Selective Involvement of p130Cas/Crk/Pyk2/c-Src in Endothelin-1–Induced JNK Activation

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Abstract—Both integrin-based focal adhesion complexes and receptor tyrosine kinases have been proposed as scaffolds on which the G protein–coupled receptor (GPCR)–induced signaling complex might assemble. We have recently reported that Ca\textsuperscript{2+}–sensitive tyrosine kinase, Pyk2, and epidermal growth factor receptor (EGFR) act as independently regulated scaffolds in cardiomyocytes. In this report, we investigated the activation and regulation of p130Cas, Crk, Pyk2, and c-Src by a well-known hypertrophic agonist, endothelin-1 (ET), and determined their contributions to the activation of c-Jun NH\textsubscript{2}-terminal kinase (JNK) and extracellular signal–regulated kinase (ERK) in cardiomyocytes. Like Pyk2, ET-induced tyrosine phosphorylation of p130Cas was significantly inhibited by either chelating intracellular Ca\textsuperscript{2+} ([Ca\textsuperscript{2+}], or a protein kinase C inhibitor, calphostin C. This activation of p130Cas was also abrogated by the tetrapeptide RGDS, which disrupts integrin heterodimerization; cytochalasin D, which depolymerizes the actin cytoskeleton; or a selective Src family kinase inhibitor, PP2, but not by an EGFR inhibitor, AG1478. We also observed ET-induced temporal associations of Pyk2 with active c-Src, followed by p130Cas with Pyk2, c-Src, and Crk. Overexpression of a dominant-negative mutant of p130Cas (Cas\textsubscript{SD}), Crk (CrkSH2m), Pyk2 (PKM), or C-terminal Src kinase (Csk), but not of a deletion mutant of EGFR (533delEGFR), attenuated ET-induced JNK activation. Similarly, an ET-induced increase in c-jun promoter luciferase activity was inhibited by overexpression of Cas\textsubscript{SD}, CrkSH2m, PKM, or Csk. In contrast, ET-induced ERK activation and c-fos gene expression were predominantly regulated by EGFR. Collectively, the focal adhesion–dependent p130Cas/Crk/Pyk2/c-Src–mediated pathway is selectively involved in ET-induced JNK activation in cardiomyocytes. (Hypertension. 2003;41:1372-1379.)

Key Words: endothelin-1 ■ cardiac hypertrophy ■ kinase ■ focal adhesion ■ phosphorylation

Cardiac hypertrophy is characterized by both remodeling of the extracellular matrix (ECM) and the hypertrophic growth of cardiomyocytes.\textsuperscript{1} Focal adhesions are regions of a cell in direct contact with the ECM, providing anchorage sites linking the ECM to the actin cytoskeleton by way of the integrin family of cell-surface receptors.\textsuperscript{2,3} The ECM can regulate reorganization of the cytoskeletal architecture, and ECM-mediated signaling has also been implicated in the growth factor–induced alterations of gene transcription in cardiomyocytes.\textsuperscript{4} Mitogen-induced changes in the actin cytoskeleton are accompanied by dynamic changes in several proteins present in focal adhesions.

A 130-kDa Crk-associated substrate, p130Cas, was originally identified as a protein highly tyrosine-phosphorylated in cells transformed by v-Src and v-Crk oncogenes.\textsuperscript{5} Molecular cloning of p130Cas revealed a docking protein that contains an SH3 domain, proline-rich regions, and a cluster of 15 putative SH2-binding motifs.\textsuperscript{6} This unique structure of p130Cas suggests a role in assembling multiprotein signaling complexes.\textsuperscript{7} Indeed, p130Cas localizes to focal adhesions and associates not only with focal adhesion proteins, such as focal adhesion kinases (FAK) and paxillin, but also with other SH2 domain–containing signaling molecules, including Crk.\textsuperscript{7,8} p130Cas is also phosphorylated during cell adhesion or after stimulation with various growth factors, such as angiotensin II,\textsuperscript{9} platelet-derived growth factor, and endothelin-1 (ET).\textsuperscript{10}

One of the prime candidates of tyrosine kinase responsible for p130Cas activation is Pyk2,\textsuperscript{2,11} a close relative of FAK. Moreover, Pyk2 has been shown to be responsible for linking c-Src to downstream signaling pathways, such as the activation of extracellular signal–regulated kinases (ERKs)\textsuperscript{11,12} and c-Jun NH\textsubscript{2}-terminal kinases (JNKs).\textsuperscript{11} Recent studies also suggest that the activation of p130Cas is critical in cardiac development, because targeted disruption of the p130Cas gene led to an impaired cardiovascular system demonstrating marked systemic congestion and a poorly developed heart.\textsuperscript{14}

Among the many signaling molecules that are activated by hypertrophic stimuli, members of the mitogen-activated pro-
tein kinase (MAPK) family, including ERK, JNK, and p38 MAPK, are likely to play an important role in cardiac hypertrophic gene expression. However, very little is known about the signals downstream of focal adhesion proteins, including p130Cas, Crk, and Pyk2, which mediate selective activation of the JNK pathway in contrast to the ERK pathway in cardiomyocytes.

In a previous report, we showed that ET activated the 2 distinct tyrosine kinase pathways requiring Pyk2 or epidermal growth factor receptor (EGFR) in cardiomyocytes. EGFR was Ca\(^{2+}\)-independently activated, recruited Shc, and predominantly contributed to ERK/c-fos activation, whereas Pyk2 or c-Src contributed less to ERK activation. We show here that [Ca\(^{2+}\)], PKC, c-Src, and focal adhesion integrity are also required for ET-induced tyrosine phosphorylation of p130Cas as well as Pyk2. Furthermore, we demonstrate that ET-induced JNK activation is preferentially regulated by Pyk2, c-Src, and the p130Cas/Crk complex but not by EGFR. Thus, the p130Cas/Crk/Pyk2/c-Src-JNK signaling described here might represent a pathway clearly dissociable from the EGFR-mediated ERK cascade in cardiomyocytes.

**Methods**

**Materials**

PP2, AG1478, and AG490 were purchased from Calbiochem. ET, myelin basic protein (MBP), calphostin C, phorbol 12-myristate 13-acetate (PMA), BAPTA, BQ123, A23187, RGDS, and cytochalasin D were purchased from Sigma.

**Cell Culture and Transfection**

Primary cultured cardiomyocytes were prepared from ventricles of 1-day-old neonatal Wistar rats as described previously. Hemagglutinin (HA)-tagged JNK1 (HA-JNK1) and HA-ERK2 were provided by E. Nishida and M. Karin, respectively. C-terminal Src kinase (Csk), the deletion mutant of EGFR (533delEGFR), the dominant-negative mutant of Jak2 (d.n.Jak2), and the kinase-inactive mutant of Pyk2 (PKM)\(^{11}\) were provided by H. Sabe, H. Matsuhara, J. Ihle, and J. Schlessinger, respectively. pSSRα-p130CasΔSD (deletion of 213 to 514 amino acids; CasΔSD) and pSSRα-Crk-SH2m (Crk-SH2 R38V mutant; CrkSH2m) have been described elsewhere.\(^{18,19}\) Transfection of plasmid was performed with the use of Effectene transfection reagent (Qiagen). After 24 hours of serum depletion, cells were stimulated with ET.

**Luciferase Assays**

pGVB-438c-Jun-luc, containing segment -438 to +140 of the rat c-Jun promoter\(^{20}\) (c-Jun-luc), and pGL3-c-fos promoter, containing segment -404 to +41 of the human c-fos promoter\(^{21}\) (c-fos-luc), were provided by S. Hata and M. Tsuda, respectively. For each dish, 0.4 \(\mu\)g c-Jun-luc or c-fos-luc together with 2.0 \(\mu\)g CasΔSD, CrkSH2 m, 533delEGFR, Csk, PKM, or d.n.Jak2 were transfected into cardiomyocytes. Cell lysates were processed and assayed for luciferase activity with a luciferase assay system (Promega).

**Immunoprecipitation and Immunoblotting**

Immunoprecipitation was performed with monoclonal anti-p130Cas and anti-Crk (Transduction Laboratories); polyclonal anti-JNK1, anti-Pyk2, anti-c-Src (SRC2), and anti-EGFR antibodies (Santa Cruz Biotechnology); or monoclonal anti-HA antibodies (Roche Molecular Biochemicals), as described previously.\(^{16}\) For immunoblot analysis, immunoprecipitates were subjected to sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) and then transferred to nitrocellulose membranes. The blots were incubated with anti-phosphotyrosine (4G10), anti-p130Cas, anti-Crk, or monoclonal anti–c-Src (clone 28) antibody, which selectively recognizes the active (Tyr-530–dephosphorylated) form of c-Src.\(^{22}\) Signals were detected by enhanced chemiluminescence (Amersham).

**Kinase Assay of JNK and ERK**

JNK and ERK activities were determined by in vitro kinase reactions, as described previously.\(^{16}\) In brief, JNK1 or ERK2 immunoprecipitates were incubated with glutathione S-transferase (GST)–c-Jun(1-79) for 30 to 45 minutes at 30°C or with MBP for 10 minutes at 25°C. After SDS-PAGE, the gels were dried and subjected to autoradiography. The GST–c-Jun(1-79) construct was provided by M. Hibi.\(^{23}\)

**Reproducibility of Results and Statistical Analysis**

Unless stated otherwise, the results are representative of at least 3 separate experiments that gave similar results. Densitometric analysis was performed with Image J, version 1.6. The significance of differences among mean values was determined by ANOVA.

**Results**

p130Cas Is Tyrosine-Phosphorylated on Cell Adhesion in a Ca\(^{2+}\), PKC- and c-Src–Dependent Manner

We next studied the dependence of ET-induced p130Cas phosphorylation on changes in [Ca\(^{2+}\)], or activation of protein kinase C (PKC). ET stimulation causes rapid activation of PKC and an elevation of [Ca\(^{2+}\)], in cardiomyocytes.\(^{24}\) Direct stimulation of PKC by PMA or Ca\(^{2+}\) ionophore A23187 caused p130Cas tyrosine phosphorylation (Figure 1C). On the other hand, either the chelation of [Ca\(^{2+}\)], or the inhibition of PKC by calphostin C significantly suppressed the ET-induced p130Cas tyrosine phosphorylation (Figure 1D). These results suggest that activation by both [Ca\(^{2+}\)], and PKC is required for p130Cas tyrosine phosphorylation in cardiomyocytes. Because p130Cas colocalizes with Pyk2 or paxillin to the focal adhesion plaques,\(^{25}\) it has been suggested that p130Cas might be involved in cytoskeletal signaling, dependent on the proper assembly of focal adhesions.\(^{3}\) The tetrapeptide RGDS, which disrupts integrin heterodimerization,\(^{26}\) or cytochalasin D, which depolymerizes the actin cytoskeleton,\(^{9,26}\) fully prevented the ET-induced p130Cas phosphorylation (Figure 1E), thus suggesting that the integrity of the cardiomyocyte cytoskeleton is required for ET-induced p130Cas tyrosine phosphorylation.

ET is known to activate various tyrosine kinases, including c-Src, EGFR, and Jak2.\(^{16,27}\) To characterize the tyrosine kinase responsible for p130Cas phosphorylation by ET, we used selective tyrosine kinase inhibitors; AG1478, an EGFR inhibitor; PP2, a Src family kinase inhibitor;\(^{9,27}\) and AG490, a Jak2 inhibitor. PP2 abolished ET-induced p130Cas tyrosine phosphorylation, whereas AG1478 or AG490 had no effect, thus suggesting that activation of c-Src might lie upstream of p130Cas in ET-induced signaling (Figure 1F).
p130Cas Forms Temporal Associations With Pyk2, Active c-Src, and Crk in Response to ET

The protein sequence of p130Cas suggests that it might serve as an adapter protein, and p130Cas is thought to recruit cytoskeletal signaling molecules or other SH2 domain–containing molecules.6,7 We attempted to identify some of the proteins that were observed in p130Cas or Pyk2 immune-complex assays. ET induced a rapid, temporal association of Pyk2 with active c-Src as early as 1 minute (Figure 2A), and thereafter the autokinase activity of Pyk2 gradually increased, peaked at 5 minutes, and then returned to near basal levels at 60 minutes (Figure 2B). After Pyk2 binds to SH2 domains of Src family tyrosine kinases, c-Src is then known to phosphorylate several other sites in Pyk2, which in turn function as binding sites for signaling molecules containing SH2 domains.12 We next observed that ET increased a transient association of Pyk2 with p130Cas after the increased autokinase activity of Pyk2 (Figure 2C). ET also increased the association of p130Cas with active c-Src (Figure 2D). Moreover, ET enhanced the association of p130Cas with Crk (Figure 2E).

ET-Induced JNK Activation Requires Both Ca2+ and PKC and a c-Src–Dependent Signal in Cardiomyocytes

Kudoh et al28 reported that G protein–coupled receptor (GPCR) stimulation by angiotensin II activated JNK in cardiomyocytes and that the activation of JNK was suppressed by downregulation of PKC or by chelating [Ca2+]i. We confirmed that another GPCR ligand, ET, activated JNK in a time-dependent manner, and ET-induced JNK activation was significantly attenuated by chelating [Ca2+]i or by calphostin C (Figures 3A and 3B). Furthermore, JNK activation was abrogated by PP2, whereas AG1478 or AG490 had no effect (Figure 3C). The results of the inhibitory effect of PP2 suggested that Src family kinases were selectively involved in the activation of JNK. Either RGDS or cytochalasin D significantly inhibited JNK activation (Figure 3D). Because activation of p130Cas or Pyk216 is also dependent on PKC, [Ca2+]i, and c-Src, it is possible to speculate that JNK activation by ET might be at least partly mediated through the focal adhesion proteins p130Cas or Pyk2 associated with c-Src.

CasΔSD, CrkSH2m, Pyk2, or Csk Significantly Inhibits ET-Induced Activation of JNK but Not of ERK

To confirm that the p130Cas/Crk complex or Pyk2 is critically involved in ET-induced JNK activation, we transfected the cells with HA-JNK1 or HA-ERK2, together with CasΔSD, CrkSH2m, 533delEGFR, Csk, PKM, or d.n.Jak2
and stimulated them with ET. Overexpression of CasΔSD or CrkSH2m had been previously shown to interfere with p130Cas/Crk signaling. ET-induced JNK activation was strongly attenuated by CasΔSD, CrkSH2m, Csk or PKM, but it was not noticeably inhibited by 533delEGFR or d.n.Jak2.

Figure 2. ET augmented p130Cas protein/protein complex formation. Cells were stimulated with ET (100 nmol/L) for the indicated times. A, Pyk2 or c-Src was immunoprecipitated (IP) with an anti-Pyk2 polyclonal antibody (pAb) or an anti–c-Src (SRC2) pAb and immunoblotted (Blot) with an anti-c-Src (clone 28) monoclonal antibody (mAb). B, Pyk2 was immunoprecipitated with an anti-Pyk2 pAb and incubated with γ-32P[ATP] for 30 minutes. After SDS-PAGE, the gels were dried and subjected to autoradiography. C, Pyk2 or p130Cas was immunoprecipitated with an anti-Pyk2 pAb or an anti-p130Cas mAb and immunoblotted with an anti-c-Src (SRC2) pAb and immunoblotted with anti-c-Src (clone 28). E, p130Cas or Crk was immunoprecipitated with an anti-p130Cas pAb or an anti-Crk mAb and immunoblotted with an anti-Crk mAb.

Figure 3. ET-induced activation of JNK required both Ca2+ and PKC and c-Src. A, Cells were stimulated with ET (100 nmol/L) for the indicated times. JNK1 was immunoprecipitated (IP) with an anti-JNK1 polyclonal antibody and incubated with GST–c-Jun(1-79) as a substrate. The immunoprecipitates were electrophoresed and subjected to autoradiography. B, Cells were pretreated with BAPTA-AM (50 μmol/L) for 30 minutes or calphostin C (1 μmol/L) for 1 hour and stimulated with ET (100 nmol/L) for 15 minutes. C, Cells were pretreated with vehicle (DMSO), AG1478 (250 nmol/L), PP2 (50 μmol/L), or AG490 (20 μmol/L) for 30 minutes and stimulated with ET. D, Cells were pretreated with vehicle (DMSO), RGDS (1 mmol/L) overnight, or cytochalasin D (10 μmol/L) for 30 minutes and stimulated with ET. The amount of 32P incorporated into GST–c-Jun(1-79) was determined by densitometry. Graph indicates the fold increase in JNK activity relative to values obtained in ET-stimulated cells (lower panel). Shown is the mean±SD, n=4, *P<0.05.
In contrast, ERK activation was attenuated solely by 533delEGFR (Figure 4B). These results, taken together with the inhibitor experiment, indicated that the p130Cas/Crk/Pyk2/c-Src–mediated pathway was selectively involved in ET-induced JNK activation in cardiomyocytes.

ET-Induced Increase in \(c\)-jun but Not \(c\)-fos Promoter Activity Is Significantly Inhibited by Cas\(\Delta\)SD, CrkSH2\(\text{m}\), PKM, or Csk

It had been demonstrated that JNK phosphorylates \(c\)-Jun at the putative regulatory N-terminal serine residues and increases their transcriptional activities.2,29 The phosphorylated \(c\)-Jun forms a homodimer or a heterodimer with itself or c-Fos, thus forming the transcription factor activator protein-1, and transactivate many genes, including \(c\)-jun itself. We further analyzed the involvement of p130Cas/Crk/Pyk2/c-Src–mediated pathway in ET-induced \(c\)-jun or \(c\)-fos gene expression by transfecting the cells with \(c\)-jun-luc or \(c\)-fos-luc, together with Cas\(\Delta\)SD, CrkSH2\(\text{m}\), 533delEGFR, Csk, PKM, or d.n.Jak2. The ET-induced increase in \(c\)-jun promoter activity was significantly suppressed by Cas\(\Delta\)SD, CrkSH2\(\text{m}\), PKM, or d.n.Jak2. The ET-induced increase in \(c\)-fos promoter activity was significantly suppressed by Cas\(\Delta\)SD, 533delEGFR, PKM, or d.n.Jak2. These results shown are also consistent with our previous observation that the ET-induced increase in \(c\)-fos mRNA levels was attenuated by inhibition of EGFR; however, activation of c-Src or focal adhesion integrity was not required.16

Discussion

Tyrosine phosphorylation and protein/protein complex formation of diverse signaling molecules have been identified as prominent early events in cells stimulated by growth factors to regulate cell proliferation, migration, and apoptosis.2,3 There is considerable evidence that both FAK family kinases and p130Cas/Crk complex formation play a critical role in integrin-mediated signaling. However, most of the studies supporting the role of p130Cas, Crk, or Pyk2 have used immortalized cells, especially fibroblasts, plated on fibronectin-coated dishes, and the significance of integrin-mediated signaling in cardiomyocytes remained to be clarified.

Earlier studies from our laboratory indicated that cytoskeletal protein Pyk2 was tyrosine-phosphorylated in a \(Ca^{2+}\)- and PKC-dependent manner after ET stimulation and that the signaling pathways involving Pyk2 or c-Src and EGFR-mediated Shc/ERK activation were distinct pathways.16 In the present study, we found that p130Cas, like Pyk2, was regulated by both \([Ca^{2+}]\), and PKC, independent of transac-
tivation of the EGFR. Furthermore, both c-Src and focal adhesion integrity are relevant for its activation. Our data also demonstrated that p130Cas/Crk/Pyk2/c-Src signaling was a predominant pathway leading to JNK/c-jun activation, in contrast with the prominent EGFR-mediated ERK/c-fos activation observed in cardiomyocytes (Figure 6). Many lines of evidence suggest that focal adhesion and receptor tyrosine kinases can function as independently regulated scaffolds, especially in GPCR signaling. Della Rocca et al.26 showed the preference of signaling to be determined by the cell itself, because the expressed cellular context was significantly different among cell types. In Rat-1 cells, which do not detectably express Pyk2, GPCR-induced FAK phosphorylation is dissociable from ERK activation. Conversely, in Pyk2-expressing cells, Pyk2 can serve as a link from c-Src to the downstream ERK and JNK cascade.11–13,30 Recent data have also shown that Pyk2 expression and activation can enhance the tyrosine phosphorylation of p130Cas. Thus, in cardiomyocytes abundantly expressing both Pyk2 and p130Cas, Pyk2 can recruit p130Cas and thereby efficiently transduce signaling to the downstream effectors.

Src family tyrosine kinases have been implicated in GPCR signaling, including the ET-A receptor.27 In vascular smooth muscle cells, angiotensin II stimulation has been shown to induce an association of active c-Src with EGFR, the recruitment of Shc, and EGFR-mediated ERK activation.22 Overexpression of Csk impairs lysophosphatidic acid (LPA)-induced EGFR phosphorylation in COS-7 cells.31 In cardiomyocytes, however, overexpression of Csk or a selective Src family kinase inhibitor did not affect ET-induced tyrosine phosphorylation of EGFR, the recruitment of Shc, or ERK activation, as described previously.16 Dikic et al.12 demonstrated GPCR-induced association of Pyk2 with c-Src through the binding of autophosphorylated Tyr-402 of Pyk2 to the SH2 domain of c-Src, thereby leading to c-Src activation, thus suggesting that Pyk2 phosphorylation mediated by c-Src might generate a docking site for an additional signaling protein recruited by

Figure 5. Effect of CasΔSD, CrkSH2m, 533delEGFR, PKM, Csk, or d.n.Jak2 on ET-induced increase in c-jun and c-fos promoter activity in cardiomyocytes. A, After transfection of c-jun-luc together with mock plasmid, CasΔSD, CrkSH2m, 533delEGFR, Csk, PKM, or d.n.Jak2, cells were treated with ET (100 nmol/L) for 10 hours. B, After transfection of c-fos-luc together with mock plasmid, CasΔSD, CrkSH2m, 533delEGFR, Csk, PKM, or d.n.Jak2, cells were treated with ET (100 nmol/L) for 3 hours. Cells were harvested and lysed for luciferase assay. Graph indicates the fold increase in c-jun or c-fos promoter luciferase activity relative to values obtained in mock-transfected cells. Shown is the mean±SD, n=5, *P<0.05.
Pyk2. The functional significance and mechanisms behind the formation of the Pyk2/c-Src complex resemble those described for interactions between FAK and c-Src. The phosphorylation of Tyr-579 and 580 of Pyk2 by c-Src appears to be necessary for maximal Pyk2 kinase activity. Activated c-Src bound to Pyk2 might directly phosphorylate adjacent cellular proteins, such as p130Cas, and thus amplify signals from Pyk2 to downstream effectors. These scenarios are also supported by the present observation that the ET-induced association of Pyk2 with an active c-Src preceded the autophosphorylation of Pyk2, the association of Pyk2 with p130Cas, and that of p130Cas with c-Src and Crk. Furthermore, ET-induced p130Cas tyrosine phosphorylation was significantly inhibited by PP2. Once tyrosine-phosphorylated, p130Cas has been shown to act as a docking protein to recruit Crk and its effectors. The SH3 domains of Crk bind to several effectors able to activate JNK, including C3G and DOCK180. Dolfi et al. reported that JNK activation by the transient expression of p130Cas or Crk was effectively blocked by a dominant-negative mutant of Rac, thus suggesting a linear pathway from the p130Cas/Crk complex to the Rac-mediated JNK pathway. Furthermore, either the SH2 or SH3 mutant of Crk efficiently blocked v-Src-induced JNK activation. Recent studies have demonstrated that c-Src was specifically involved in H2O2-mediated JNK activation by way of the p130Cas/Crk signaling pathway in vascular smooth muscle cells and fibroblasts. We also found that c-Src played a critical role not only in the phosphorylation and complex formation of Pyk2 or p130Cas but also in the activation of JNK, which was independent of EGFR-mediated signaling in cardiomyocytes. These data further indicate that p130Cas/Crk signaling involving Pyk2 and c-Src might be selectively recruited in ET-induced JNK activation in cardiomyocytes.

We demonstrated that overexpression of CasΔSD, CrkSH2m, PKM, or Csk could significantly attenuate ET-induced JNK activation, whereas 533deLEGFR had no such effect. It is interesting to find that the MAPK subfamily, including ERKs and JNKs, are mediated through different scaffolds, receptor tyrosine kinases and focal adhesion complexes, respectively. The reason for this differential regulation in the MAPK subfamily is largely unknown. It might be partly due to the fact that tissue-specific expression and/or mutual interactions of Pyk2 or p130Cas/Crk with adaptor proteins, including Shc, Grb2, or Sos, will critically regulate the threshold activation of a target pathway, ERK or JNK, in a given cell type.

The physiological significance of cytoskeleton-dependent signaling in cardiac hypertrophy has yet to be clarified. Because ET-induced c-fos and c-jun gene expression was also differentially regulated by independently regulated scaffolds in a similar manner as ERK and JNK activation in cardiomyocytes, one could anticipate that a predominant scaffold will selectively regulate specific cardiac hypertrophic gene induction in response to specific stimuli. Further examination of the functional significance of these cytoskeletal molecules will ultimately improve our understanding of the diversity and heterogeneity in cardiac hypertrophy.

References


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