Hsp10 and Hsp60 Suppress Ubiquitination of Insulin-like Growth Factor-1 Receptor and Augment Insulin-like Growth Factor-1 Receptor Signaling in Cardiac Muscle

IMPLICATIONS ON DECREASED MYOCARDIAL PROTECTION IN DIABETIC CARDIOMYOPATHY*

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We have investigated the effects of two heat shock proteins, Hsp10 and Hsp60, on insulin-like growth factor-1 receptor (IGF-1R) signaling in cardiac muscle cells. Neonatal cardiomyocytes were transduced with Hsp10 or Hsp60 via adenoviral vector. Compared with the cells transduced with a control vector, overexpression of Hsp10 or Hsp60 increased the abundance of IGF-1R and IGF-1-stimulated receptor autophosphorylation. Thus, Hsp10 and Hsp60 overexpression increased the number of functioning receptors and amplified activation of IGF-1R signaling. IGF-1 stimulation of MEK, Erk, p90Rsk, and Akt were accordingly augmented. Transducing cardiomyocytes with antisense Hsp60 oligonucleotides reduced Hsp60 expression, decreased the abundance of IGF-1R, attenuated IGF-1R autophosphorylation, and suppressed the pro-survival action of IGF-1 in cardiomyocytes. Using cycloheximide to inhibit protein synthesis did not alter the effect of Hsp60 on IGF-1R signaling, and IGF-1R mRNA levels were not up-regulated by Hsp10 or Hsp60. Additional experiments showed that Hsp10 and Hsp60 suppressed polyubiquitination of IGF-1 receptor. These data indicate that Hsp10 and Hsp60 can modulate IGF-1R signaling through post-translational modification. In animal models of diabetes, diabetic myocardium is associated with decreased abundance of Hsp60, increased ubiquitination of IGF-1R, and lower level of IGF-1R protein. Declined myocardial protection is a major feature of diabetic cardiomyopathy. These data suggest that decreased Hsp60 expression and subsequent decline of IGF-1R signaling may be a fundamental mechanism underlying the development of diabetic cardiomyopathy.

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† The abbreviations used are: IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; Erk, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; MAP, mitogen-activated protein; DIG, digoxigenin; STZ, streptozotocin; ZDF, Zucker diabetic fatty; Ad, adenovirus; AS, antisense; SCR, scrambled oligo; DM, diabetes mellitus.

The insulin-like growth factor 1 (IGF-1) binds to the IGF-1 receptor, induces autophosphorylation of the receptor, activates receptor tyrosine kinase, and triggers cascades of intracellular signaling events. IGF-1 receptor signaling is involved in the regulation of multiple aspects of biological actions (1). For example, IGF-1 activation of phosphatidylinositol 3 kinase and MAP kinase suppresses cardiac muscle apoptosis and enhances myocardial protection during myocardial injuries (2, 3). In addition to phosphorylation and dephosphorylation, growth factor receptor signaling can be modulated through transcriptional and post-translational modification of ligands, receptors, and signaling intermediates. Recent studies (4, 5) have shown that insulin and IGF-1 receptor signaling can be modulated through post-translational modification of signaling molecules such as arrestin-1 and insulin receptor substrate (IRS2). There was evidence suggested that IGF-1 receptor signaling might be modulated through degradation of receptor proteins as proteolysis inhibitors prevented degradation of IGF-1 receptor (6). However, whether post-translational modification of IGF-1 receptor contributed to the regulation of IGF-1 receptor signaling in cardiac muscle has not yet been investigated.

Heat shock proteins are a group of molecular chaperones that are capable of preventing protein damages and proteolysis. In cardiac muscle, Hsp60 and Hsp10 may form mitochondrial chaperoning complexes and are believed to play a role in the maintenance of normal mitochondria function (7). Hsp60 and Hsp10 also exist in the cytosolic compartment and interact with cytosolic proteins (8), which suggests that Hsp60 and Hsp10 may regulate proteins through post-translational modification. Whether Hsp10 and Hsp60 can modulate IGF-1 receptor signaling has not been studied. This study was carried out to determine whether Hsp10 and Hsp60 can modulate IGF-1 receptor signaling in cardiomyocytes. The results showed that IGF-1 receptor signaling can be modulated by Hsp60 and Hsp10 through post-translational modification in cardiac muscle cells. Further experiments on animal models of diabetes showed that the changes of Hsp60 paralleled the levels of IGF-1 receptor in various tissues. Moreover, diabetic myocardium exhibited reduced Hsp60 and increased ubiquitination of IGF-1 receptor. These findings may have significant implications in understanding the fundamental mechanisms that lead to a decreased myocardial protection during the development of diabetic cardiomyopathy.

EXPERIMENTAL PROCEDURES

Materials—Mouse anti-Hsp60 monoclonal antibody and rabbit anti-Cpn10 (Hsp10) peptide polyclonal antibody were purchased from StressGen Biotechnologies Corp. (Victoria, British Columbia, Canada). Horseradish peroxidase-conjugated secondary antibodies to mouse and goat immunoglobulins were purchased from Jackson Immunoresearch Laboratories (West Grove, PA). Other antibodies were from Santa Cruz...
Biolabs (Santa Cruz, CA). Immobilon-P membranes were from Milli-
apore Co. (Bedford, MA). DIG RNA labeling kit, Anti-digoxigenin-AP
antibodies, DNase I, protector RNase inhibitor, β-actin RNA probe, DIG
Easy Hyb, Wash and Block Buffer Set, and positively charged nylon
membranes were from Roche. A 0.71 kb fragment of IGF-1R cDNA
(EcoRI insert from ATCC clone pIGF-1R.8, subcloned into pGEM7Zf)
was kindly provided by Dr. Murray Korc (University of California, Irvine, CA). Other chemicals were purchased from Sigma or Fisher
Scientific.

Animal Models of Diabetes—Two different models of diabetes were
used in this study. Streptozotocin (STZ)-induced diabetes was obtained by
injecting STZ (75 mg/kg body weight, intravenous) to 5-week-old
Sprague-Dawley rats. Zucker Fatty rats (ZDF fa/ fa) and lean control
rats were obtained from Charles River Laboratories (Lebanon, NH). Blood glucose levels were determined by tail vein
sampling. The diaphragm and heart were removed and harvested 10 days after the onset of diabetes (random glucose > 200
mg/dL). The animal experimental protocol was approved by the IACUC
at University of California, Irvine.

Cell Culture and Transduction of Adenoviral Constructs—Primary
cultures of neonatal cardiomyocytes were prepared from Sprague-Daw-
ley rats according to a protocol we previously described (2). The con-
struction of recombinant adenoviruses expressing Hsp10, Hsp60, and
the control adenovirus Ad-SR was described previously (7, 10). In brief,
the human HSP60 and HSP10 genes were cloned into the multiple
 cloning site of the adenoviral shuttle plasmid pACCMVpL derivative.
The viruses were replicated in 293 cells, purified by VirakitTM from Virapau
(Carlslab, CA), and the viral titers were determined by plaque assay in
293 cells. The adenoviruses were plated in 10-mm Petri dishes in 100-
glucose Dulbecco’s modified Eagle’s medium containing 10% fetal
bovine serum and 1% penicillin/streptomycin. When indicated, the cells
were infected with adenoviruses of Ad-SR, Ad-Hsp10, or Ad-Hsp60 and
incubated for 36–48 h at 37 °C, 5% CO2.

Cell Viability—Cell viability was performed by staining the cells with
calcium AM (Molecular Probe, Eugene, OR) as previously described (2).
Calcine AM hydrolyzes to calcine and retains only in live cells, thus
serves as an indicator for cell viability. To measure cell viability, car-
diomyocytes were plated in 48-well plates. After rinsing twice with 1×
PBS buffer (pH 7.4), 200 μL of 1 μM calcine AM (in 1× PBS) were added
to each well and incubated for 45 min at room temperature in the dark.
The plates were analyzed with the Cytofluor 2300 Fluorescence
Measurement System (Millipore) at excitation of 485 nm and emission
of 530 nm.

Western Blot—Cardiomyocytes were infected with Ad-SR (control
cells), Ad-Hsp10, or Ad-Hsp60 for 48 h and incubated in serum-free
medium overnight. The cells were treated with IGF-1 or vehicles when
indicated. Then the cells were lysed with lysis buffer (157 mM NaCl, 20
mM Tris-HCl, pH 7.5, 10% glycerol, 1% Triton X-100, 0.5% Nonidet
P-40, 2 mM EDTA, pH 8.0, 3 mM aprotinin, 3 μg/ml leupeptin, 2 mM
phenylmethylsulfonyl fluoride, 20 mM NaF, 10 mM Na3P04, and 2 mM
Na3VO4). Equal amounts of proteins from each sample were separated
by SDS-PAGE and then transferred to polyvinylidene difluoride mem-
brane and incubated with a blocking buffer (5% nonfat milk in 20 mM
Tris-HCl, pH 7.5, 137 mM NaCl, 0.1% Tween 20) for 1 h at room
temperature. The membranes were sequentially incubated with pri-
mary antibodies overnight at 4 °C, washed three times (20 mM Tris-
HCl, pH 7.5, 137 mM NaCl, and 0.1% Tween 20), incubated with
horse- radish peroxidase-conjugated secondary antibodies (1:5000 dilu-
tion) for 1 h at room temperature, washed three times, and then
detected with Enhanced Chemiluminescence.

Immunoprecipitation—Immunoprecipitation was carried out as we
previously reported (8). The cells were lysed and the lysates (500 μg
proteins in 1 ml) were pre-absorbed with 20 μl protein A/garose beads
(Volcano Biotechnology) at 4 °C for 30 min on a rocking platform,
spun for 5 min at 10,000 rpm for 10 s, and the supernatant was incubated with specific primary antibody at 4 °C overnight.
After incubation, 2 μl protein A/garose beads for 1.5 h at 4 °C, the
immunocomplexes were collected by centrifugation and washed three
times with ice-cold washing buffer (137 mM NaCl, 20 mM Tris-HCl, pH
7.5, 1% Triton X-100, 2 mM EDTA, pH 8.0, 2 mM PMSF, and 2 mM
Na3VO4). The final products were briefly boiled and resolved with
SDS-PAGE, and immunoblotted with specific antibodies as indicated.

Northern Blot Analysis—Total RNAs were isolated with TRIzol re-
gent (Invitrogen). The quality of RNA was verified by electrophoresis
with 1% agarose gel containing 6% formaldehyde. Northern blots were
performed with a non-radioactive method according to the manufactur-
er’s instructions (Roche). In brief, equal amounts of total RNA were
resolved with 1% agarose gel (6% formaldehyde), blotted, and cross-
linked onto nylon membranes. IGF-1 receptor RNA probes were labeled
with digoxigenin by in vitro transcription in the presence of digoxi-
genin-11-UTP. Hybridization was performed at 68 °C overnight in DIG
Easy Hyb solution (Roche) containing denatured digoxigenin-labeled
RNA probes (100 ng/ml). After hybridization, the membranes were
washed two times in 2× SSC + 0.1% SDS for 10 min at room temper-
ature and two times in 0.1× SSC + 0.1% SDS at 60 °C for 15 min.
Membranes were sequentially incubated with a blocking solution for 30
min, anti-digoxigenin antibodies conjugated with alkaline phosphatase
(1:10000) for 30 min at room temperature, and rinsed twice in the
washing buffer (15 min each). After equilibrating for 5 min in the
detection buffer, the blots were developed with the CDP-Star and ex-
posed to film. β-actin probes were used as control probe in these blots.

Reducing Hsp60 Expression with Ad-Hsp60 Antisense Oligo—Hsp60 an-
tisense oligonucleotides (AS) were introduced to cardiomyocytes to re-
duce the expression of endogenous Hsp60. Phosphorothioite oligonu-
cleotides were obtained from TriLink BioTechnologies (San Diego, CA).
The antisense Hsp60 (AS) sequence corresponds to bases 109 to 123
(5’-TAAAGGTCCGAGCATC-3’) of rat Hsp60 and a scrambled oligo
(SCR) (5’-GCTGTTGGTCAATAC-3’) was used as a control oligo as
previously described (8). Cardiomyocytes were incubated with AS or
SCR (25 μg/ml) in serum-free medium for 24 h.

Statistical Analysis—The data were expressed as mean ± S.E. based on
data derived from three to six independent experiments. The inten-
sity of bands from Western and Northern blots were scanned with
densitometry and digitally analyzed. The statistical significance was
tested by Student’s t test or analysis of variance with post hoc analysis
when appropriate. A p value below 0.05 was considered statistically
significant.

RESULTS

IGF-1 Signaling in the Cardiomyocytes Overexpressing
Hsp10 or Hsp60—If Hsp10 or Hsp60 can modulate IGF-1 re-
ceptor signaling, overexpression of Hsp10, and Hsp60 should
change IGF-1 receptor autophosphorylation. To this end, neo-
natal cardiomyocytes were transduced with adenoviral vectors
carrying Hsp10 or Hsp60. As shown in Fig 1A, the abundance of
Hsp10 and Hsp60 respectively increased (Hsp60, 321 ± 31%;
Hsp10, 401 ± 29%; p < 0.001 versus Ad-SR) in the cardiomyo-
cytes infected with Ad-Hsp10 and Ad-Hsp60. Autophosphoryl-
at of IGF-1 receptor was accordingly enhanced in the car-
diomyocytes transduced with Hsp10 or Hsp60 (Fig. 1B). Immu-
nobLOTS with anti-IGF-1 receptor β subunits antibodies
showed that the abundance of IGF-1 receptor protein was in-
creased in the cells overexpressing Hsp10 or Hsp60 (Fig. 1B).
Further analysis on receptor phosphorylation showed an in-
creased stoichiometry of phosphorylation/receptor protein in
the cells overexpressing Hsp10 or Hsp60 (Fig. 1B).

The Effect of Hsp10 and Hsp60 Involves Post-translational
Modification of IGF-1 Receptor—To determine whether the
Effect of Hsp10 and Hsp60 on IGF-1 Receptor involves increased
synthesis IGF-1 receptor, cycloheximide or vehicles were added
to the culture medium in the cells overexpressing Hsp10 or
Hsp60 (Fig. 2A). In these cells, cycloheximide reduced the abun-

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dance of IGF-1 receptor; the relative elevation of IGF-1R in the Hsp10/60-transduced cells treated with cycloheximide was the same as in the controls. However, the level of IGF-1 receptor remained higher in the cells overexpressing Hsp10 or Hsp60. This suggests that the effect of Hsp10 and Hsp60 on IGF-1 receptor did not involve protein synthesis. To further confirm that Hsp10 or Hsp60 did not increase IGF-1 receptor synthesis, we had analyzed the abundance of IGF-1 receptor mRNA with Northern blots (Fig. 2b). The results showed that IGF-1 receptor mRNA level was not up-regulated by Hsp10 or Hsp60.
next analyzed the abundance of ubiquitinated IGF-1 receptor β subunits. As shown in Fig. 2c, the abundance of ubiquitinated IGF-1 receptor β subunits was significantly reduced in the cells transduced with Hsp10 and Hsp60. The ubiquitinated IGF-1 receptors migrated around 180 Kd and around 130–140 Kd, suggesting that these receptors were polyubiquitinated. Thus, the effect of Hsp10 and Hsp60 on IGF-1 receptor degradation might have involved inhibition of IGF-1 receptor polyubiquitination. In consistent with the effect of Hsp10 and Hsp60 on IGF-1 receptor signaling, the effect of Hsp60 on receptor ubiquitination is more robust than the effect of Hsp10. These findings suggest that the effect of Hsp10 and Hsp60 on IGF-1 receptor signaling involves post-translational modification of receptor.

**Antisense Hsp60 Reduced IGF-1 Receptor Signaling**—If Hsp60 plays a major role in the modulation of IGF-1 receptor signaling in cardiac muscle, reduced expression of Hsp60 should lead to a reduction in IGF-1 receptor protein and receptor signaling. To this end, an antisense Hsp60 was transfected to the cardiomyocytes to reduce endogenous Hsp60 expression as shown in Fig. 3a. The control oligo (SCR) did not affect the expression of Hsp60. The reduction of Hsp60 was accompanied by a decrease of IGF-1 receptor protein in the cells transfected with antisense Hsp60. Using this approach, we have characterized the abundance of IGF-1 receptor protein and receptor tyrosine phosphorylation in the control and IGF-1-stimulated cardiomyocytes (Fig. 3b). IGF-1-stimulated receptor tyrosine phosphorylation was significantly reduced in the cells transfected with antisense Hsp60, and was accompanied by decreased activation of Akt, MEK, Erk, and p90Rsk. Thus, reducing Hsp60 expression lead to attenuation of IGF-1 receptor signaling. To determine whether down-regulation of Hsp60 attenuated survival action of IGF-1, cardiomyocytes were subjected to serum withdrawal in the presence or absence of IGF-1 (Fig. 3c). Serum withdrawal reduced cell survival in the cardiomyocytes. As expected, IGF-1 rescued cardiomyocytes from the effect of serum withdrawal in the un-transfected cells and the control-oligo-transfected cells. However, the pro-survival effect of IGF-1 was inhibited in the cells transfected with the antisense Hsp60.

**The Relationship of Hsp60 and IGF-1 Receptor Protein in Diabetic Myocardium**—Our findings thus far suggest that Hsp60 is involved in the regulation of IGF-1 receptor signaling in cardiac muscle cells. Because IGF-1 signaling enhances myocardial protection, Hsp60 may modulate myocardial survival through modulation of IGF-1 receptor signaling. An important feature of diabetic cardiomyopathy is decreased myocardial protection against myocardial injuries. To investigate whether the occurrence of diabetes lead to perturbation of Hsp60 and IGF-1 receptor, we first analyzed the abundance of myocardial Hsp60 and IGF-1 receptor protein in STZ-induced diabetes (Fig. 4a). The abundance of Hsp60 and IGF-1 receptor was concomitantly reduced in the STZ-diabetic myocardium. In contrast, the abundance of insulin receptor was up-regulated as expected (11). In addition to Hsp60, we also investigated Hsp10 in the liver, but Hsp60 and IGF-1 receptor were simultaneously increased in the kidney (Fig. 4c). These observations support...
our hypothesis that Hsp60 modulates the abundance of IGF-1 receptor. If the reduction of myocardial IGF-1 receptor in diabetic myocardium involves post-translational modification, ubiquitination of IGF-1 receptor should have increased in the diabetic myocardium. To this end, we have analyzed ubiquitination of IGF-1 receptor in the ZDF myocardium. As shown in Fig. 4c, there was increased polyubiquitination of IGF-1 receptor in the diabetic myocardium. These observations suggest that the mechanisms underlying the reduction of IGF-1 receptor in diabetic myocardium may involve down-regulation of Hsp60 and subsequent alterations in post-translational modification.

**DISCUSSION**

IGF-1 plays an important role in myocardial protection and remodeling (12). The biological actions of IGF-1 are mediated through activation of IGF-1 receptors on cell surface. Previous studies (1, 13, 14) have shown that IGF-1 receptor signaling can be modulated in a number of ways, such as increased synthesis of IGF-1 receptors, formation of hybrid IGF-1/insulin receptors, different IGF-1 receptor isoforms, and interactions between IGF-1 receptors and secondary signaling/adaptor proteins. In this study we have identified Hsp10 and Hsp60 as novel modulators of IGF-1 receptor signaling in cardiac muscle. This is the first report showing that members of the heat shock
protein family can augment IGF-1 receptor signaling in cardiac muscle cells through post-translational modification of the receptor.

There are growing interests in the role of heat shock proteins in cardiac muscle biology (15). Heat shock proteins were originally discovered as a set of proteins induced by temperature increase. A wide array of biological actions of heat shock proteins have been identified, such as protein folding/unfolding, protein degradation, anti-oxidative stress, and anti-apoptosis. During the last two years, several studies showed important function of Hsp60 in the heart (7, 16, 17). The expression of myocardial Hsp60 is increased under ischemic distress (17), and overexpression of Hsp60 lead to inhibition of apoptosis in the cardiomyocytes underwent ischemic and reperfusion injuries (10). These findings, along with studies showed protective role of Hsp60 in tissues other than cardiac muscle (18), emphasized the protect effect of Hsp60. The present study showed a causal relationship between the abundance of Hsp60 and the magnitude of IGF-1 receptor signaling, which suggests the pro-survival action of Hsp60 may involve augmentation of IGF-1 receptor signaling. Although both Hsp10 and Hsp60 modulated IGF-1 receptor signaling, the effects of Hsp10 were less profound than that of Hsp60. Furthermore, the abundance of myocardial Hsp10 is low and cannot be reliably detected with Western blots in the two lines of normal/diabetic rats we studied (data not shown). Thus, between these two heat shock proteins, it appears that Hsp60 is the major modulator of IGF-1 receptor signaling in myocardium.

Emerging evidence suggest that heat shock proteins are involved in the regulation of intracellular signaling. Hsp90 chaperones STAT3 signaling at plasma membrane and during the formation of cytosolic STAT3 signaling complexes (19). Hsp90 also chaperones steroid receptor, Raf, Akt, and cdk4 (20, 21, 22). The role of Hsp60 on intracellular signaling is rarely explored, but Hsp60 was recently identified as a protein associated with integrin and is involved in the activation of integrin in breast cancer cells (23). As shown in the present study, Hsp60 likely modulates intracellular signaling at more than one signaling step. Some heat shock proteins, such as Hsp90, are known for their inhibitory effect on protein ubiquitination and degradation. Ubiquitin/proteasome pathway enables rapid protein degradation. Sepp-Lorenzino et al. (6) had shown that chemical inhibitors of the 20S proteasome can prevent degradation of IGF-1 receptor, which suggests ubiquitination of IGF-1 receptor play a major role in the regulation of IGF-1 receptor degradation.

Diabetic myocardium is different from other forms of cardiomyopathy regarding the expression of Hsp60. As discussed
earlier, Hsp60 expression is increased during ischemic/reperfusion injury, probably representing a myocardial self-defense mechanism (17). But we have found that Hsp60 expression was reduced in diabetic myocardium. Down-regulation of myocardial Hsp60 and its functional implications in the context of diabetic cardiomyopathy have not been investigated previously. The changes of myocardial Hsp60 and IGF-1 receptor were consistent in both STZ-DM (type 1 DM model) and ZDF-DM (type 2 DM model) rats, which indicates down-regulation of Hsp60 and IGF-1 receptor axis represents a new paradigm contributing to the development of diabetic cardiomyopathy.

IGF-1 signaling will likely lead to better myocardial protection and thus may play a fundamental role during the development of diabetic cardiomyopathy. These findings provide evidence that reduced Hsp60 proteins may contribute to an escalation of oxidative stress, inhibition of cardiac muscle apoptosis, enhancement of contractile function, and modulation of cardiac-specific genes (2, 3, 24). Reduced IGF-1 receptor abundance can lead to decreased myocardial protection during myocardial ischemia and thus may play a fundamental role during the development of diabetic cardiomyopathy.

Our data not only raise the possibility that dysregulation of IGF-1 receptor signaling will likely lead to better myocardial protection in diabetic cardiomyopathy (25). Further insight into the mechanisms responsible for the effect of Hsp10 and, especially, Hsp60 on ubiquitination of cardiac IGF-1 receptor may provide new opportunities to design novel therapeutic strategies for diabetic cardiomyopathy.

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