Original Article
ABCG2 regulated by MAPK pathways is associated with cancer progression in laryngeal squamous cell carcinoma

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Abstract: ATP-binding cassette, subfamily G, member 2 (ABCG2) overexpression has been associated with multidrug resistance and cancer progression by promoting proliferation and/or suppressing apoptosis, but how this process happens remains to be determined. In this study, the roles and the mechanisms of ABCG2 in the progression of Laryngeal squamous cell carcinoma (LSCC) were investigated. We found that introduction of ABCG2 siRNA into Hep-2 and Hep-2T cells significantly enhanced the intracellular accumulation of mitoxantrone (MX). Down-regulation of ABCG2 by transient RNAi inhibited cell proliferation and blocked cell cycle progression by regulating the expression of cyclin D3 and p21 Cip1. ABCG2 silence also induced cell apoptosis by regulating the expression of surviving, bcl-2 and the cleavage of poly (ADP-ribose) polymerase (PARP) in Hep-2 and Hep-2T cells. ABCG2-specific inhibitor, fumitremorgin C (FTC), and mitogen-activated protein kinase (MAPK) pathway inhibitor, U0126, inhibited cell proliferation and promoted cell apoptosis by degrading endogenous ABCG2 in Hep-2T cells. Furthermore, inhibition of MAPK pathway by U0126 enhanced anti-cancer effects of MX in vivo. In conclusion, suppression of ABCG2 inhibits the process of LSCC tumor growth by regulating cell proliferation and apoptosis. Our data also provide more evidence for the importance of the MAPK pathway as a suitable therapeutic target for LSCC.

Keywords: ABCG2, laryngeal squamous cell carcinoma, fumitremorgin C, MAPK pathway, mitoxantrone

Introduction

Laryngeal squamous cell carcinoma (LSCC), is the second most common malignancy in the head and neck region and the eleventh-most common cancer among men worldwide [1]. Except for the invasive and metastatic behaviors, resistance to chemotherapy has been a major obstacle to the effective management of laryngeal carcinoma. Among the many reasons for multidrug resistance, it has been reported that the family of ATP-binding cassette transporters plays a critical role [2].

ATP-binding cassette, subfamily G, member 2 (ABCG2), is a member of the ABC transporter family, which was first cloned from doxorubicin-resistant human MCF-7 breast cancer cells and was named breast cancer resistance protein (BCRP) [3]. Up to now, ABCG2 overexpression has been observed in many tumor types, including bladder cancer, lung, leukemias, and several squamous cell carcinomas [4-11], where it functions to pump a wide variety of endogenous and exogenous compounds out of cells [12-14]. Elevated expression of ABCG2 in vitro causes resistance to anticancer drugs, including topotecan, irinotecan, mitoxantrone (MX) and doxorubicin [3, 15]. Furthermore, ABCG2 was demonstrated to be associated with a molecular determinant of the side population phenotype, characteristics of which are reminiscent of stem cells [16, 17].

Recently, the effects of ABCG2 on apoptosis and proliferation have been a topic of debate. Based on a RNA interference approach, Chen et al. showed that the suppression of ABCG2 could significantly inhibit cancer cell proliferation [18]. ABCG2 is predictive for malignant pro-
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ABCG2 regulated by MAPK pathways and cancer progression is an independent prognostic factor in LSCC [9]. The mechanism of ABCG2 may contribute to chemotherapy resistance by promoting proliferation and/or suppressing apoptosis [9], but how this process happens remains to be determined. In our study, we demonstrated that the proliferation of cells expressing ABCG2 was significantly inhibited by ABCG2 gene-specific siRNA and the chemical inhibitor, fumitremorgin C (FTC). Suppression of ABCG2 led to G0/G1 cell cycle arrest associated with downregulation of cyclin D3 and up-regulation of p21. These data suggest that ABCG2 correlates with cell cycle progression, highlighting a novel, previously unrecognized role of ABCG2.

Activation of mitogen-activated protein kinase (MAPK) pathway down-regulated ABCG2 expression, suggesting that the expressions of ABCG2 genes were regulated through MAPK pathways in the human ALL cell lines [19]. In the contrary, dephosphorylation of MAPK pathway induces transcriptional upregulation and prompts protein degradation of endogenous ABCG2 in breast cancer MCF-7 cells [20]. MAPK inhibitors, U0126, also causes prompted degradation of exogenous ABCG2 and potentiates anticancer agents in MCF-7 and gastric cancer NCI-N87 cells [20]. Below, the results of our studies demonstrate that inhibition of the MAPK pathway is able to cause the degradation of endogenous ABCG2 and the MAPK pathway can be exploited for overcoming ABCG2-mediated multidrug resistance in LSCC.

Material and methods

Cell line and culture

The human laryngeal carcinoma cell line Hep-2 was obtained from the American Type Culture Collection (ATCC). These cells were grown as a monolayer in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% bovine calf serum at 37°C in a humidified atmosphere containing 5% CO₂. A Taxol resistant cell line (Hep-2T) was developed by continuous exposure of Hep-2 cells to stepwise escalating concentrations of Taxol (Bristol-Myers Squibb Company) for over 12 months.

RNA interference

Stealth siRNAs specific to human ABCG2 were designed by the program offered by Invitrogen. Stealth RNA is 25 bp blunt-end-dsRNA chemically modified to eliminate the nonspecific stress response of interferon and reduce off-target effects. A pool of 3 target-specific siRNAs was synthesized by Invitrogen (Stealth) with sequences of 5’-GCA GAC UUC UUC UUG GAC AUC AUU A-3’; 5’-UAU GAU GAC ACU CUG UAG UAU CCG C-3’ and 5’-GGG GAU ACA UCU A-3’, respectively. Scrambled siRNAs with similar guanine cytosine (GC) content were also purchased from Invitrogen and used as negative controls. We confirmed the specificity of these sequences in BLAST. Cell transfection with siRNA was conducted with Lipofectamine 2000 (Invitrogen) following the manufacturer’s protocols. The medium was completely exchanged after 12 hours of transfection.

Flow cytometric analysis

For accumulation assay, cells were cultured in 6-well culture plates and washed 2 times with phosphate buffered saline solution. MX (Sigma) was added to a final concentration of 10 μmol/L, and cells were incubated for 60 minutes at 37°C. Analysis and cell sorting were performed with a FACScan flow cytometer (BD Biosciences, Heidelberg, Germany). To analyze cell cycle profiles, samples made of 1 × 10⁶ cells were harvested, washed, and fixed in ice-cold 70% ethanol overnight. The DNA content and percentage of cells in different phases of the cell cycle were assayed by FACScan flow cytometer and quantified with Cell Quest software (BD Biosciences, Heidelberg, Germany).

MTT colorimetric assay

Cells were seeded in triplicate in 96-well plates (1 × 10³ cells/well) and grown under normal conditions for 24 hours. Then cells were transfected with ABCG2 siRNA or control siRNA. For the experiments conducted in the presence of pharmacological inhibitor of ABCG2, the cells were incubated with FTC at different concentrations. The viable cell numbers were estimated by MTT assay. Absorbance was measured at 570 nm with a spectrophotometer (ELISA reader, Dynatech MR 5000; Dynatech Laboratories, Chantilly, VA).

Apoptosis assay

Apoptosis was determined by flow cytometry analysis using annexin-V FITC and PI double staining assay in accordance with the manufacturer’s instructions (Jingmei, Shenzhen, China). Briefly, after treatment, both floating and tryp-
sinized adherent cells were harvested and resuspended at density of $1 \times 10^6$ cells/mL in 200 mL binding buffer containing 5 mL of annexin-V fluorescein isothiocyanate and 5 mL of PI, then incubated for 10 minutes in the dark at room temperature. Analysis was immediately performed using flow cytometer.

Western blot analysis

After treatment, cells were scraped off the plates and lysed in ice-cold RIPA buffer with protease inhibitor cocktail (Sigma). Protein concentration of the lysates was quantified by the Bradford protein assay (Pierce Rockford, IL). Equal amounts of protein (50 μg) were electrophoresed in 10% or 12% SDS-PAGE and transferred to PVDF membranes (Millipore, Bedford, MA). The membranes were blocked for 2 hours with 5% skim milk in TBS, and incubated with primary antibodies followed by incubation with corresponding secondary antibody. The Western blots were visualized using GE Healthcare ECL Western Blotting Analysis System and exposed to Kodak x-ray film. Expression of GAPDH served as a control for protein loading.

In vivo subcutaneous xenograft model

Animal experiments were performed and conducted in accordance to regulatory guidelines. Twenty three female athymic CD1 nude mice (Shanghai, China) were injected with RT112 SP and NSP sorted cells into the right flank subcutaneous tissue. Tumour growth was monitored by two dimensional measurement with electronic callipers with tumor volume calculated using the formula $a \times b/2$, where $a$ is the smallest measurement and $b$ the largest. The mice experiments were terminated when tumors grew to a maximum of 750 mm$^3$. The tumors were removed and halved for immunohistochemical studies and Western blot analysis.

Statistical analysis

All data are presented as mean ± standard deviation (SD) of at least 3 independent experiments. Analysis of variance with a subsequent Bonferroni/Dunnett test was used to determine the significance of differences in multiple comparisons. A probability value $< 0.05$ was considered statistically significant.
Results

Functional knock-down of ABCG2 by gene specific siRNA

To study the cellular role of ABCG2, we performed gene silencing by gene-targeted siRNA method. As shown in Figure 1A and 1B, ABCG2 mRNA and protein expression in Hep-2 and Hep-2T cells were strongly decreased by 85% and 90%, respectively, with densitometric analysis. ABCG2 reduction persisted from 2 days to 4 days after transfection. Moreover, the expression level of ABCG2 in Hep-2T was much higher than that in Hep-2.

Next, we examined whether ABCG2 siRNA can result in the functional knock-down of ABCG2.

Accumulation assays were performed 3 days after siRNA transfection. It was found that the introduction of ABCG2 siRNA into Hep-2 and Hep-2T cells significantly enhanced the intracellular accumulation of MX (Figure 1C). These data indicate that both expression and function of ABCG2 are markedly suppressed by genespecific siRNA.

Down-regulation of ABCG2 by transient RNAi inhibited cell proliferation and blocked cell cycle progression

The effect of ABCG2 knockdown on cell proliferation were assayed by MTT colorimetric assay. Cells were seeded in 96-well plates overnight and then treated with either ABCG2 or scrambled siRNA. As shown in Figure 2A, treat-

Figure 2. Down-regulation of ABCG2 by transient RNAi inhibited cell proliferation and blocked cell cycle progression. Hep-2 and Hep-2T cells were treated with either scrambled siRNA or ABCG2 siRNA and then harvested at 3 days. A. Cell proliferation was determined with MTT colorimetric assay at indicated times. B. Cells cycles were analyzed by flow cytometry. Results are representative of three experiments. The bars represent the mean ± SD of triplicate determinations. *P < 0.05, **P < 0.01 and ***P < 0.001 versus scrambled siRNA-treated cells.
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Western blot analysis demonstrated that silencing of ABCG2 gene resulted in pronounced increase in p21 Cip1 levels, and down-regulation of cyclin D3 in Hep-2 and Hep-2T cells (Figure 3). In these cell lines, no significant change was found for other cell cycle-related proteins, such as cyclin D1 and p27 Kip1. These data suggest that ABCG2 participates in the G1 to S transition by regulating the expression of cyclin D3 and p21 Cip1.

**Down-regulation of ABCG2 by transient RNAi led to cell apoptosis**

To detect the role of ABCG2 in the survival of multidrug resistant cell lines, apoptosis induction after ABCG2 or scrambled siRNA transfection was analyzed by flow cytometry analysis. ABCG2 siRNA transfection significantly enhanced the apoptosis of Hep-2 and Hep-2T cells, comparing with the equivalent transfection with scrambled siRNA (Figure 4A). Poly (ADP-ribose) polymerase (PARP) cleavage as a key event of apoptosis and survivin, bcl-2 as markers for blocking apoptosis and regulating cell division, were conducted by Western blot analysis. The result indicated that ABCG2 siRNA transfection could inhibit the expression of surviving and bcl-2 and induce the cleavage of PARP in Hep-2 and Hep-2T cells (Figure 4B).

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**Table:**

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**Figure 3.** Down-regulation of ABCG2 by transient RNAi modulated cell cycle-related genes expression. Hep-2 and Hep-2T cells were treated with either scrambled siRNA or ABCG2 siRNA and then harvested at 3 days. Representative bands of cyclin D1, cyclin D3, p21 Cip1 and p27 Kip1 proteins.

We performed the cell cycle analysis on cells transfected with siRNA against ABCG2. At 3 days after transfection, cells were harvested and analyzed by flow cytometry. As shown in Figure 2B, enhanced G0/G1 ratio and reduced S-phase entry were observed in ABCG2 siRNA treated Hep-2 and Hep-2T cells. The percentage of cells in G0/G1 phase was dramatically increased by ABCG2 siRNA treatment compared to scrambled siRNA treatment.

**Down-regulation of ABCG2 by transient RNAi modulated cell cycle-related genes expression**

To gain insight into the molecular mechanism underlying the ABCG2-mediated G1 accumulation in the tumor cells, we examined the expression levels of cell-cycle regulatory proteins. 

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**Figure 3.** Down-regulation of ABCG2 by transient RNAi modulated cell cycle-related genes expression. Hep-2 and Hep-2T cells were treated with either scrambled siRNA or ABCG2 siRNA and then harvested at 3 days. Representative bands of cyclin D1, cyclin D3, p21 Cip1 and p27 Kip1 proteins.
Thus, ABCG2 silence induced the apoptosis of Hep-2 and Hep-2T cells by regulating the expression of apoptosis-related protein.

**Inhibition of MAPK pathway down-regulated ABCG2 expression level and increased MX accumulation**

To examine whether ABCG2 was down-regulated by inhibition of MAPK pathway, the ABCG2 protein expression levels were determined by Western blot analysis. The known ABCG2 inhibitor, FTC, was used as a positive control. As shown in **Figure 5A** and **5B**, 10 μM FTC treatment for 48 hours significantly down-regulated ABCG2 expression in Hep-2T cells, but did not affect the expression levels of P-p38 and P-ERK in Hep-2T cells. Interestingly, an inhibitor of MAPK pathway U0126 treatment for 48 hours suppressed ABCG2 protein expression, as well as P-p38 and P-ERK expression, in Hep-2T cells (**Figure 5A** and **5B**), indicating that is regulated by MAPK pathway. Furthermore, FTC and U0126 treatment significantly increased MX accumulation in Hep-2T cells by 4.6 and 3.2 times, respectively (**Figure 5C**).

**Suppression of ABCG2 function by FTC and U0126 inhibited cell proliferation and induced cell apoptosis**

The effects of U0126 on the ABCG2 protein level and on the accumulation of MX suggested that MAPK inaction might be able to sensitize the Hep-2T cells to MX. We thus further assessed the efficacy of MAPK signaling inhibitors in combination with MX. As shown in **Figure 6A-C**, FTC treatment synergistically enhanced the effect of MX on cell proliferation, cell apoptosis and cell viability in Hep-2T cells. U0126 enhanced G0/G1 ratio and reduced S-phase entry in MX treated Hep-2T cells (**Figure 6A**).
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**Figure 5.** Inhibition of MAPK pathway down-regulated ABCG2 expression and increased MX accumulation. Hep-2T cells were treated with either FTC or U0126 in complete medium for 48 hours. A. Represent bands of ABCG2 protein in Hep-2T cells after FTC or U0126 treatment. B. Represent bands of P-p38, p38, P-ERK and ERK proteins in Hep-2T cells after FTC or U0126 treatment. Cells were incubated with MX (10 μmol/L) in complete medium for 60 minutes at 37 °C. C. Cellular content of MX was measured by flow cytometry. Results are representative of three experiments. The bars represent the mean ± SD of triplicate determinations. **P < 0.01 and ***P < 0.001 versus scrambled siRNA-treated cells.

Compared with the control cells (0.1% DMSO and MX), there were significantly more apoptotic cells in U0126 treatment group (U0126 and MX) in Hep-2T cells (Figure 6B). The MTT assay demonstrated that the inhibitory effect of MX on Hep-2T cell viability was enhanced after combination treatment with U0126 for 48 hours (Figure 6C). Western blot analysis revealed that U0126, as well as FTC, modulate cell cycle-related and apoptosis-related proteins expression by decreasing cyclin D3, surviving and bcl-2, but increasing p21 Cip1 and
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Figure 6. Suppression of ABCG2 function by FTC and U0126 inhibited cell proliferation and induced cell apoptosis. Hep-2T cells were treated with either FTC or U0126 in complete medium for 48 hours. A. Cell cycles were analyzed by flow cytometry. B. Cell apoptosis was determined by flow cytometry analysis. C. Cell proliferation was analyzed using MTT colorimetric assay. Data represent 3 different experiments. Values are expressed as percentage of DMSO-treated cells, and each bar represents the mean ± SD of triplicate determinations. **P < 0.01 and ***P < 0.001 versus DMSO-treated cells. D. Represent bands of cyclin D3, p21 Cip1, surviving, bcl-2 and the cleavage of PARP proteins in Hep-2T cells.

the cleavage of PARP (Figure 6D). These data indicate that inhibition of ABCG2 expression by suppressing MAPK pathway could increase the resistance of Hep-2T cells to MX.

Inhibition of MAPK pathway by U0126 enhanced anti-cancer effects of MX in vivo

To investigate the role of ABCG2 in Hep-2 and Hep-2T cells to form viable tumors in vivo, sorted cells from each sub-population were separately injected subcutaneously into CD1 nude mice and the implant sites monitored for growth. Rapid tumour growth was observed in animals following implantation of Hep-2 and Hep-2T cells respectively, while either Hep-2 or Hep-2T cells with ABCG2 siRNA transfection did not form viable tumors in CD1 nude mice (Figure 7A). U0126, as well as FTC, enhanced the suppression of MX on Hep-2T cell tumor
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growth from 14 days (Figure 7B). Western blot and immunohistochemical analysis of ABCG2 expression in tumors showed that decreased expression in ABCG2 was observed both in U0126 and FTC treatment mice (Figure 7C and 7D).

Discussion

The effective chemotherapy is severely limited by multidrug resistance for patients who suffer from malignant tumors, including metastatic colorectal cancers. ABCG2 is an efflux transporter conferring multidrug resistance on cancer cells [3, 15]. It has been reported that ABCG2 is widely present in untreated LSCC cells, raising the possibility that ABCG2 may be a simple independent unfavorable prognostic factor for LSCC, and may be a clinically relevant mechanism of anticancer drug resistance [8]. In the present study, we found that ABCG2 was involved in the development of LSCC by promoting cell proliferation and suppressing cell apoptosis. Inhibition of the MAPK pathway is able to down-regulate ABCG2 and the MAPK pathway could be exploited for overcoming ABCG2-mediated multidrug resistance in LSCC.

To better elucidate the molecular mechanisms involved in ABCG2-mediated cell proliferation, Hep-2 and Hep-2T cells were used as 2 independent cell models. Study has revealed that expression of ABCG2 varied in the two types of LSCC cell lines [8]. Hep-2 is a MX-selected, mul-
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tidrug-resistant laryngeal carcinoma cell line with moderate expression of ABC2G2. This cell line exhibits a strong SP phenotype and is considered the source of endogenous ABC2G2 expression. Hep-2T, a taxol-resistant cell line, overexpresses ABC2G2 compared with parental Hep-2 cells and is regarded as the source of induced ABC2G2 expression [8, 9]. The expression of ABC2G2 in Hep-2 and Hep-2T is significantly correlated with the function and sensitivity to MX [8]. Our results showed suppression of ABC2G2 in both cell lines enhanced MX accumulation, suggesting that they are suitable cell models. We found that ABC2G2 gene-specific siRNA inhibited the proliferation of Hep-2 and Hep-2T. Suppression of ABC2G2 led to G0/G1 cell cycle arrest associated with downregulation of cyclin D3 and up-regulation of p21. These results are consistent with the previous study in breast cancer cell lines [18]. In addition, ABC2G2 gene-specific siRNA promoted cell apoptosis in these cell lines, in which downregulation of survivin and bcl-2, as well as increased PARP cleavage were involved. We also found ABC2G2 gene-specific siRNA inhibited rapid tumour growth of Hep-2 and Hep-2T cells in vivo. It was worthy to note that the effects of ABC2G2 inhibition on cell proliferation and apoptosis were stronger in Hep-2T than Hep-2 cells, which may be due to the higher expression of multidrug resistance associated proteins and P-glycoprotein (P-gp) in Hep-2T cells. P-gp may have an effect on chemotherapy resistance and progression of LSCC through promoting proliferation and/or suppressing apoptosis [21]. These results directly demonstrated that ABC2G2 correlates with the development in LSCC.

FTC, a specific ABC2G2 inhibitor, restored the sensitivity of multidrug resistant cells to MX by regulating the efflux of this compound [22]. It has been demonstrated that FTC inhibited the proliferation of breast and lung cancer cell lines by suppressing ABC2G2 expression [18]. As expected, FTC inhibited the proliferation and promoted cell apoptosis of these cell lines by moderating the cell cycle and apoptosis-related genes expression. The results of the drug accumulation studies showed that FTC strongly enhanced the intracellular accumulation of MX in the ABC2G2-overexpressing Hep-2T cells. In vivo study revealed that FTC enhances the anticancer effect of MX in CD1 nude mice with Hep-2T cell tumor. These results provided another evidence for that ABC2G2 regulates tumor growth in LSCC by promoting cell proliferation and suppressing cell apoptosis.

It has demonstrated that ABC2G2 expression in human trophoblasts, BeWo, and MCF7 cells was diminished by inhibitors of MEK, thereby were associated with increased the accumulation of MX [23]. MEK inhibition has also been shown to down-regulate ABC2G2 expression by promoting its degradation and downregulating a cisplatin-induced SP [20]. Similarly to observations reported in colon and breast cancer cells [20, 24], we found inhibition of the MAPK/ERK signaling pathway by MEK1/2-specific inhibitor U0126 to reduce ABC2G2 expression and increase MX accumulation in Hep-2T cells. U0126 was also found to inhibit cell proliferation and induce cell apoptosis in this cell line by regulating the cell cycle and apoptosis-related genes expression including cyclin D3, p21 Cip1, surviving and bcl-2, as well as increased PARP cleavage. Furthermore, inhibited MAPK/ERK pathway and decreased ABC2G2 expression by U0126 were detected in CD1 nude mice with Hep-2T cell tumor, leading to the enhanced anti-tumor effect of MX in vivo. These in vitro and in vivo effects of U0126 are comparable with that of FTC. These results further support our hypothesis that inhibition of MAPK/ERK pathway could also regulate cancer cell growth mediated by ABC2G2 reduction. Our data therefore goes some way to support the MAPK pathway being central to maintenance of SP phenotype and potentially highlights strategies to usefully modulate LSCC; this approach being already a focus of preclinical and clinical studies for a number of malignancies [25-27]. There are encouraging results from clinical trials with MEK inhibitors [28].

In conclusion, we confirm that suppression of ABC2G2 inhibits LSCC tumor growth by regulating cell proliferation and apoptosis. Our data also provide evidence for the importance of the MAPK pathway as a suitable therapeutic target for LSCC.

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Disclosure of conflict of interest

None.

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