Drug resistance of bladder cancer cells through activation of ABCG2 by FOXM1

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Recurrence is a serious problem in patients with bladder cancer. The hypothesis for recurrence was that the proliferation of drug-resistant cells was reported, and this study focused on drug resistance due to drug efflux. Previous studies have identified FOXM1 as the key gene for recurrence. We found that FOXM1 inhibition decreased drug efflux activity and increased sensitivity to Doxorubicin. Therefore, we examined whether the expression of ABC transporter gene related to drug efflux is regulated by FOXM1. As a result, ABCG2, one of the genes involved in drug efflux, has been identified as a new target for FOXM1. We also demonstrated direct transcriptional regulation of ABCG2 by FOXM1 using ChIP assay. Consequently, in the presence of the drug, FOXM1 is proposed to directly activate ABCG2 to increase the drug efflux activation and drug resistance, thereby involving chemoresistance of bladder cancer cells. Therefore, we suggest that FOXM1 and ABCG2 may be useful targets and important parameters in the treatment of bladder cancer. [BMB Reports 2018; 51(2): 98-103]

INTRODUCTION

Bladder cancer (BC) is the sixth common cancer in men worldwide (1), with more than 70% of patients diagnosed with non-muscle invasive bladder cancer (NMIBC) (2). Frequent recurrence in NMIBC patients is a serious problem and NMIBC patients are stratified into three risk groups (low, intermediate, high) (3). NMIBC patients considered high risk for recurrence are usually treated with transurethral resection, bacillus Calmette-Guérin (BCG) immunotherapy and chemotherapy [e.g. doxorubicin (DOX) and mitomycin C (4, 5)]. However, NMIBC recurs in more than 50% of patients within 2 years and 10-30% of recurrence patients progress to muscle invasive bladder cancer (MIBC) (6). Therefore, new strategies for treatment and diagnosis of recurrence are needed to address frequent recurrence.

The mechanism of recurrence is not yet clear, but the current hypothesis suggests that small populations of cells reside in cancerous tissue, survive chemotherapy and form tumors again through proliferation (7). This hypothesis is partially similar to cancer stem cell theory in terms of drug resistance (8). Anticancer drug resistance mechanisms are reported to be caused by an increase in the DNA repair, anti-apoptosis and efflux (9). We have previously shown that the expression of ABCG2 increased when BC cell lines overexpressing E2F1, EZH2 or SUZ12 were treated with mitomycin C (10). E2F1 is known to regulate the expression of FOXM1 and ABCG2 (11, 12), respectively, but the correlation between FOXM1 and ABCG2 has not been known until now.

Forkhead box M1 (FOXM1) is a key factor in progression of the G2/M cell cycle in normal cells (13). Recent studies have demonstrated FOXM1 as abnormally overexpressed in many types of cancers (14, 15) and is known to associated with proliferation, DNA repair, apoptosis (16), metastasis, recurrence and resistance to various anticancer drugs (11, 15). FOXM1 expression has been reported to have unfavorable clinical response to chemotherapy for patients with breast cancer (17). Interestingly, recent studies have reported that increased expression of FOXM1 provokes cancer cells to transform into cancer stem cells (18).

Drug efflux is one of the causes of drug resistance (19). In the ABC transporter family, ABCB1, ABCC1 and ABCG2 have been reported as major genes related to drug resistance (20). In
particular, ATP-binding cassette sub-family G member 2 (ABCG2) is a major cancer stem cell marker (21). In general, ABCG2 is expressed in certain tissues such as the placenta, mammary gland and testis (22), but exhibits abnormal expression in various cancer, cancer stem cells and drug-resistant cells (23). Recent studies have shown that ABCG2 can protect cancer stem cells by efflux of anticancer drugs such as DOX, mitoxantrone and topotecan (24). Abnormal expression of ABCG2 has also been reported to be associated with recurrence of a variety of cancers such as colorectal, lung and prostate cancer (25, 26). Despite these findings, the transcriptional regulation of ABCG2 has not yet been fully understood.

In this study, we focused on the mechanism of drug resistance by drug efflux pathways to identify the mechanism of recurrence. Therefore, we investigated the correlation between FOXM1, a recurrent factor identified in previous studies, and the ABCG2 gene associated with drug efflux. We found that FOXM1 binds directly to the ABCG2 promoter and regulates ABCG2 transcription, thereby revealing new regulatory pathways that influence drug efflux. Based on these findings, we propose a treatment strategy for BC recurrence by inhibiting FOXM1, which could reduce the drug resistance.

RESULTS

Inhibition of FOXM1 expression reduces DOX resistance and drug efflux

Acquisition of resistance to anticancer agents has been reported to be related to recurrence (9). In our previous study, we suggested FOXM1 as a major gene for recurrence and investigated whether this gene correlates with drug excretion (14).

First, we investigated the effects of FOXM1 on drug sensitivity and efflux (Fig. 1A) and clonogenic assays (Fig. 1B) were used to measure cell viability and proliferative activity. Overexpression or knockdown of FOXM1 showed a significant increase and decrease in cell viability in both the untreated and 0.5 μM DOX-treated conditions (Fig. 1A). Similar results were also obtained in clonogenic assays (Fig. 1B). These results suggest that FOXM1 plays an important role in resistance to DOX in BC cells.

We then used a side population (SP) assay to measure drug efflux capacity to verify whether FOXM1 can affect drug efflux. KU7 cells were transiently transfected with scRNA and siFOXM1 to investigate efflux activity. The effluent efficiency of the Hoechst 33342 dye is shown in the lower left quadrant of the FACS profile in Fig. 1C, labeled SP. The distribution of SP cells in the control cells was 1.45%, but it was reduced to 0.52% in the drug efflux inhibitor verapamil-treated cells. Similarly, the distribution of SP cells in siFOX1 treated cells was reduced to 0.62%, half the level of the control, indicating decreased drug efflux activity due to FOXM1 deficiency (Fig. 1C).

We also examined the effect of FOXM1 levels on the rate of apoptosis induced by DOX-treatment. There was no difference in apoptotic rate between scRNA-transfected KU7 cells and siFOX1-transfected KU7 cells when the drug was not treated. In contrast, treatment with 0.5 μM DOX resulted in an apoptosis rate of 13.4% in cells transfected with scRNA, but increased significantly in siFOX1-transfected cells by 23% (Fig. 1D). This increase in apoptosis by DOX treatment was also observed in 5637 cells (Fig. 1D).

FOXM1 regulates the expression of ABCG2 in BC cells

Drug efflux is known to be regulated by ABC transporter family (20). Previous our studies have shown that the ABCG2 is increased by anticancer drug treatment in BC cells (10). Therefore, we confirmed whether the decrease of drug efflux activity by inhibition of FOXM1 is due to the regulation of ABC transporter expression by FOXM1. To investigate whether FOXM1 regulates the ABC transporter family, KU7 cells were treated with scRNA or siFOX1 to compare the transcription amount of the ABC transporter family according to the expression of FOXM1 (Fig. S1A). When FOXM1 was depleted, the level of ABCG2 transcription among the ABC transporter family was significantly reduced (Fig. S1A). Thus, we examined the mRNA and protein levels of FOXM1 and ABCG2 in BC cell lines and found that FOXM1 and ABCG2
we are highly expressed in KU7 cells and poorly expressed in 5637 cells (Fig. S1B and S1C). We also examined cell viability for DOX in BC cell lines and selected KU7 cell lines with relatively high viability and 5637 with a low survival rate in subsequent experiments (Fig. S1D).

At first, the effect of FOXM1 overexpression on mRNA and protein levels of ABCG2 was examined using KU7 and 5637 cells (Fig. 2A and 2B). We also investigated the effect of depleted FOXM1 on ABCG2 levels (Fig. 2C and 2D). The ABCG2 mRNA and protein were significantly increased by overexpression of FOXM1 (Fig. 2A and 2B), whereas the knockdown of FOXM1 significantly decreased the ABCG2 expression compared to the control (Fig. 2C and 2D). These results indicate that ABCG2 expression in these two cell lines are regulated by FOXM1.

**FOXM1 binds directly to the ABCG2 promoter to regulate expression**

We investigated whether FOXM1 binds to the ABCG2 promoter and regulates transcription. We found three putative FOXM1 binding sites (I, II and III) in the ABCG2 promoter (Fig. 3A). To examine whether FOXM1 regulates transcription of ABCG2, we used a promoter vector to drive a luciferase reporter gene in transient co-transfections with an expression vector in BC cells (Fig. 3B). The transcriptional activity of the ABCG2 promoter was significantly increased in FOXM1-overexpressed BC cells. FOXM1 binds directly to the ABCG2 promoter to regulate transcription.

**Fig. 2.** FOXM1 regulates ABCG2 expression in BC cells. pcDNA and pFOX1 were transfected into KU7 (A) and 5637 cells (B). scramble RNA (scRNA) and siFOXM1 were transfected into KU7 (C) and 5637 cells (D). After 24 h, mRNA and protein levels were analyzed using qRT-PCR (left panel) and Western blotting (right panel).

**Fig. 3.** FOXM1 binds directly to the ABCG2 promoter to regulate transcription. (A) Schematic diagram of ABCG2 promoter vector (ABCG2P). The ABCG2 promoter (+2106/+22) was inserted into the pGL3 basic vector and the three putative FOXM1 binding sites (−1946/−1934, −1070/−1059 and −279/−268) are represented. The black bars on the promoter region indicate the positions of the primers (I: −2098/−1903, II: −1144/−1027, III: −326/−198 and non-target site (NTS): −1489/−1388) for qChIP amplification. (B) BC cells were transformed with pGL3-basic, ABCG2P or ABCG2P+pFOX1, respectively. (C) BC cells were transformed with pGL3-basic, ABCG2P or ABCG2P+siFOXM1, respectively. Transcriptional activity was measured by luciferase assay. (D) ChIP assay in the ABCG2 promoter. 5637 cells were transfected with pcDNA or pFOX1+V5 tag vector. Immunoprecipitation was performed using rabbit IgG (control), FOXM1 and V5 antibody. The chromatin fragments were amplified using primers for the three putative FOXM1 binding sites (loci I, II, III) and NTS primers shown in (A).
induced cells (Fig. 3B). Conversely, cells were co-transfected with a promoter vector and siRNA to determine whether reduced FOXM1 affects the transcription of the ABCG2 promoter (Fig. 3C). Similarly, ABCG2 transcriptional activity was significantly decreased in FOXM1-depleted cells, indicating that FOXM1 affects the expression of ABCG2 (Fig. 3C). To determine whether the effect shown above is due to direct binding of the FOXM1 to the ABCG2 promoter, a ChIP assay was performed (Fig. 3D). As a result, when the locus I region was used, the PCR fragment was significantly amplified in pFOX-M1-transfected cells (Fig. 3D). When the locus II, III and non-target site (NTS) loci were used, there were no differences between the two different transfected cells (Fig. 3D). These results show that FOXM1 can directly bind to the locus I region of the ABCG2 promoter to regulate ABCG2 transcription.

To investigate whether ABCG2 expression in DOX-treated cells is regulated by FOXM1, cells transfected with over-expressed vector (pFOX-M1) or siRNA for FOXM1 (siFOX-M1) were treated with DOX and the expression of ABCG2 were compared. mRNA (Fig. 4A) and protein levels (Fig. 4B and 4C) of FOXM1 and ABCG2 were significantly accelerated by DOX treatment. These ABCG2 and FOXM1 expressions by DOX treatment were additionally induced in pFOX-M1 cells, then significantly reduced in siFOX-M1 transfected cells. As a result, expression of FOXM1 and ABCG2 is induced in DOX-treated conditions, indicating that FOXM1 regulates the expression of ABCG2.

DISCUSSION

About 70% of BC patients diagnosed with BC have NMIBC and the survival rate is better than for MIBC (27). Nonetheless, about 50% of NMIBC patients have frequent recurrences and the treatment is difficult and costly (6). Therefore, if biomarkers are found that can predict the recurrence of BC to prevent these problems, accurate diagnosis and effective treatment will be possible.

Drug resistance mechanisms have been reported to be due to increased efflux activity of anticancer agents associated with the ABC transporter family (14, 15). There have been many studies on the drug efflux process of ABCG2, but studies on transcriptional regulation have yet to be revealed except for factors such as SP1, c-Myc and Hif-1α (28). Therefore, we investigated the relationship between FOXM1 and the drug efflux pathway which inhibits chemotherapy and recurrence. In this study, it was confirmed that FOXM1 directly binds to the ABCG2 promoter to regulate the transcription of ABCG2, and drug resistance is caused by the drug efflux activity of FOXM1–ABCG2. These results suggest that reducing the expression of FOXM1 in NMIBC patients may provide effective results in chemotherapy. Furthermore, since SP analysis is used to measure the population of cancer stem cells, it may be suggested that the abnormal expression of FOXM1 is also linked to the increase of cancer stem cells (29).

Recent studies have reported that ABCG2 is associated with drug release and cancer recurrence in breast cancer (30), but analysis of the gene expression profiles of the patients used in this study showed no correlation between FOXM1 and ABCG2 expression (data not shown). These results suggest that the expression of ABCG2, a marker of cancer stem cells, is not highly induced in cancer tissues before anticancer therapy, but when treated with an anticancer agent, FOXM1 is induced and leads to an increase in ABCG2. In other words, considering that cancer stem cells survive treatment with a chemotherapeutic agent and increase in number, it is thought that the function of cancer stem cells may be related to the drug release of FOXM1–ABCG2.

In summary, in drug-treated cells, FOXM1 directly regulates the transcription of ABCG2 and acts on drug efflux and drug resistance. These results may give important implications for the hypothesis of the relationship between FOXM1 and cancer stem cells (29). In addition, FOXM1 could affect cancer cell proliferation and survival by treatment with anticancer drugs. Based on these results, we propose that FOXM1 modulates drug resistance and can be used as a predictor of BC recurrence and target gene therapy.
MATERIALS AND METHODS

Cell culture and chemotherapeutic agent

BC cell lines KU7, EJ, T24 and 5637 were purchased from the American Type Culture Collection (ATCC). Cells from ATCC were certified by results of short tandem repeat (STR) DNA profiling, cytochrome C oxidase I and mycoplasma contamination assays.

T24, EJ and KU7 cells were grown in DMEM (HyClone) supplemented with 10% FBS (HyClone) and 1% penicillin/streptomycin (Gibco). 5637 cells were maintained in RPMI 1640 medium (HyClone) supplemented with 10% FBS and 1% penicillin/streptomycin. DOX (Sigma) was dissolved in sterile water.

Plasmids, small interfering RNA and transfection

pcDNA6-V5-His was purchased from Invitrogen. pFOXM1 was provided by Dr. Ju-Seog Lee (MD Anderson Cancer Center). To generate the pFOXM1-V5 tag, the coding sequence (CDS) region from −2105 to +22 was cloned by PCR from human genomic DNA using the indicated primer sets (Table S1). Scrambled RNA (scRNA) was purchased from Shanghai GenePharma (Shanghai GenePharma). siFOX1 was synthesized from ST Pharm Oligo center (ST Pharm). Transfection was carried out according to the manufacturer’s protocol (Jetprime).

qRT-PCR

cDNA synthesis and qPCR analysis used a PrimeScript RT reagent kit and SYBR Premix Ex Taq II Tli RNaseH Plus (TaKaRa) according to the manufacturer’s protocol. mRNA of FOXM1, ABCG2 and β-actin was detected using the indicated primer sets (Table S2). The experiment was performed using the CFX384™ Optics Module (Bio-Rad), and the data analyzed using CFX Manager™ (Bio-Rad).

Western blotting

Western blotting was performed as described previously (10). The following antibodies were used: anti-FOXM1 (Bethyl), anti-ABCG2 (Abcam) and anti-β-actin (Cell Signaling).

Luciferase assay

A luciferase assay was performed as described previously (10). The plasmid DNA used was pGL3-basic, pGL3-basic-ABCG2 promoter, pcDNA6, pFOXM1 and pRL Renilla luciferase control reporter vector (Promega).

Chromatin immunoprecipitation (ChIP) assay

A ChIP assay was performed as described previously (31). The following antibodies were used: anti-v5, anti-FOXM1 and normal rabbit immunoglobulin G (IgG) antibody (Cats. A190-120A, A301-532A and A120-101P, Bethyl Lab). The indicated qChIP primer sets were used to amplify the precipitated DNA fragments (Table S2).

Flow cytometry apoptosis assay

Cells were incubated with Muse™ Annexin V & Dead Cell Reagent (Millipore) for 20 min at RT in the dark. Apoptotic and necrotic cell analysis was performed using a Muse™ Annexin V & Dead Cell Kit (Millipore) and Muse™ Cell Analyzer (Millipore).

Cell viability assay

A methyl thiazolyl tetrazolium (Sigma) assay was performed as described previously (10). Cell reproductive ability was detected by clonogenic assay. siRNA transfected cells were seeded at 5 × 10^4 cells/well in a six-well plate and incubated for 24 h. The cells cultured were treated with 0.5 μM DOX for 24 h. After 10 days, formed colonies were stained with crystal violet (Sigma) and counted using a Carl Zeiss Axiovert 40 CFL microscope (Carl Zeiss).

Side population assay

Cells were treated with 5 μg/ml of Hoechst 33342 (1 mg/ml, Sigma) and incubated for 45 min at 37°C. After staining, cells were incubated again for 45 min for the efflux period. Verapamil (100 μg/ml, Sigma) was treated as a negative control for side population. Cells were resuspended in cold PBS with 2 μg/ml propidium iodide (Sigma) to exclude non-viable cells. A BD FACSAria TM II (BD Biosciences) equipped with 360 nm UV and 488 nm argon lasers was used to read the fluorescence of Hoechst 33342 and PI, respectively. 424/44 BP and 675 LP filters, in combination with a 640 nm long pass dichroic mirror, were used for detection of Hoechst blue and red, respectively.

Statistical analysis

Data were analyzed by Student’s t-test for multiple comparisons as indicated. Results are shown as the mean ± SEM from at least three independent experiments. Differences were considered significant at the values of P < 0.05 (*), P < 0.01 (**) and P < 0.001 (***) Statistical analyses were done using GraphPad Prism 5.0 software.

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CONFLICTS OF INTEREST
The authors have no conflicting interests.

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