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Effect of methionine sulfoxide reductase B1 (SelR) gene silencing on peroxynitrite-induced F-actin disruption in human lens epithelial cells

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ABSTRACT

F-actin plays a crucial role in fundamental cellular processes, and is extremely susceptible to peroxynitrite attack due to the high abundance of tyrosine in the peptide. Methionine sulfoxide reductase (Msr) B1 is a selenium-dependent enzyme (selenoprotein R) that may act as a reactive oxygen species (ROS) scavenger. However, its function in coping with reactive nitrogen species (RNS)-mediated stress and the physiological significance remain unclear. Thus, the present study was conducted to elucidate the role and mechanism of MsrB1 in protecting human lens epithelial (hLE) cells against peroxynitrite-induced F-actin disruption. While exposure to high concentrations of peroxynitrite and gene silencing of MsrB1 by siRNA alone caused disassembly of F-actin via inactivation of extracellular signal-regulated kinase (ERK) in hLE cells, the latter substantially aggravated the disassembly of F-actin triggered by the former. This aggravation concurred with elevated nitration of F-actin and inactivation of ERK compared with that induced by the peroxynitrite treatment alone. In conclusion, MsrB1 protected hLE cells against the peroxynitrite-induced F-actin disruption, and the protection was mediated by inhibiting the resultant nitration of F-actin and inactivation of ERKs.

1. Introduction

Actin is a protein that exists in three isoforms (α, β, and γ) and in various states ranging from monomeric globular actin (G-actin) to polymeric filamentous actin (F-actin) [1,2]. F-actin plays a crucial role in fundamental cellular processes [3]. Actin also belongs to a group of proteins that are targeted for calpain mediated degradation in different types of experimental cataract [4,5]. Based on the result of actin-related globular degeneration, Mousa et al. speculated that it might be a contributing factor in cortical cataractogenesis [6].

The ERK signaling pathway is a major determinant in the control of diverse cellular processes [7]. Previous studies have indicated that F-actin may provide a scaffold for ERK signaling complexes [8,9]; and ERK1/2 activation mediates the formation of F-actin, whereas depolymerizing F-actin increased pERK1/2 expression [10]. However, Yang et al. reported that disassembly of the actin cytoskeleton inhibited phosphorylation of ERK and stabilizing actin prevented dephosphorylation of ERK [11]. Nevertheless, mechanisms for the interactions between pERK1/2 and F-actin are not well understood.

Peroxynitrite ($ONOO^-$) is the reaction product of superoxide (O_2^-) and nitric oxide (NO). The molecule rapidly breaks down at physiological pH to yield hydroxyl radical (·OH) and nitrogen dioxide radical ($\cdot NO_2$) [12]. As a potent oxidant and nitrating species, peroxynitrite is proposed to be an effector of cell damage in diabetic cataract [13], by oxidizing and/or nitrating biological molecules including proteins, lipids, and DNA [14,15]. The $ONOO^-$-induced nitration of actin protein can result in depolymerization of F-actin [16–18]. Furthermore, $ONOO^-$ oxidizes methionine (Met) residues of proteins to methionine sulfoxide (MetO) [19,20], and this oxidation may interfere a multitude of biological functions through direct inactivation of relevant proteins [21,22]. Recent evidence suggests that Mical (an actin disassembly factor) can

Abbreviations: bFGF, basic fibroblast growth factor; DMEM, Dulbecco's Modified Eagle's Medium; ECL, enhanced chemiluminescence; ERK, extracellular signal-related kinase; F-actin, filamentous actin; G-actin, globular actin; hLE, human lens epithelial; MAPK, mitogen-activated protein kinase; MetO, methionine sulfoxide; MEK, mitogen-activated protein kinase kinase; Msr, methionine sulfoxide reductase; NCS, newborn calf serum; PBS, phosphate-buffered saline; RNS, reactive nitrogen species; ROS, reactive oxygen species; RT, room temperature; SelR, selenoprotein R; siRNA, short interfering RNA; T-TBS, tris-buffered saline with Tween.

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regulate F-actin assembly and disassembly by the oxidation of Met 44 residue within the D-loop of actin [23]. Oxidation of critical Met residues can inhibit actin polymerization and distablizes F-actin [24]. Unlike most protein modifications, MetO can be converted back to Met through the action of a class of enzymes known as methionine sulfoxide reductases (Msrs) [25]. Mammals have two forms of Msrs: MsrA and MsrB catalyze the thioredoxin-dependent reduction of S-MetO and R-MetO derivatives to Met [26], respectively. MsrB1 is a selenoprotein named selenoprotein R (SelR), and is localized in the cell nucleus and cytosol [19,27]. MsrB1 is widely distributed throughout different tissues of mammals [11,27]. Previous studies by Marchetti et al. [21] and our group [28,29] demonstrated that MsrB1 could serve as a ROS scavenger and inhibit $ONOO^-$-induced apoptosis of human lens epithelial cells (hLEC). However, its potential role in protection against $ONOO^-$ and in protecting the F-actin assembly in hLE cells exposed to various doses of peroxynitrite remains largely unknown.

To explore the cytoprotection of MsrB1 against $ONOO^-$-induced damage in hLE cells, here, we preliminarily examined the effect of $ONOO^-$ on ERK phosphorylation and the regulation of pERK1/2 expression on F-actin assembly in cultured hLE cells before and after MsrB1 gene silencing by RNAi.

2. Materials and methods

2.1. Reagents

Dulbecco's Modified Eagle's Medium (DMEM) and newborn calf serum (NCS) were obtained from Gibco BRL (Gaithersburg, MD). Penicillin G and streptomycinsulfate were purchased from Amersco. Lipofectamine 2000 was obtained from Invitrogen. Protease inhibitor cocktail was purchased from Sigma Co. (St. Louis, MO). Recombinant human basic fibroblast growth factor (bFGF) was obtained from Peprotech (Rocky Hill, CT). All other reagents were of analytical or biochemical reagents.

$ONOO^-$ was synthesized from sodium nitrite and acidic hydrogen peroxide as previously described [30], and excess hydrogen peroxide was removed by treatment with MnO_2. Concentration of $ONOO^-$ was determined spectrophotometrically at 302 nm ($\varepsilon = 1670\ M^{-1}\ cm^{-1}$).

2.2. Cell culture and treatment with $ONOO^-$

The hLE cells (SRA01/04, Sciencell, Carlsbad, CA) [25] were cultured in DMEM medium supplemented with 10% (v/v) heat-inactivated NCS and antibiotics (penicillin, 100 U/mL; streptomycin, 100 μg/mL) at 37 °C in the presence of 5% CO_2. Before experimentation, cells at approximately 80% confluence were serum-starved for 24 h, washed twice with phosphate- buffered saline (PBS), and subsequently placed in modified PBS (50 mM Na_2HPO_4, 90 mM NaCl, 5 mM KCl, 0.8 mM $MgCl_2$, 1 mM $CaCl_2$, and 5 mM glucose, pH 7.4). To avoid increases in pH, $ONOO^-$ was added at a maximum volume of 1% of the culture to yield the given final concentrations. The cells were incubated for 20 min at 37 °C, then were washed, incubated with culture medium, and maintained for the additional time required for each experiment. In control experiments, cells were treated with aliquots of $ONOO^-$ stock solutions that were allowed to decompose completely by overnight (vehicle control) [31,32].

2.3. MsrB1 RNA interference

Double-stranded short interfering (si) RNAs specifically designed for MsrB1 were 5′-GCGUCCGGAGCACAAUAGATT-3′ (sense) and 5′-UCUAUUGUGCUCCGGACGCTT-3′ (antisense) [21], and for the negative control were 5′-UUCUCCGAACGUGUCACGUTT-3′ (sense) and 5′-ACGUGACACGUUCGGAGAATT-3′ (antisense). The siRNA fragments were synthesized by Shanghai GenePharma (Shanghai, China).

The hLE cells were plated in 6-well plates or 60 mm plates, grown until 70–80% confluence, then transfected with siRNA and Lipofectamine 2000 according to the manufacturer's instructions. At 24 h after the transfection, the cells were treated with various concentrations of $ONOO^-$ and incubated with fresh serum-free media for 1 h or 24 h before being harvested for analysis.

2.4. Inhibition test

U0126 (1,4-diamino-2,3-dicyano-1,4-bis[2-aminophenylmercapto]butadiene; Beyotime, China) was used as a highly selective inhibitor of both mitogen-activated protein kinase kinase (MEK1/2) and ERK1/2. In all inhibition test, 25 μM U0126 was added at 1 h before the addition of bFGF or $ONOO^-$. The inhibitor was added to the culture one more time during the culture period. The control dishes were supplemented with an equivalent volume of solvent dimethylsulfoxide [7].

2.5. Immunofluorescence and confocal microscopy

The hLE cells were plated on 20-mm glass bottom cell culture dish, and grown to confluence at 37 °C. After treatment with $ONOO^-$, the cells were treated as reference [2], washed with PBS, fixed with 3.7% formaldehyde solution at room temperature (RT) for 20 min and then permeabilized with 0.1% Triton X-100 in PBS at RT for 15 min. The cells were washed with PBS and then blocked in 10% NCS at RT for 1 h. F-actin was stained with FITC-Phalloidin (Enzo Life Sciences, Farmingdale, NY) at RT for 1 h and washed sufficiently. The cells were imaged with a Zeiss LSM 510 laser scanning confocal microscope (Carl zeiss, Jena, Germany).

2.6. Immunoprecipitation and Western blot analysis

The cells were lysed in RIPA buffer (50 mM Tris–HCl, pH 7.4, 150 mM NaCl, 0.5% sodium deoxycholate, 0.1% SDS, 1% Triton X-100, 1 mM NaF, 1 mM Na_3VO_4, 1 mM EDTA, 10 uL/mL protease inhibitor cocktail P8340). Soluble proteins were separated on 10% polyacrylamide gels and blotted onto a nitrocellulose membrane. Subsequently, the membranes were incubated with specific antibodies against target protein (GAPDH, ERK1/2 and phosphor-ERK1/2 (Tyr 204) (Santa Cruz Biotechnology, Dallas, TX); F-actin (Xing Xing Tang Biotechnology, Beijing, China); nitrotyrosine antibody (Millipore, Billerica, MA)), and antigen–antibody complexes were visualized by enhanced chemiluminescence.

For immunoprecipitation experiments, hLE cell lysates containing 0.5 mg of total protein were incubated with 4 μg of anti-F-actin for 1 h at 4 °C. After collection on protein A/G plus-Agarose, the immune complexes were washed three times with lysis buffer, boiled in Laemmli buffer for 5 min, and thereafter subjected to Western blotting analysis.

2.7. Statistical analysis

All data were expressed as mean ± SD. The statistical significance of difference between groups was evaluated using analysis of variance (ANOVA) followed by Tukey test for multiple comparisons, and a P value less than 0.05 was considered statistically significant.

3. Results

3.1. Effect of the $ONOO^-$ exposure and the MsrB1 gene silencing on assembly of F-actin

To investigate effects of the MsrB1 gene silencing on disassembly of F-actin induced by $ONOO^-$, at first, we detected the effect of different concentrations of $ONOO^-$ on F-actin protein levels. After hLE cells were exposed to low concentrations of $ONOO^-$ (50 or 100 μM) for 1 h (Fig. 1A), the levels of F-actin protein were increased, indicating that low concentrations of $ONOO^-$ actually induced the assembly of F-actin. The increase of F-actin level was almost same as that of treating with 40 ng/mL bFGF. Seemingly, low concentrations of $ONOO^-$ had bFGF-like effect. In contrast, the levels of F-actin protein were decreased to the level lower than the control-after hLE cells were exposed to 200 μM $ONOO^-$ for 1 h. Thus, there was a bidirectional effect of $ONOO^-$ on the expression of F-actin protein.

After hLE cells were transfected with MsrB1 siRNA (Fig. 1B), level of F-actin was decreased by 15%, compared with the vehicle control. After MsrB1-gene-silenced hLE cells were exposed to low or high concentrations of $ONOO^-$, the bidirectional effects disappeared. The level of F-actin protein was decreased by 18% and 44%, respectively.

To explore the effects of $ONOO^-$ on cytoskeletal assembly, we examined the structures of F-actin in hLE cells using FITC-phalloidin staining. Representative micrographs obtained by confocal immunofluorescence microscopy were shown in Fig. 1C. While the vehicle control showed the typical, fine weblike network of cellular actin (Fig. 1C(I)), F-actin in the cells treated with $ONOO^-$ or transfected with MsrB1 siRNA displayed a defective disassembly (Fig. 1C(II) and (III)). Moreover, when hLE cells were transfected with MsrB1 siRNA and then exposed to 200 μM $ONOO^-$ for 1 h, the F-actin was partially disintegrated and total staining actin was obviously decreased (Fig. 1C(IV)).

3.2. Effects of bFGF and $ONOO^-$ on ERK activation or inactivation

As shown in Fig. 2A, after hLE cells were exposed to low concentration of $ONOO^-$ (50 μM) for 1 h, level of p-ERK1/2 was increased to the level similar to that treated with bFGF for 1 h. The level of p-ERK1/2 was gradually decreased with increase of concentration of $ONOO^-$. When hLE cells were exposed to 200 μM $ONOO^-$ for 1 h, the level of p-ERK1/2 was decreased by 60%. A similar change was observed after hLE cells were exposed to 200 μM $ONOO^-$ for 24 h.

To evaluate the influence of MsrB1 gene silencing on ERK signal pathway, we also determined the levels of p-ERK1/2 before and after MsrB1gene silencing in hLE cells. As shown in Fig. 2B, the level of p-ERK1/2 in MsrB1-gene-silenced cells was 75% of the control. When these MsrB1-gene-silenced cells were exposed to 50 μM $ONOO^-$, level of p-ERK1/2 was not up-regulated, compared with the wild-type control group treated with the same concentration of $ONOO^-$ (Fig. 2A), but the level was about 31% of normal cells. When MsrB1-gene-silenced cells were exposed to 200 μM $ONOO^-$, level of p-ERK1/2 was only 10% of the vehicle control cells, or 25% of the control cells treated with the same concentration of $ONOO^-$.

U0126 is an inhibitor of MEK and was used to explore if the effect of $ONOO^-$ was mediated by activating ERK1/2. As shown in Fig. 3, treating hLE cells with U0126 blocked the ERK1/2 phosphorylation in both control group and bFGF-treated group, indicating that bFGF-activated ERK1/2 phosphorylation was dependent on MEK activity. In contrast, the up-regulation of ERK1/2 phosphorylation by $ONOO^-$ (50 μM) was not blocked by the same MEK inhibitor, indicating that $ONOO^-$ activated ERK1/2 via a MEK-independent pathway.

3.3. Correlation between loss of F-actin and nitration of F-actin

To reveal the mechanism for MsrB1 gene silencing effect on $ONOO^-$-induced F-actin disassembly, we determined the level of

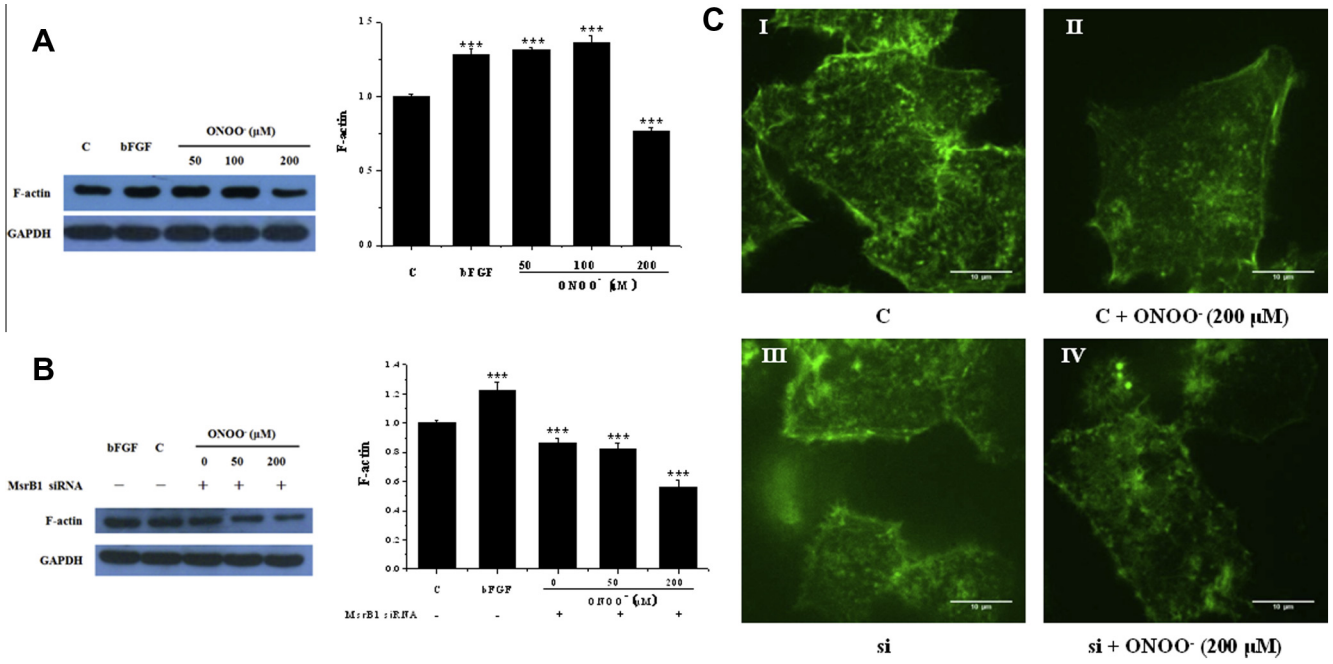

Fig. 1. $ONOO^-$ induced assembly or disassembly of F-actin before and after MsrB1 gene silencing in hLE cells. (A, B) Influence of $ONOO^-$ on the assembly or disassembly of F-actin before and after MsrB1 gene silencing. (C) Fluorescent staining of the F-actin cytoskeleton assessed by laser scanning confocal microscope in hLE cells, Scale bar, 10 μm. Data are the mean ± SD of at least three independent experiments. $^{***}P < 0.001$, compared to vehicle control. C, vehicle control; bFGF, the group treated with bFGF.

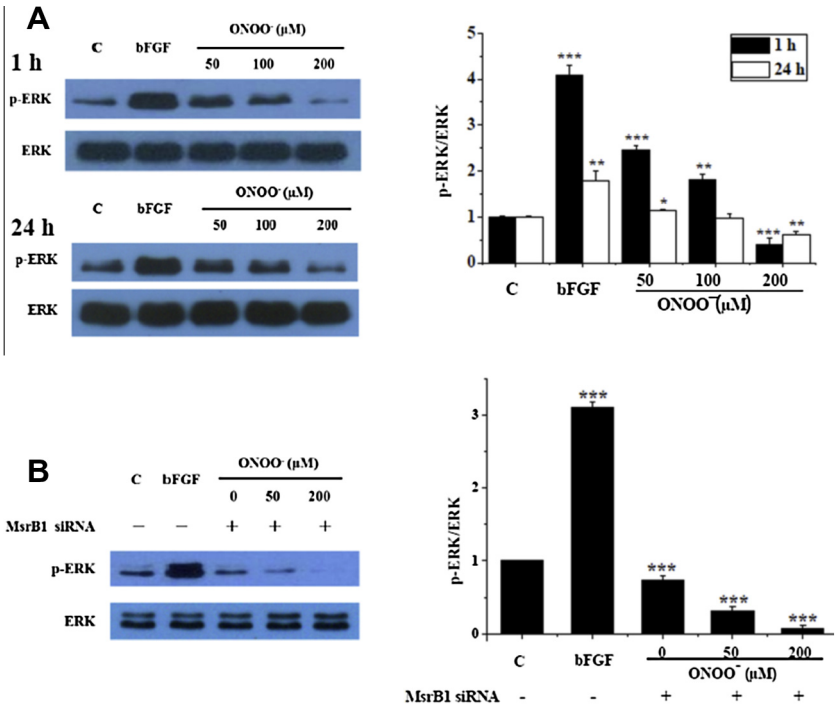

Fig. 2. Effect of different concentrations of $ONOO^-$ on ERK1/2 phosphorylation before and after MsrB1 gene silencing in hLE cells. (A) $ONOO^-$ induced a dose- and time-dependent manner in ERK1/2 phosphorylation. (B) Effect of MsrB1 gene silencing on the $ONOO^-$-induced ERK1/2 phosphorylation. Data are the mean ± SD of at least three independent experiments. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, compared to vehicle control. C, vehicle control; bFGF, the group treated with bFGF.

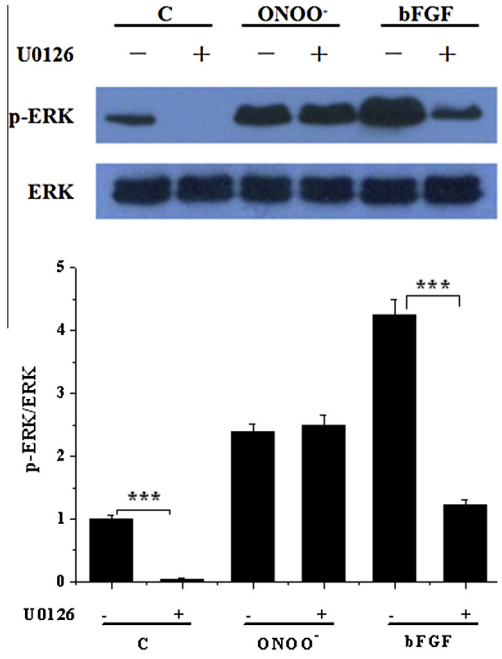

Fig. 3. bFGF mediated ERK1/2 phosphorylation via a MEK-dependent pathway and $ONOO^-$ activated ERK1/2 via a MEK-independent pathway. Data are the mean ± SD of at least three independent experiments. $^{***}P < 0.001$, compared to the group without treatment of U0126. C, vehicle control; $ONOO^-$, the group treated with $ONOO^-$ (50 μM); bFGF, the group treated with bFGF (40 ng/mL).

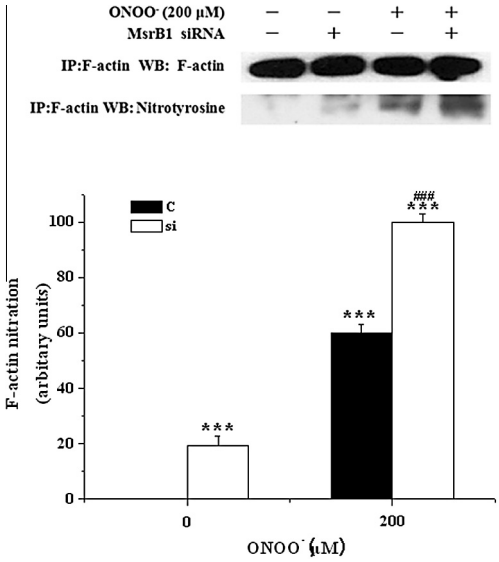

Fig. 4. Quantitative immunoblotting analysis of the levels of F-actin nitration in hLE cells. Data are the mean ± SD of at least three independent experiments. $^{***}P < 0.001$, compared to vehicle control. $^{\#\#\#}P < 0.001$, compared to the group treated with $ONOO^-$ alone.

F-actin nitration using immunoprecipitation and Western blot. As shown in Fig. 4, the level of F-actin nitration in MsrB1-gene-silenced cells and those treated with 200 μM $ONOO^-$ for 1 h was increased. Furthermore, after the vehicle control cells were treated with both MsrB1 siRNA and 200 μM $ONOO^-$, the level of F-actin nitration was elevated to 5.2-fold of that in MsrB1-gene-silenced cells and 1.7-fold of that in $ONOO^-$-treated cells.

4. Discussion

MsrA has been shown to play an important role in protecting lens cells against oxidative damage and to be required for the maintenance of lens transparency in vivo [33,34]. MsrB1, as a selenoprotein, is also important for lens cell in coping with oxidative

stress and potentially cataractogenesis [21]. Our previous study [28] proved that MsrB1 gene silencing elevated ROS level and aggravated $ONOO^-$-induced apoptosis in hLE cells. In this study, when MsrB1-gene-silenced hLE cells were exposed to $ONOO^-$, levels of F-actin protein and pERK/ERK were further decreased, and the bidirectional effects of peroxynitrite no longer existed. Consequently, the F-actin cytoskeleton was partially disintegrated and total staining actin was obviously decreased. These results suggest that MsrB1 plays important roles in protecting hLE cells against peroxynitrite-induced nitration of F-actin and damage of cytoskeleton via regulating ERK signaling pathway through balancing ERK1/2 phosphorylation.

$ONOO^-$ is a potent RNS that plays crucial roles in the physiologic regulation of important biological processes such as proliferation and differentiation [35]. Our results from the present study showed a dose-dependent, dual role of $ONOO^-$ on the expression of F-actin. Specifically low concentrations of $ONOO^-$ induced assembly of F-actin, whereas high concentrations of $ONOO^-$ attenuated the assembly. This finding is consistent with our previous observation of bidirectional effects of $ONOO^-$ on insulin signaling in HepG2 cells [32] and the survival and proliferation of hLE cells [28].

MAPK/ERK1/2 signaling pathways is required for FGF-induced lens cell differentiation [7,36] and F-actin also plays an important role in this process [3]. In the present study, we demonstrated that low concentrations of $ONOO^-$ activated ERK1/2, but high concentrations of $ONOO^-$ inhibited ERK1/2 activation. These opposite responses of ERK1/2 to low and high concentrations of $ONOO^-$ were in parallel with their induced impacts on assembly or disassembly of F-actin (Figs. 1A and 2A). Similarly, Liaudet et al. revealed that low concentration of $ONOO^-$ activated tyrosine phosphorylation and high concentration of $ONOO^-$ inhibited tyrosine phosphorylation [37]. Activation of ERK by $ONOO^-$ has also been shown in rat-1 fibroblasts [38] and H9C2 cardiomyocytes [39]. However, these studies did not illustrate the bidirectional effects of $ONOO^-$ on ERK phosphorylation. This discrepancy from the present study might be related to the experimental conditions including the $ONOO^-$ exposure dose by time and the cell types.

Recent evidences suggested that $ONOO^-$-induced depolymerization of F-actin was associated with increased nitrotyrosine [16–18,40,41]. Therefore, Maneen and Cipolla conjectured that the mechanism for causing disruption of the normal state of F-actin and subsequent depolymerization was possibly attributed to the nitrotyrosine formation-mediated structural/conformational changes of F-actin [17]. Our results indicate that disruption of F-actin was accompanied by increase in F-actin nitration (Figs. 1 and 4). Furthermore, our results reveal that bFGF activated ERK1/2 phosphorylation via an MEK-dependent pathway, whereas low concentrations of $ONOO^-$ activated ERK1/2 phosphorylation via an MEK-independent pathway (Fig. 3). The latter may be mediated by activation of a calcium-dependent PKC [38].

It is well known that in physiological condition peroxynitrite may be decomposed into hydroxyl radical, a strong oxidizing agent, and nitric oxide radical, a strong nitrating agent:

$$ONOO^- + H^+ \rightarrow ONOOH \rightarrow {\cdot}OH(ROS) + {\cdot}NO_2$$
$$Tyr\text{-}P + {\cdot}NO_2 \rightarrow n\text{-}Tyr\text{-}P$$

In present study, when MsrB1-gene-silenced hLE cells were exposed to $ONOO^-$, the nitration of F-actin was further increased. Meanwhile, inhibition of ERK1/2 phosphorylation and disassembly of F-actin were further aggravated. All these collective findings prompt us to speculate that the selenocysteine-containing MsrB1 might act as a peroxynitrite reductase in preventing the induced oxidation and nitration reactions with ERK or F-actin. This function may be carried out by directly or indirectly scavenging RNS and ROS:

$$E\text{-}SeH + ONOO^- \rightarrow E\text{-}SeOH + NO_2^-$$

$$E\text{-}SeH + {\cdot}OH\ (ROS) \rightarrow E\text{-}SeOH$$

$$E\text{-}SeOH + GSH \text{ or } Trx \rightarrow E\text{-}SeH$$

$$E\text{-}Met + {\cdot}OH\ (ROS) \rightarrow E\text{-}MetO$$
$$\uparrow\ \_\_\_\_\_\ \text{MsrB1}$$

In summary, both high concentrations of $ONOO^-$ and MsrB1 gene silencing accelerated disassembly of F-actin and induced inactivation of ERK in hLE cells. Furthermore, MsrB1 gene silencing aggravated disassembly of F-actin by $ONOO^-$ through increase of nitration of F-actin and inactivation of ERK. Overall, MsrB1 played important roles in protecting hLE cells against $ONOO^-$-induced F-actin disruption, and part of the mechanism was via inhibiting nitration of F-actin and inactivation of ERK. However, a complete understanding of the mechanisms needs further research studies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.12.055.

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