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Possible mechanism of heme oxygenase-1 expression in rat malignant meningioma KMY-J cells subjected to talaporfin sodium-mediated photodynamic therapy

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ABSTRACT

Background: We previously demonstrated that heme oxygenase-1 (HO-1) induction may contribute to a protective response against photodynamic therapy (PDT) using talaporfin sodium (TS) in rat malignant meningioma KMY-J cells. In the present study, we examined the mechanism of HO-1 induction by PDT with TS (TS-PDT) in KMY-J cells.

Methods: KMY-J cells were incubated with 25 μM TS for 2 h and then exposed to 664 nm diode laser irradiation at 1 J/cm^2. The gene and protein expression levels of HO-1 and hypoxia-inducible factor-1α (HIF-1α) were determined by real-time RT-PCR and western blot analysis, respectively. Cell viability was measured using the cell counting kit-8 assay.

Results: mRNA and protein levels of HO-1 in KMY-J cells were increased significantly at 3, 6, and 9 h after laser irradiation and the increased mRNA level of HO-1 was decreased by antioxidant *N*-acetyl cysteine treatment. The protein level of HIF-1α, which mediates transcriptional activation of the HO-1 gene, was increased significantly at 1 h after laser irradiation. Additionally, induction of mRNA expression of HO-1 by TS-PDT was diminished by HIF-1α inhibitor echinomycin. We also demonstrated that echinomycin significantly augmented the cytotoxic effect of TS-PDT.

Conclusions: Our findings indicate that TS-PDT may induce HO-1 expression *via* reactive oxygen species production and then HIF-1 pathway activation in KMY-J cells, and the HO-1 induction may cause attenuation of the therapeutic effect of TS-PDT.

1. Introduction

Photodynamic therapy (PDT) induces tumor cell death *via* production of singlet oxygen, a reactive oxygen species (ROS), by applying laser light to a photosensitizer that accumulates in tumor cells [1,2]. Glioblastomas are serious tumors of the central nervous system and the prognosis for glioblastoma remains poor with no improvement over the last 2 decades [3]. Our and other groups have reported the efficacy of PDT using a second-generation photosensitizer, talaporfin sodium (TS, mono-L-asparthyl chlorine e6; Laserphyrin®) in patients with malignant brain tumors [4–6]. Our previous studies showed that TS-PDT exhibits an antitumor effect against glioblastoma cells *via* apoptotic and necroptotic cell death accompanied by necrosis *in vitro* [7–10]. Recently, we have also shown that TS-PDT is effective in malignant meningioma cells [11–13].

PDT exerts cytotoxic effects in tumor cells through ROS production. Moreover, ROS production as an intracellular defense response induces the expression of oxidative stress response proteins. These proteins are highly expressed in various human tumor tissues and act in a suppressive manner against anti-cancer therapies such as chemotherapy and radiation therapy [14,15]. However, the involvement of oxidative stress response proteins in antitumor effect of PDT is not yet fully understood. Our recent study using rat malignant meningioma KMY-J cells showed that TS-PDT induces expression of heme oxygenase-1 (HO-1), an

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antioxidant, before cytotoxicity is observed, and HO-1 inhibitor zinc protoporphyrin IX augments the cytotoxic effect of TS-PDT [12]. These results suggest that HO-1 induction contributes to a protective response against TS-PDT in malignant meningioma cells.

HO-1 degrades heme and produces bilirubin that has antioxidative properties [16]. Hypoxia inducible factor-1α (HIF-1α) and NF-E2-related factor-2 (Nrf2) are well-known transcription factors involved in the regulation of HO-1 expression [17]. Because increased expression of downstream target genes of the Nrf2 pathway was not observed after TS-PDT, we speculated that the increased expression of HO-1 was mediated by the HIF-1 pathway [12]. In the present study, we examined the possible mechanism of HO-1 induction by TS-PDT in rat malignant meningioma KMY-J cells *in vitro*.

2. Materials and methods

2.1. Cell culture

Rat malignant meningioma KMY-J cells (Riken BRC Cell Bank, Tsukuba, Japan) were cultured as described previously [12]. Briefly, the cells were seeded at 3×10^5, 1.2×10^5, or 1×10^4 cells/well in uncoated 6-, 12-, or 96-well plates (Nippon Genetics Co., Ltd., Tokyo, Japan), respectively, in Eagle's minimum essential medium (EMEM, Fujifilm Wako Pure Chemical, Osaka, Japan) supplemented with 10% fetal bovine serum (FBS; Biowest, Nuaillé, France) and incubated at 37°C with 5% CO_2 for 24 h. All experimental protocols were approved by the Regulations for Biological Research at Tokyo University of Pharmacy and Life Sciences and carried out in accordance with the approved protocols.

2.2. TS-PDT and real-time RT-PCR analysis

The *in vitro* PDT experiment was performed as described previously with minor modifications [12]. At 24 h after seeding in six-well plates, KMY-J cells were treated with 25 μM TS (Meiji Seika Pharma Co., Ltd., Tokyo, Japan) for 2 h in the presence or absence of 5 and 10 mM *N*-acetyl cysteine (NAC; Sigma-Aldrich, St. Louis, MO, USA), a ROS inhibitor, or 1 nM echinomycin (ECH; Sigma-Aldrich), a HIF-1-specific inhibitor [18], at 37°C with 5% CO_2. The cells were washed once with phosphate buffered saline (PBS), and fresh 10% FBS-EMEM with or without NAC or ECH was added. Then, the cells were subjected to laser irradiation (wavelength: 664 nm; laser irradiance: 3.4 mW/cm^2; irradiation time: 300 s; laser fluence: 1 J/cm^2) using a semi-conductor laser irradiator ZH-L5011HJP (Panasonic Healthcare Co., Ltd., Tokyo, Japan) and subsequent incubation for 1, 3, 6, and 9 h at 37°C with 5% CO_2. Total RNA extraction from the cells and subsequent real-time PCR analysis were performed as described previously [11,12]. Briefly, the culture medium was removed and the cells were washed in cold PBS and then incubated in 300 μL cold Isogen II reagent (Nippon Gene Co., Ltd., Tokyo, Japan) per well. The cells were collected by scraping and homogenized by pipetting. RNA quality was ensured by spectrophotometric analysis (OD 260/280) using a NanoDrop Lite spectrophotometer (Thermo Fisher Scientific, Tokyo, Japan). Reverse transcriptome was performed using qPCR RT Master Mix (Toyobo Co., Ltd., Osaka, Japan) and a GeneAmp PCR system 9700 (Thermo Fisher Scientific). Real-time PCR was performed using THUNDERBIRD® SYBR qPCR Mix (Toyobo), 0.5 μM primers (Table 1), and a LightCycler 96 (Roche, Tokyo, Japan). The thermal conditions were 95°C for 10 min, and then 45 cycles of 95°C for 10 s and 60°C for 30 s. HO-1 (*Hmox1*), vascular endothelial growth factor A (*Vegfa*), and β2-microglobulin (*B2m*) mRNA levels in each RNA sample were determined using the relative standard curve method. Fold changes in the expression of each gene were assessed after normalization to that of *B2m*.

2.3. Western blot analysis

Western blot analysis was performed as described previously with minor modifications [19]. At 24 h after seeded in 12-well plates, KMY-J cells were treated with 25 μM TS in the presence or absence of 1 nM ECH for 2 h at 37°C with 5% CO_2. Then, the cells were washed with PBS and fresh 10% FBS-EMEM with or without ECH was added. The cells were subjected to laser irradiation as described above and then incubated for 1, 3, 6, or 9 h. After incubation, the cell layers were washed twice with cold PBS and lysed with RIPA buffer [1 mM Tris-HCl (pH 7.4), 1% NP-40, 0.1% sodium deoxycholate, 0.1% SDS, 150 mM NaCl, 1 mM EDTA, 1 μg/mL leupeptin, 1 μg/mL pepstatin, and 1 mM PMSF]. After collection, the solution was centrifuged at 15,000 × *g* for 5 min at 4°C. The supernatant was collected and the protein concentration was determined using a DC protein assay kit (Bio-Rad, Hercules, CA, USA). Protein samples were separated by SDS-polyacrylamide gel electrophoresis, transferred to an Immobilon-P membrane (Merck KGaA, Darmstadt, Germany), and visualized using primary antibodies against HO-1 (Enzo Life Sciences, Farmingdale, NY, USA), HIF-1α (GeneTex, Irvine, CA, USA), or β-actin (Abcam, Cambridge, UK) and a secondary antibody, anti-rabbit IgG-horseradish peroxidase (Thermo Fisher Scientific).

2.4. Cell viability assay

Twenty-four hours after seeding in 96-well plates, KMY-J cells were treated with 12.5, 25, 37.5, 50, or 62.5 μM TS for 2 h in the presence or absence of 1 nM ECH at 37°C with 5% CO_2. Twenty-four hours after laser irradiation, cell viability was measured using a cell counting kit-8 assay (Dojindo, Kumamoto, Japan) as described previously [20]. Phase contrast imaging was performed using a DMi1 inverted microscopy (Leica Microsystems, Wetzlar, Germany).

2.5. Statistical analysis

All statistics were calculated using Excel software (Microsoft, Redmond, WA, USA) with the Statcel3 add-in (OMS, Tokyo, Japan). Data are expressed as the mean ± standard deviation (S.D.). The statistical significance of the data was determined using one-way ANOVA with the Bonferroni-Dunn *post-hoc* test or Student's *t*-test as appropriate. *P*-values of less than 0.05 were considered as statistically significant.

3. Results

3.1. TS-PDT induces HO-1 expression in KMY-J cells

HO-1 induction may contribute to a protective response against TS-PDT in rat malignant meningioma KMY-J cells [12]. First, the time

Table 1
Oligonucleotide primers used for real-time PCR.

Gene	Forward Primer(5′-3′)	Reverse Primer(5′-3′)	Product Size (bp)
B2m	GTCGTGCTTGCCATTCAGAA	GGGTGGAACTGAGACACGTA	107
Hmox1	TCTATCGTGCTCGCATGAAC	GAAGGCGGTCTTAGCCTCTT	80
Vegfa	AAAACACAGACTCGCGTTGC	TGGCTTGTCACATCTGCAAG	71

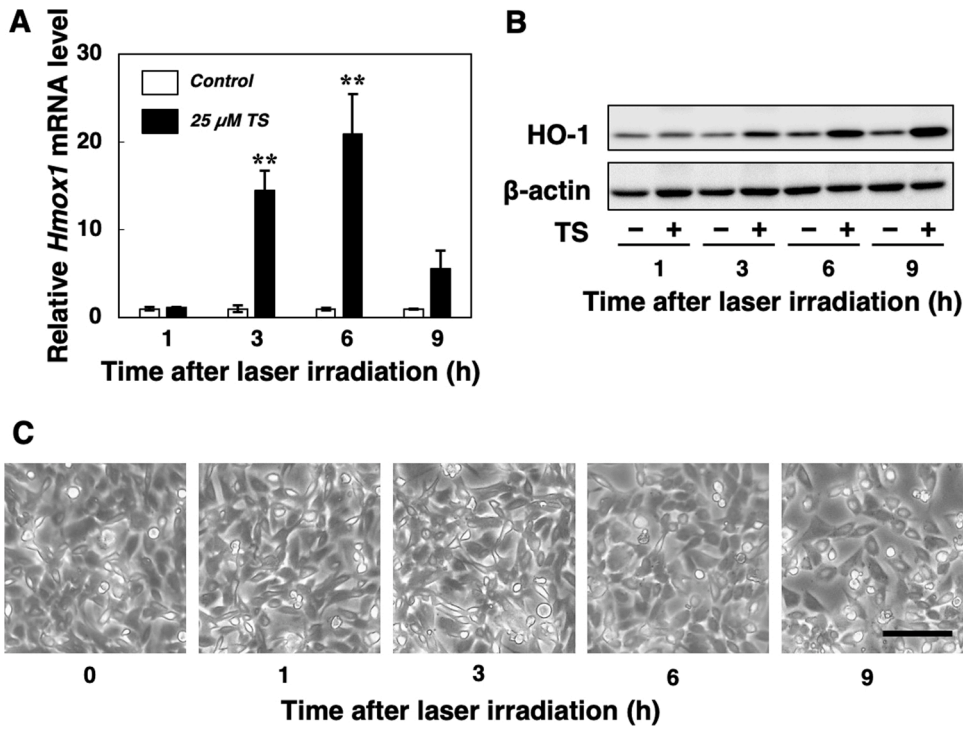

Fig. 1. TS-PDT induces HO-1 expression in KMY-J cells. KMY-J cells were incubated at 37℃ for 2 h in the presence or absence of 25 μM TS. The cells were subjected to laser irradiation and then incubated for 1, 3, 6, or 9 h. (A) *Hmox1* mRNA levels were measured by real-time RT-PCR. Data are represented as the mean ± S.D. (n = 3). Statistical significance compared with the corresponding control: $^{**}p <$ 0.01. (B) HO-1 protein levels were measured by western blot analysis. (C) Representative image of KMY-J cells subjected to TS-PDT at 0, 1, 3, 6 or 9 h after laser irradiation. Scale bar = 100 μm.

course of HO-1 expression in KMY-J cells after TS-PDT was examined using 25 μM TS (Fig. 1). After laser irradiation, *Hmox1* mRNA levels were increased significantly by 25 μM TS-PDT at 3 and 6 h (Fig. 1A). In accordance with the results, TS-PDT increased HO-1 protein levels in KMY-J cells after 3, 6, and 9 h of laser irradiation (Fig. 1B). Additionally, this time course experiment revealed morphological cell damage after 9 h of laser irradiation when cells were treated with 25 μM TS (Fig. 1C). These results suggest that TS-PDT induces HO-1 expression from 3 h after laser irradiation, when cell death has not yet occurred.

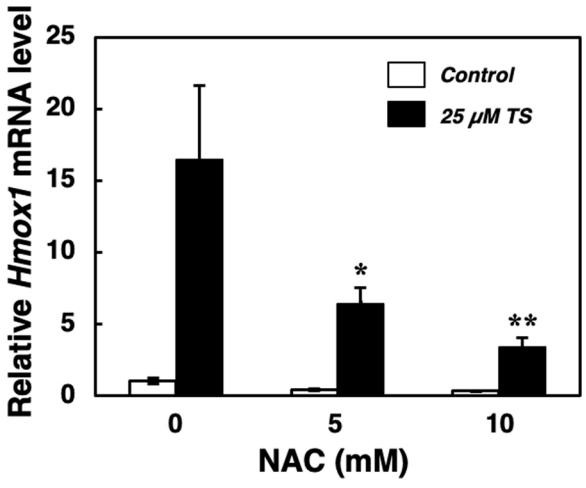

Fig. 2. Effect of *N*-acetylcysteine (NAC) on TS-PDT-induced expression of *Hmox1* mRNA in KMY-J cells. KMY-J cells were incubated at 37℃ for 2 h in the presence or absence of 25 μM TS with or without 5 or 10 mM NAC and then subjected to laser irradiation. After 6 h of incubation in the presence or absence of 5 or 10 mM NAC, *Hmox1* mRNA levels were measured by real-time RT-PCR. Data are represented as the mean ± S.D. (n = 3). Statistical significance compared with the corresponding "absence of NAC group": $^{*}p <$ 0.05 and $^{**}p <$ 0.01.

3.2. NAC inhibits Hmox1 mRNA expression in KMY-J cells

We next examined the effect of NAC, a ROS inhibitor, on TS-PDT-induced expression of *Hmox1* mRNA in KMY-J cells, because PDT exerts a cytotoxic effect in tumor cells through ROS production. As shown in Fig. 2, TS-PDT-induced expression of *Hmox1* mRNA was inhibited significantly by NAC treatment in a dose-dependent manner. This result indicates that ROS induced by TS-PDT is involved in the induction mechanism of HO-1 expression.

3.3. TS-PDT increases the HIF-1α protein level in KMY-J cells

ROS induces activation of the HIF-1 pathway [21] and several transcription factors induce HO-1 expression [22], including HIF-1α [23]. Fig. 3 shows the expression of HIF-1α protein in KMY-J cells after TS-PDT. TS-PDT increased the HIF-1α protein level after 1, 3, 6, and 9 h of laser irradiation, indicating that TS-PDT-induced upregulation of HIF-1α protein occurred before HO-1 protein expression in the cells.

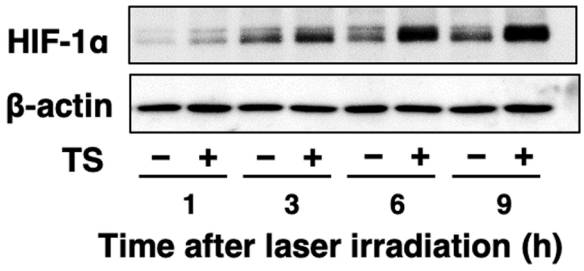

Fig. 3. TS-PDT increases the HIF-1α protein level in KMY-J cells. KMY-J cells were incubated at 37℃ for 2 h in the presence or absence of 25 μM TS and then subjected to laser irradiation. After 1, 3, 6, or 9 h of incubation, HIF-1α protein levels were measured by western blot analysis.

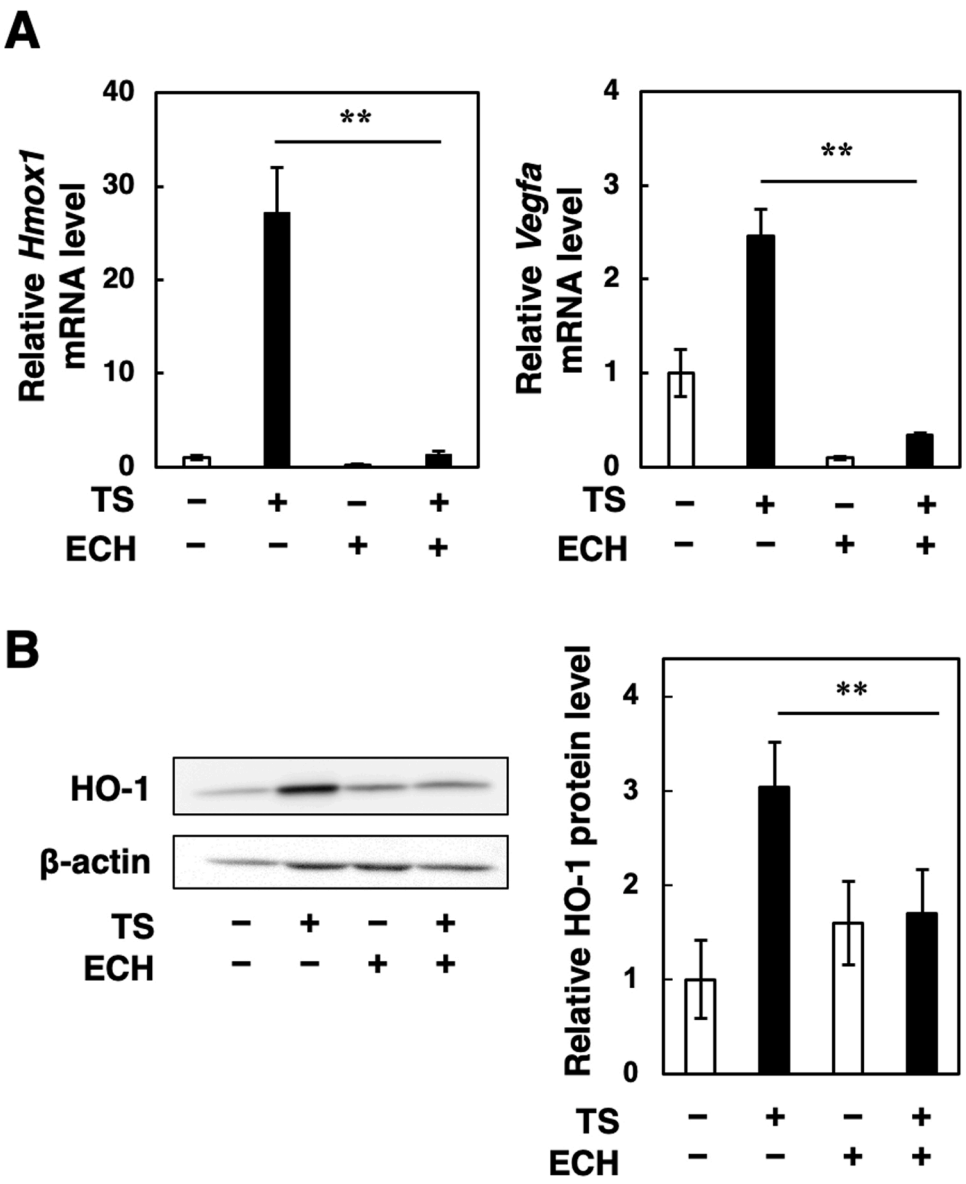

Fig. 4. Echinomycin (ECH) abolishes TS-PDT-induced HO-1 expression in KMY-J cells. KMY-J cells were incubated at 37°C for 2 h in the presence or absence of 25 μM TS with or without 1 nM ECH (and then subjected to laser irradiation. (A) After 6 h of incubation in the presence or absence of 1 nM ECH, *Hmox1* and *Vegfa* mRNA levels were measured by real-time RT-PCR. Data are represented as the mean ± S. D. (n = 3). Statistical significance compared with the corresponding "absence of ECH group": $^{**}p < 0.01$. (B) After 6 h of incubation in the presence or absence of ECH, HO-1 protein levels were measured by western blot analysis. Representative images are shown (left panel). β-Actin was used to normalize protein levels. Intensities are presented as the relative HO-1 protein level to 0 μM TS and 0 μM ECH (right panel). Data are represented as the mean ± S.D. (n=3). Statistical significance compared with the corresponding "absence of ECH group": $^{**}p < 0.01$.

3.4. ECH abolishes the TS-PDT-induced HO-1 expression in rat malignant meningioma KMY-J cells

To examine the involvement of the HIF-1 pathway in the induction of HO-1 expression, KMY-J cells were treated with TS in the presence of ECH, a HIF-1α inhibitor [18], and then subjected to laser irradiation, followed by determination of *Hmox1* mRNA and HO-1 protein levels. Fig. 4A and B shows that TS-PDT-induced expression of *Hmox1* mRNA and HO-1 protein was completely attenuated by ECH treatment. Additionally, the increase in the expression of *Vegfa* mRNA, a downstream gene of HIF-1α, by TS-PDT was significantly suppressed by ECH treatment. These results suggest that TS-PDT induces HO-1 expression *via* the HIF-1 pathway.

3.5. ECH treatment increases the susceptibility to TS-PDT-induced cytotoxicity in KMY-J cells

Fig. 5 shows the effect of ECH treatment on TS-PDT-induced cytotoxicity in KMY-J cells. KMY-J cells were treated with TS in the presence or absence of ECH and then the cells were subjected to laser irradiation. After 18 h of incubation, cell viability was decreased significantly by ECH treatment compared with 12.5 and 25 μM TS-PDT alone-treated groups.

4. Discussion

In this study, we aimed to elucidate the mechanism of the intracellular defense response to TS-PDT in brain tumor cells and the induction mechanism of HO-1 expression by TS-PDT in rat malignant meningioma KMY-J cells. As expected, TS-PDT rapidly activated the HIF-1 pathway and then induced HO-1 expression through ROS production in KMY-J cells. Because TS-PDT-induced HO-1 expression was induced before cell death (Fig. 1), it was unlikely that HO-1 expression induced by TS-PDT was the result of non-specific cell damage and probably one of the rapid protective responses of KMY-J cells against TS-PDT. Additionally, the HIF-1α inhibitor ECH increased susceptibility to TS-PDT-induced cytotoxicity in KMY-J cells (Fig. 5). We have previously shown that treatment with the HO-1 inhibitor ZnPPIX as well as ECH enhances the sensitivity of KMY-J cells to TS-PDT [12]. Therefore, the HIF-1α-HO-1 pathway may contribute to attenuation of the cytotoxic effect of TS-PDT in malignant meningioma KMY-J cells.

Similar results have been obtained in other tumor cells. In colon

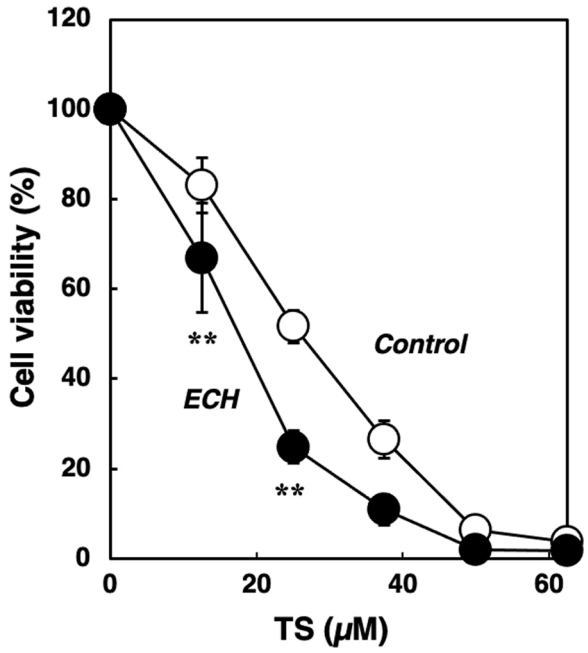

Fig. 5. Effect of echinomycin (ECH) treatment on TS-PDT-induced cytotoxicity in KMY-J cells. KMY-J cells were incubated at 37℃ for 2 h in the presence or absence of 12.5, 25, 37.5, 50, and 62.5 μM TS with or without 1 nM ECH and then subjected to laser irradiation. After 18 h of incubation, cell viability was measured by a cell counting kit-8 assay. Data are represented as the mean ± S. D. (n = 4). Statistical significance compared with the corresponding control: $^{**}p < 0.01$.

adenocarcinoma [24] and melanoma cells [25], HO-1 is involved in an important protective mechanism against PDT-mediated phototoxicity and downregulation of HO-1 may be an effective approach to potentiate the anti-tumor effectiveness of PDT. We also confirmed induction of HO-1 expression by TS-PDT in not only rat malignant meningioma KMY-J cells, but also human malignant meningioma HKBMM cells, human glioblastoma U251 cells, A172 cells, and T98 G cells (Fig. S1). Thus, induction of HO-1 expression may also play an important role in the protective response against TS-PDT in these HO-1-inducible brain tumor cell lines.

In general, stabilization of HIF-1α mRNA or protein, or both, is involved in activation of the HIF-1 pathway [26–28]. In the present study, TS-PDT immediately increased the HIF-1α protein level (Fig. 3), but did not increase the HIF-1α mRNA level (data not shown), suggesting that stabilization of HIF-1α protein was involved in activation of the HIF-1 pathway in KMY-J cells after TS-PDT. The levels of HIF-1α are regulated by degradation *via* the ubiquitin-proteasome pathway following hydroxylation of HIF-1α in its oxygen-dependent degradation domain by prolyl hydroxylase domain-containing protein (PHD) [29]. PHD enzymes are inactivated under reduced oxygen tension, leading to stabilization of HIF-1 protein [28,30]. Additionally, ROS inactivate PHD enzymes [21]. The present study showed that the TS-PDT-induced HO-1 expression was inhibited by NAC, a ROS inhibitor (Fig. 2). Therefore, it is possible that ROS produced by TS-PDT activates the HIF-1 pathway by reducing PDH enzyme activity, resulting in the induction of HO-1 expression in KMY-J cells. Furthermore, previous reports have demonstrated that HO-1 expression is also induced by other transcription factors such as Nrf2 [17,31], YY1 (yin yang 1) [32], and AP-1 (activator protein-1) [33]. Thus, it is possible that these transcription factors are also involved in the HO-1 expression in KMY-J cells subjected to TS-PDT. However, in our previous study, TS-PDT did not appear to induce activation of the Nrf2 pathway [12]. Additionally, the HO-1 expression was not induced by TS-PDT in the presence of HIF-1 inhibitor ECH (Fig. 4). These observations clearly indicate that the HIF-1 pathway is the major pathway for HO-1 expression in KMY-J cells subjected to TS-PDT. Lamberti et al. also demonstrated that resistance to PDT is in part mediated by activation of a ROS-ERK1/2-HIF-1 axis [34]. Further research is needed to elucidate the activation mechanisms of the HIF-1 pathway in TS-PDT-treated KMY-J cells.

HO-1 is a rate-limiting enzyme that catalyzes oxidative degradation of heme and releases carbon monoxide, iron, and biliverdin, the latter of which is reduced to bilirubin. The bilirubin produced from biliverdin is a highly potent antioxidant [35]. Thus, such an enhancement of antioxidant capacity through HO-1 production is thought to be a resistance factor against chemotherapy and radiation therapy [36,37]. Additionally, HO-1 has attracted attention as a target molecule for cancer treatment in recent years because it has been reported that HO-1 is involved in tumor formation [36,37]. Furthermore, therapeutic drugs targeting HIF-1 are being developed [36] because HIF-1 induces the expression of other genes involved in tumor malignancy, such as VEGF and glucose transporter [38,39]. Therefore, we believe that combining TS-PDT with HO-1 and/or HIF-1 targeting drugs may lead to the development of more effective treatments for malignant brain tumors.

5. Conclusion

Our results suggest that TS-PDT induces HO-1 protein expression *via* ROS production and then HIF-1 pathway activation in rat malignant meningioma KMY-J cells, and the HO-1 induction may contribute to attenuation of the therapeutic effect of TS-PDT.

Author contributions

T.T., S.M., S.S., and N.S. conducted the experiments. T.T., Y.S., Y.T., J.A., and Y.F. wrote the manuscript. T.T. and Y.F. conceptualized the study.

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Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pdpdt.2020.102009.

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