Bio-Rad Coomassie protein assay (Bio-Rad Laboratories), was loaded and run on 10% Laemmli sodium dodecyl sulfate–polyacrylamide gel as described. Optimal enzyme-linked chemiluminescence (ECL; Amersham Pharmacia Biotech) exposure time for each antibody was determined during preliminary studies. Actin and histone H1, Western blots were run at the same time to ensure equal protein loading for cell fractioning and nuclear protein, respectively. Duplicate Western blots from 5 WKY and 5 SHHF rats were exposed sequentially in 3-second intervals around optimal ECL exposure time. Films with similar density of actin or histone H1 band were scanned and quantified with ImageQuaNT (version 4.1; Molecular Dynamics). The integrated intensity of each band was regarded as relative densitometry units (du) for protein content. The density of the duplicate Western blots was averaged.

Immunoprecipitation
Total proteins of the TSS for FAK immunoprecipitation were adjusted so that equal amounts of FAK could be pulled down from LVs of SHHF and WKY rats. Tissue lysates were precleared by incubation with 20 μL of protein G beads (Santa Cruz Biotechnology) for 1 hour at 4°C. After centrifuging at 15 000g for 5 minutes at 4°C, the supernatant was incubated with agarose-conjugated anti-FAK monoclonal antibody overnight at 4°C. The immune complexes were separated and blotted with anti-FAK or antiphosphotyrosine antibodies as above. The density of each band was quantified by densitometry as described previously.

Statistics
Data are expressed as mean±SD. Two-sample, independent-group t test was performed to compare the density of FAK, FRNK, and their phosphorylated forms in different cellular compartments between WKY and SHHF groups. A value of P<0.05 was regarded as significant.

Results
Increased Expression and Membrane Translocation of FAK and FRNK in Hypertrophic LV of SHHF Rats
Because the amino-acid sequence of FRNK and the C-terminus of FAK are identical, both FAK and FRNK can be identified by using antibodies against the C-terminus of FAK. Western blots with mouse and rabbit antibodies against the C-terminus of FAK showed that 2 bands at ≈125 kDa and 41–43 kDa were present in the TSS from the LV of both SHHF and WKY rats. Evidently, the band at 125 kDa represents FAK, and the other band at 41–43 kDa corresponds to FRNK (Figure 1A). FAK was phosphorylated on serine 722 but not on serine 910 (Figure 1B). In contrast, FRNK was phosphorylated on serine 217 (Figure 1C), the equivalent site of FAK serine 910, but not on serine 30, the homologous site of FAK serine 722. To examine the distribution of FAK and FRNK, we further separated the LV tissue lysates into 3 fractions: CF, MSF, and TIF. We found that FAK and FRNK were expressed mainly in the CF and the
Translocation of FAK to the Intercalated Disks in SHHF Rat Myocytes

Compared with FRNK, FAK has a unique N-terminus. Specific antibody against FAK N-terminus (A-17) was used to investigate its subcellular distribution. FAK showed weak, evenly distributed, cytoplasmic dots that aligned to form a striated pattern in cardiac myocytes from both SHHF and WKY rats (Figure 3). Double labeling demonstrated that FAK co-localized with α-actinin (data not shown). In contrast to weak signals at intercalated disks in WKY rats (Figures 3A, 3B, 3E, and 3F), strong FAK fluorescence accumulated at intercalated disks in SHHF rats (Figures 3C, 3D, 3G, and 3H). The myocyte staining was completely removed by incubating anti-FAK antibody with specific blocking peptide. FAK at intercalated disks also co-localized with cadherin as demonstrated by double labeling (Figures 3F and 3H), indicating that FAK translocated to intercalated disks in LV myocytes of SHHF rats. Labeling with anti-FAK kinase domain antibody demonstrated a similar but weaker staining pattern (data not shown). Examination of intact myocardium by using frozen sections showed identical results (data not shown).

Translocation of FAK to the Nucleus in Myocytes of SHHF Rats

Immunolabeling of FAK also demonstrated that only weak FAK staining was present in myocyte nuclei of WKY rats (Figures 3A and 3B), but strong FAK fluorescence in myocyte nuclei of SHHF rats (Figures 3C and 3D). To further
confirm nuclear translocation of FAK, we extracted the NP from LV tissues of SHHF and WKY rats and performed Western blots. We found that FAK was significantly increased in the NP (Figure 2) of the LV from SHHF rats when compared with that from WKY rats (215 ± 11006 165 versus 30 ± 11006 15 du, n=5, P<0.05). These results suggested that FAK is translocated to the nucleus in hypertrophied myocardium of SHHF rats.

Phosphorylation of FAK at Tyrosine 397 Is Accumulated in the Membrane and the Intercalated Disk But Not in the Nucleus

Immunoprecipitation with FAK antibody followed by Western blots with phosphotyrosine antibody demonstrated that FAK tyrosine phosphorylation (Figure 4) increased significantly in the LV of SHHF rats when compared with WKY controls (259 ± 11006 71 versus 44 ± 11006 23 du, n=5, P<0.05) without significant changes in the CF (737 ± 11006 526 versus 694 ± 11006 318 du, n=5, P>0.05) when compared with WKY rats. No significant amount of FAK phosphorylation at this site was present in the NP (Figure 2). Despite a strong FAK signal in the CF and MSF, as shown by Western blots with FAK-pTyr397 antibody, we first failed to demonstrate any signal with the same antibody by immunolabeling. We suspected that the FAK-pTyr397 antigen site was covered by its cellular partner in intact cardiac myocytes. Thus, we dissociated the FAK binding partner by using an antigen retrieval technique. Compared with WKY myocytes (Figure 5A), SHHF myocytes (Figure 5B) showed stronger FAK-pTyr397 labeling in peripheral cell membranes and intercalated disks after antigen retrieval.

FAK Phosphorylation at Serine 722 and Its Accumulation in the Nucleus

To determine serine-phosphorylated sites of FAK and their roles in FAK translocation, we investigated series 722

Figure 4. Representative Western blots with FAK and phosphotyrosine (pTyr) antibodies from 5 blots after FAK immunoprecipitation in 5 WKY and 5 SHHF rats. FAK tyrosine phosphorylation increased significantly in LVs of SHHF rats (left), whereas a similar amount of FAK was pulled down as shown by Western blot on the same membrane after stripping (right).

Figure 5. The distribution of FAK-pTyr397 (A, B), FAK-pSer722 (C through F), and FRNK-pSer217 (G through J) in cardiac myocytes by immunolabeling and counterstaining with propidium iodide (red) collected from 400 cells in 5 WKY (A, C, D, G, H) and 5 SHHF (B, E, F, I, J) rats. A and B, After antigen retrieval, only weak green fluorescence of FAK-pTyr397 was diffusely distributed in the cytoplasm of both WKY (A) and SHHF (B) rat myocytes, but stronger green fluorescence of FAK-pTyr397 evidently accumulated in peripheral cytoplasmic membranes and intercalated disks of SHHF myocytes. C through F, Weak green fluorescence of FAK-pSer722 was diffusely distributed in the cytoplasm of both WKY (C, D) and SHHF (E, F) rat myocytes. In contrast to very weak fluorescence in nuclei of WKY myocytes, obviously bright fluorescence was observed in nuclei of SHHF rat myocytes. Further examination revealed ≥2 distinct bright dots present in positive nuclei (inserts). G through J, Weak green fluorescence of FRNK-pSer217 was diffusely distributed in the cytoplasm of both WKY (G, H) and SHHF (I, J) rat myocytes. Compared with very weak fluorescence in nuclei of WKY myocytes, obviously bright fluorescence has been observed in nuclei of SHHF rat myocytes. Detailed examination revealed ≥1 distinct bright dots present in positive nuclei (inserts). Scale bar, 50 μm.
protein kinase 2 involved in G-protein signaling also accumulated at intercalated disks of cultured neonatal cardiac myocytes undergoing hypertrophy. Our previous study also demonstrated that G protein–coupled receptor kinase 2 involved in G-protein signaling also accumulated at intercalated disks in hypertrophic LVs of SHHF rats. Taken together, these data suggest that intercalated disks may be the important signaling center for regulating and coordinating sarcomeric organization during cardiac hypertrophy. The accumulation of FAK to intercalated disks in 6-month SHHF rats may promote serial addition of sarcomeres at both ends of cardiac myocytes. Further examination of FAK localization in a temporal manner during the development of compensated and decompensated hypertrophy in SHHF rats will determine this potential role of FAK in myocyte elongation.

Protein phosphorylation plays a central role in the regulation of many cellular events, including cell growth and division. Activation of FAK involves autophosphorylation at tyrosine 397. FAK tyrosine phosphorylation at 397 has been shown to be among the earliest events during myocyte hypertrophy. Our results showed that FAK phosphorylation at this site increased significantly in the hypertrophic myocardium of SHHF rats, resulting in its association with the membrane cytoskeleton. FAK-Tyr397 also strongly associated with intercalated disks. However, phosphorylation at this site seems to be uninvolved in the nuclear translocation of FAK.

During integrin-mediated signal transduction, protein serine and threonine phosphorylation follow initial tyrosine protein phosphorylation. FAK and FRNK are phosphorylated on multiple serine sites. During mitosis, FAK

and 910 phosphorylation of FAK with 2 anti-FAK phosphorylation site-specific antibodies against FAK-pSer722 and FAK-pSer910. FAK-pSer722 antibody is selective for the phosphorylated form of FAK at serine 722, whereas FAK-pSer910 antibody is specific for the phosphorylated form of FAK at serine 910. FAK was phosphorylated at serine 722 but not at serine 910 in both SHHF and WKY rats (Figures 1B and 1C). FAK-pSer722 showed a similar level in the CF between SHHF and WKY rats (768±94 versus 731±210 du, n=5, P>0.05) but increased significantly in the MSF (550±152 versus 80±18 du, n=5, P<0.05) of the LV from SHHF rats (Figure 2).

Immunolabeling showed that weak fluorescence of FAK-pSer722 diffusely distributed in the cytoplasm of cardiac myocytes from both SHHF and WKY rats (Figures 5C through 5F). In contrast to weak FAK-pSer722 fluorescence in myocardial nuclei of WKY rats (Figures 5C and 5D), obviously bright FAK-pSer722 fluorescence was observed in myocardial nuclei of SHHF rats (Figures 5E and 5F). By using higher magnification and lower photo multiplier tube voltage and gain settings for the confocal microscope, several distinct bright dots were present in positive nuclei (Figures 5E and 5F, inserts). The myocyte staining was completely removed by incubating FAK-pSer722 antibody with specific blocking peptide. Nuclear extraction also confirmed that increased FAK-pSer722 was present in the NP (Figure 2) from the LV of SHHF rats in comparison with that from WKY rats (183±67 versus 50±20 du, n=5, P<0.05). This result suggested that FAK phosphorylation at serine 722 might be involved in its translocation to nuclei and membranes in the hypertrophic myocardium of SHHF rats.

**FRNK Phosphorylation at Serine 217 and Its Translocation to the Nucleus**

FAK-pSer910 antibody specific to phosphorylated serine of FAK at 910 or serine of FRNK at 217 (FRNK-pSer217) reacted only with 41–43-kDa FRNK but not with 125-kDa FAK (Figure 1C). FRNK-pSer217 was mainly present in the CF and the MSF (Figure 2). FRNK-pSer217 showed a similar level in the CF between SHHF and WKY rats (1215±211 versus 1105±219, n=5, P>0.05). An increased level of FRNK-pSer217 was observed in the MSF of LVs from SHHF rats when compared with that of WKY controls (599±183 versus 119±75, n=5, P<0.05). Because FAK-pSer910 antibody only reacted with FRNK, it can be used to investigate subcellular distribution of FRNK. Immunolabeling showed that weak fluorescence of FRNK-pSer217 diffusely distributed in the cytoplasm of cardiac myocytes from both SHHF and WKY rats (Figures 5G through 5J). In contrast to weak FRNK-pSer217 fluorescence in myocardial nuclei of WKY rats (Figures 5G and 5H), strong FRNK-pSer217 label was present in myocardial nuclei of SHHF rats (Figures 5I and 5J). Further examination revealed that several distinct brighter dots of FRNK-pSer217 were present in positive nuclei by increasing the magnification and lowering the photo multiplier microscope (Figures 5I and 5J inserts). The myocyte staining was completely removed by incubating FRNK-pSer217 antibody with specific blocking peptide. Western blots also confirmed that FRNK-pSer217 significantly increased in the NP extracted from the LV of SHHF rats compared with that from WKY rats (203±86 versus 41±23, n=5, P<0.05). This result suggested that FRNK phosphorylation at serine 217 might be involved in its nuclear redistribution in SHHF rat myocytes.

**Discussion**

A series of studies have showed that FAK might play an important role in linking hypertrophic stimuli to the cellular machinery that promotes sarcomeric assembly and cytoskeletal remodeling in cardiac myocytes. In the present study, we showed significant redistribution of FAK to the membrane cytoskeleton and intercalated disks in the hypertrophic myocytes of 6-month-old SHHF rats. The membrane cytoskeleton contains many signaling molecules and cytoskeletal proteins, and plays an important role in mediating signal transduction events at sites of integrin-cytoskeleton interactions. Thus, FAK redistribution to the membrane cytoskeleton in hypertrophic myocytes in SHHF rats may represent an important step in the activation of integrin-mediated signal transduction in vivo during chronic hypertension. On the other hand, intercalated disks of cardiac myocytes are the structures involved in cell–cell contact and organization of actin filaments in myofibrils between adjacent cells. It has been shown that FAK accumulated at intercalated disks of cultured neonatal cardiac myocytes undergoing hypertrophy. Our previous study also demonstrated that G protein–coupled receptor kinase 2 involved in G-protein signaling also accumulated at intercalated disks in hypertrophic LVs of SHHF rats. Taken together, these data suggest that intercalated disks may be the important signaling center for regulating and coordinating sarcomeric organization during cardiac hypertrophy. The accumulation of FAK to intercalated disks in 6-month SHHF rats may promote serial addition of sarcomeres at both ends of cardiac myocytes. Further examination of FAK localization in a temporal manner during the development of compensated and decompensated hypertrophy in SHHF rats will determine this potential role of FAK in myocyte elongation.
is phosphorylated on serines, reducing its association with p130Cas in chicken embryo fibroblasts.¹⁴ The direct role of FAK in mitosis is unclear at this time. Serines 722 and 910 are 2 major serine phosphorylation sites of FAK in certain cell types.⁷ FAK serine 722 of chicken, mouse, and rat corresponds to serine 30 of chicken FRNK. FAK serine 910 of mouse represents serine 911 of chicken FAK, serine 913 of rat FAK, and serine 217 of chicken FRNK. Currently, no rat FRNK sequence is available for comparison. In this paper, we used the designation of serine 722 and serine 910 as described previously.¹⁴ Our result showed that FAK is phosphorylated on serine 722 but not on serine 910. Conversely, FRNK is phosphorylated on serine 217, the equivalent site of FAK serine 910, but not on serine 30, the equivalent site of FAK serine 722. Both serine-phosphorylated FAK and FRNK accumulated in the nucleus of hypertrophic myocytes in SHHF rats. These results indicate that the accumulation of FAK and FRNK in the nucleus of SHHF rat myocytes is likely mediated by serine phosphorylation.

FRNK is a shortened form of FAK and is identical to the C-terminus of FAK without catalytic activity. Overexpression of FRNK inhibits FAK tyrosine phosphorylation and delays cell spreading on fibronectin.⁷ In cardiac myocytes, endothelin-induced cardiac myocyte hypertrophy and FAK tyrosine phosphorylation is also diminished by FRNK overexpression.² A recent study showed that FRNK is phosphorylated on serines after FAK tyrosine phosphorylation. Inhibition of serine phosphorylation on FRNK delays cell spreading and FAK tyrosine phosphorylation,⁷ indicating that FRNK serine phosphorylation plays a key role in FAK activation and downstream signal transduction. Our data showed that FRNK was phosphorylated on serine 217 during maladaptive cellular remodeling in the hearts of 6-month-old SHHF rats.

The dynamic properties of proteins in the nucleus are critical for gene transcription and RNA processing. Many nuclear subdomains, such as Cajal bodies, Sam68 nuclear bodies, and the nucleolus, have been discovered.¹⁷ These functional nuclear compartments are directly involved in RNA transcription and processing. Traditional cell surface and extracellular matrix proteins, such as fibroblast growth factor and heparan sulfate proteoglycan, have demonstrated their ability to translocate to nuclei.¹⁸ More importantly, nuclear SH2/SH3 binding adaptor proteins, such as the Sam68 family, bind both RNA and signaling molecules such as Src family kinases, Grb2, and phospholipase Cγ-1.¹⁹ Furthermore, nuclear proteins, such as extracellular signal–regulated kinase, translocate to focal adhesions and regulate cell spreading.²⁰ Therefore, direct communication and interaction between molecules in focal adhesions and nuclei are key to cell growth and shape regulation. We clearly demonstrated for the first time that FAK translocated to the nucleus in the hypertrophic myocardium of SHHF rats. This finding indicates that FAK not only regulates signal transduction at focal adhesions but also might directly control hypertrophic gene transcription in nuclei. Although FAK contains no nuclear localization sequence, it could bind to other nuclear partner proteins and translocate to the nucleus after activation. The nuclear protein, Sam68, interacts with Src family kinases that bind to activated FAK. Therefore, activated FAK can be shuttled to the nucleus by protein–protein interaction. A recent study showed that FAK enhanced atrial natriuretic peptide gene expression.¹⁵ Thus, FAK is a potential candidate for hypertrophic gene transcription and RNA processing in the nucleus during cardiac hypertrophy in chronic hypertension.

Perspectives

In the present study, we demonstrated that FAK and FRNK increased and redistributed to membrane cytoskeleton, intercalated disks, and nuclei in the heart of SHHF rats during the transition from concentric cardiac hypertrophy to maladaptive myocyte lengthening. Differential tyrosine and serine phosphorylation of FAK and FRNK was involved in redistribution in different cellular compartments. Further investigation with site-directed mutagenesis of FAK and FRNK will determine the exact phosphorylation site involved in the compartmentalization of FAK and FRNK. With these mutant constructs, the functions of compartmentalized FAK and FRNK in cardiac hypertrophy will also be clarified.

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