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E. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得  
なし
2. 実用新案登録  
なし
3. その他  
研究協力者  
滋賀医科大学  
林 秀樹、伊藤英樹、大野聖子、川村美朋子、川口民郎、内貴乃生、木村絃美、王 琦

## Ⅱ. 研究成果の刊行に関する一覧表

## 研究成果の刊行に関する一覧表

### 書 籍

著者氏名	論文タイトル名	書籍全体の 編集者名	書籍名	出版社名	出版地	出版年	ページ
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<u>堀江 稔</u>	15章 細胞内灌流法	岡田泰伸	最新パッチクラン プ実験技術法	吉岡書店	京都	2011	145-152
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### Ⅲ. 研究成果の刊行物・別刷

# Reciprocal Control of hERG Stability by Hsp70 and Hsc70 With Implication for Restoration of LQT2 Mutant Stability

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**Rationale:** The human ether-a-go-go-related gene (hERG) encodes the  $\alpha$  subunit of the potassium current  $I_{Kr}$ . It is highly expressed in cardiomyocytes and its mutations cause long QT syndrome type 2. Heat shock protein (Hsp)70 is known to promote maturation of hERG. Hsp70 and heat shock cognate (Hsc70) 70 has been suggested to play a similar function. However, Hsc70 has recently been reported to counteract Hsp70.

**Objective:** We investigated whether Hsc70 counteracts Hsp70 in the control of wild-type and mutant hERG stability.

**Methods and Results:** Coexpression of Hsp70 with hERG in HEK293 cells suppressed hERG ubiquitination and increased the levels of both immature and mature forms of hERG. Immunocytochemistry revealed increased levels of hERG in the endoplasmic reticulum and on the cell surface. Electrophysiological studies showed increased  $I_{Kr}$ . All these effects of Hsp70 were abolished by Hsc70 coexpression. Heat shock treatment of HL-1 mouse cardiomyocytes induced endogenous Hsp70, switched mouse ERG associated with Hsc70 to Hsp70, increased  $I_{Kr}$ , and shortened action potential duration. Channels with disease-causing missense mutations in intracellular domains had a higher binding capacity to Hsc70 than wild-type channels and channels with mutations in the pore region. Knockdown of Hsc70 by small interfering RNA or heat shock prevented degradation of mutant hERG proteins with mutations in intracellular domains.

**Conclusions:** These results indicate reciprocal control of hERG stability by Hsp70 and Hsc70. Hsc70 is a potential target in the treatment of LQT2 resulting from missense hERG mutations. (*Circ Res.* 2011;108:458-468.)

**Key Words:** hERG ■ Hsp70 ■ Hsc70 ■ stabilization ■ long QT2

The human ether-a-go-go-related gene (hERG) encodes the  $\alpha$  subunit of a rapidly activating delayed-rectifier  $K^+$  current ( $I_{Kr}$ ),<sup>1-3</sup> which controls the action potential duration in cardiomyocytes. Mutations in the gene cause long-QT syndrome type 2 (LQT2), a disorder that leads to life-threatening arrhythmia. To date, more than 200 naturally occurring mutations of hERG have been identified. Functional analysis of mutant proteins showed that most of them had an impairment of protein maturation and/or trafficking.<sup>4-6</sup> They are recognized by the quality control machinery of the endoplasmic reticulum (ER), ubiquitinated, and eventually degraded by the proteasomal degradation system.<sup>6-8</sup> The maturation of hERG can be evaluated by comparing the levels of the 2 forms of this protein; a core-glycosylated, immature form of 135-kDa localized in the ER, and a fully glycosylated mature

form of 155 kDa localized either in the Golgi apparatus or on cell surface.<sup>7,9</sup>

Molecular chaperones participate in every step of hERG biogenesis, including synthesis, folding, assembly, and translocation.<sup>8,10,11</sup> The heat shock protein (Hsp)70 family, including stress-induced Hsp70 and constitutively expressed heat shock cognate protein (Hsc)70, interact with the core-glycosylated form of hERG.<sup>8,12</sup> Hsp70 increases the levels of both immature and mature forms of hERG,<sup>8</sup> whereas the role of Hsc70 remains unknown. In other channel proteins, such as the murine epithelial sodium channel, Hsc70 has been shown to counteract the action of Hsp70 and, thus, decreases the level of the channel protein.<sup>13</sup> The primary purpose of this study was to examine whether Hsc70 had a similar action on hERG. For this purpose, we investigated the effects of Hsp70 and Hsc70 on the level of

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hERG proteins by biochemical and electrophysiological methods. Their effects were examined on exogenous hERG expressed in HEK293 cells as well as on endogenous proteins expressed in HL-1 cardiomyocytes. We also extended our study to examine an interaction of Hsc70 with mutant hERG proteins harboring disease-causing missense mutations.

### Methods

An expanded Methods section is available in the Online Data Supplement at <http://circres.ahajournals.org>.

HEK293 cells were cultured in DMEM (Sigma) supplemented with 10% FBS (JRH) and penicillin/streptomycin/geneticin at 37°C, 5% CO<sub>2</sub>.<sup>14–17</sup> HL-1 mouse cardiomyocytes were maintained as previously described.<sup>18</sup> An expression construct pcDNA3/hERG-FLAG was engineered by ligating an oligonucleotide encoding a FLAG epitope to the carboxy terminus of hERG cDNA. Missense mutations were introduced into pcDNA3/ hERG-FLAG by site-directed mutagenesis. Transfection into HEK293 and HL-1 cells were performed using Lipofectamine 2000 (Invitrogen) or Nucleofector technology (Amaxa Biosystems, Gaithersburg, MD), respectively, following the protocol of the manufacturer. pEGFP was added into all the experiments of transfection to trace the transfection efficiency. HEK293 cells stably expressing hERG-FLAG were transfected with pcDNA3/ Hsc70 or Hsp70 together with pEGFP. Twenty-four hours after transfection, cells were visualized by EGFP fluorescence and hERG channel currents corresponding to  $I_{Kr}$  were measured at 37°C using whole-cell patch-clamp techniques. Procedures for the current measurement in HL-1 cells were essentially the same as described previously.<sup>19</sup> The membrane potential was held at -50 mV to inactivate the T-type Ca<sup>2+</sup> channel current ( $I_{Ca,T}$ ) and avoid the hyperpolarization-activated cation current ( $I_p$ ) activation.<sup>20,21</sup> depolarized by 1-second test pulses (from -40 and +40- in 10-mV increments), then repolarized back to the holding potential; 0.4 μmol/L nisoldipine was included in the bath solution to block the L-type Ca<sup>2+</sup> channel current ( $I_{Ca,L}$ ).<sup>20</sup> Action potentials were also measured in the current-clamp mode, elicited at a rate of 0.5 Hz by 5-ms square current pulses of 1 nA, and sampled at 20 kHz in the absence or presence of 10 μmol/L E4031 (WAKO, Japan).

### Results

#### Hsp70 and Hsc70 Exert Opposite Effects on the Maturation of hERG

We first examined effects of Hsp70 on hERG-FLAG expressed in HEK293 cells. As expected, hERG-FLAG gave 2 bands on the anti-FLAG immunoblot (IB), a fully glycosylated mature form of 155-kDa and an immature core-glycosylated form of 135-kDa (Figure 1A). Coexpression of Hsp70 increased the levels of both forms in a dose-dependent manner with a concomitant decrease in the ubiquitinated form of the protein. hERG was recovered in the detergent-soluble fraction, whether Hsp70 was expressed or not, suggesting that Hsp70 did not induce changes in protein solubility (Online Figure I, A). Hsp70 did not alter the level of hERG-FLAG mRNA (Online Figure I, B). Small interfering (si)RNAs targeted against Hsp70 caused marked decreases of both immature and mature forms of hERG-FLAG and also an increase in its ubiquitinated form (Figure 1B).

In contrast, coexpression of Hsc70 decreased the levels of both forms of hERG in a dose-dependent manner. The decreases were accompanied by an increase in its ubiquitinated form (Figure 1C). siRNAs targeted against Hsc70 caused a marked increase of both forms and also a decrease in its ubiquitinated form (Figure 1D). Hsc70 did not alter either solubility of hERG-FLAG or the level of its mRNA (Online Figure I, C and

#### Non-standard Abbreviations and Acronyms

APD	action potential duration
APD <sub>90</sub>	action potential duration at 90% repolarization
ER	endoplasmic reticulum
ERG	ether-a-go-go-related gene
hERG	human ether-a-go-go-related gene
HS	heat shock
Hsp70	heat shock protein 70
Hsc70	heat shock cognate protein 70
IB	immunoblot
$I_{Kr}$	rapidly activating delayed rectifier K <sup>+</sup> current
IP	immunoprecipitates
LQT2	long QT syndrome type 2
mERG	mouse ether-a-go-go-related gene
siRNA	small interfering RNA
WT	wild type

D). We then determined the half-life of hERG-FLAG by chase experiments (Figure 2). The half-life of the 135-kDa immature form was 9.5±3.1 hour in the control and was prolonged to 13±2.5 hours when cotransfected with Hsp70, whereas it was shortened to 6.8±2.3 hours by coexpression of Hsc70.

Next, we examined effects of Hsp70 and Hsc70 on intracellular localization of hERG-FLAG (Figure 3A). The immunoreactivity of hERG-FLAG was localized in the ER (nos. 1 to 3), the Golgi apparatus (nos. 4 to 6), and on the cell membrane (nos. 7 to 9), as evidenced by colocalization with calnexin, Golgi-GFP and GFP-Mem, respectively. Hsp70 appeared to increase the signals in all of these cellular components; and Hsc70 caused opposite effects. The changes in immunoreactivities were confirmed by a quantification analysis (Figure 3B).

The intracellular localization of hERG-FLAG was further confirmed by subcellular fractionation on the Optiprep gradient (Figure 3C). A membrane marker Na<sup>+</sup>/K<sup>+</sup> ATPase was enriched in fractions 2 to 5, whereas an ER marker calnexin was enriched in nos. 10 to 15. Hsp70 increased the levels of hERG-FLAG in both fraction nos. 2 to 5 and nos. 11 to 16. Both Hsp70 and Hsc70 were enriched in fraction nos. 11 to 16, suggesting that the main site of action of these proteins was the ER.

To see whether Hsp70/Hsc70 affected the levels of functional hERG, we measured hERG channel currents in HEK293 cells stably expressing hERG-FLAG. Depolarizing pulses activated time-dependent outward currents corresponding to  $I_{Kr}$  (Figure 4A), and these currents were completely blocked by E4031 (10 μmol/L) as indicated by the disappearance of the tail currents (Online Figure II, A). The kinetics of the currents through hERG without the FLAG tag was nearly identical to those of the currents through hERG-FLAG, excluding an effect of the tag on hERG currents (Online Figure II, B). Hsp70 caused remarkable increases in both the peak and tail current amplitudes (Figure 4A through 4C). In contrast, Hsc70 reduced the peak currents during depolarization by approximately 49% and tail currents by approximately 58% (Figure 4A through 4C).