Dexamethasone reduces side population fraction through downregulation of ABCG2 transporter in MCF-7 breast cancer cells

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Abstract. Side population (SP) cells represent a rare population among breast cancer cells. SP cells have been reported to act as cancer stem-like cells, and to participate in the development of multidrug resistance via modulating the expression of ATP-binding cassette subfamily G member 2 (ABCG2). Dexamethasone is a corticosteroid drug that has been used as an adjuvant treatment to enhance the efficacy of chemotherapeutic agents; however, its effects in breast cancer have yet to be thoroughly investigated. In the present study, the effects of dexamethasone were investigated using the human MCF-7 breast cancer cell line, and SPs were examined in detail. Cellular proliferation, SP fractions and ABCG2 expression were examined following treatment of MCF-7 cells with dexamethasone. Dexamethasone was revealed to cause a dose- and time-dependent decrease in cancer cell proliferation, and it also decreased the size of the SP fraction of MCF-7 cells and the expression of the ABCG2 transporter. The effects of dexamethasone on cellular proliferation, SP fraction and ABCG2 expression were abolished following the administration of the glucocorticoid antagonist RU486. These results suggested that dexamethasone may target breast cancer cell SPs and thus increase the sensitivity of tumor cells to chemotherapy. Therefore, it may be hypothesized that dexamethasone can be used as a chemosensitizer in the adjuvant treatment of patients with breast cancer.

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Introduction

Dexamethasone is a glucocorticoid that has been reported to act on normal mammary epithelial cells and breast cancer cells (1,2); however, its inhibitory effects on cancer cell growth remain controversial. Dexamethasone has been reported to suppress estrogen-dependent breast cancer growth (2) and induce breast cancer cell apoptosis *in vitro* (3,4). Contradictory reports have demonstrated that dexamethasone exerted protective effects against cell death (5) and promoted the proliferation of MCF-7 breast cancer cells (6). Notably, dexamethasone has also been reported to enhance the sensitivity of cancer cells to the effects of chemotherapy *in vitro* (7) and *in vivo* (8).

The effects of dexamethasone on the sensitivity of cancer cells to anticancer drugs have been associated with ATP-binding cassette (ABC) transporters, including ABC transporter subfamily G member 2 (ABCG2; originally termed breast cancer resistance protein) (9,10). Side population (SP) cells have been identified in breast cancer and have been reported to efflux the fluorescent dye Hoechst 33342, possibly via the ABCG2 transporter (11). SP cells are rare populations among breast cancer cells (12), and have also been detected among embryonic (13) and adult stem cells (14). SP cells have demonstrated self-renewing and differentiating capabilities (15), tumorigenic activity (16) and have been reported to give rise to heterogeneous cell populations during cancer development (17). Therefore, it may be hypothesized that SP cells act as cancer stem-like cells and serve a critical role in the development of multidrug resistance (18,19). ABC transporters, including ABCG2, have also been implicated in the development of multidrug resistance, due to their role as efflux pumps for chemotherapeutic agents (11).

The effects of dexamethasone in breast cancer and breast cancer stem-like cells have yet to be thoroughly investigated. The present study aimed to assess the putative inhibitory effects of dexamethasone on cancer cell growth and investigate the molecular mechanisms underlying its actions. The present study demonstrated that dexamethasone exerted dose- and time-dependent effects on MCF-7 cancer cell proliferation. The Hoechst-based flow cytometry profiles suggested that

dexamethasone may target breast cancer stem-like cells, identified as the SP, in accordance with previous studies (11,20).

Materials and methods

Cell culture. Human MCF-7 breast adenocarcinoma cells (American Type Culture Collection, Manassas, VA, USA) were cultured in Dulbecco's modified Eagle's medium (DMEM; Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA), supplemented with 10% fetal bovine serum (FBS; Gibco; Thermo Fisher Scientific, Inc.). For the creation of an anchorage-dependent culture, MCF-7 cells ($5x10^5$) were seeded in a Falcon™ Standard Tissue Culture Dish (Thermo Fisher Scientific, Inc.). Cells were incubated at 37˚C in a humidified 5% CO_2 atmosphere.

MCF-7 cell viability. MCF-7 cells ($5x10^5$) were seeded in DMEM supplemented with 10% FBS. Following 24 h of culture, cells were washed twice with PBS, and fresh medium was added. Various concentrations (1, 10, 100 nM and 1 μM) of dexamethasone (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany) and/or the glucocorticoid inhibitor RU486 (1 μM; Sigma-Aldrich; Merck KGaA) were added to the cells. The numbers of viable cells were estimated at a number of time points (following 24, 48 and 72 h of culture) using trypan blue staining.

Flow cytometry. Following incubation for 72 h, cells ($1x10^5$) were fixed in 70% ethanol for 1 h at 4˚C, washed with PBS and treated with 100 μg/ml RNase A (Sigma-Aldrich; Merck KGaA) for 1 h at 37˚C. Cells were then stained with 25 μg/ml propidium iodide (PI; Sigma-Aldrich; Merck KGaA) for 15 min at 37˚C. For Annexin V-fluorescein isothiocyanate (FITC) staining, cells were washed with PBS, treated with diluted trypsin-EDTA solution, centrifuged at 25˚C for 3 min at 150 x g, washed twice with cold PBS, and resuspended in binding buffer (10 mM HEPES pH 7.4, 150 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, and 1.8 mM $CaCl_2$). A 100 μl aliquot of the suspension (~$1x10^5$ cells) was incubated with 5 μl Annexin V-FITC and 5 μl PI for 15 min in the dark at room temperature. Binding buffer (400 μl) was added to each mixture, and the samples were analyzed by flow cytometry within 1 h. Flow cytometry was performed using the FACSCalibur™ system (BD Biosciences, San Jose, CA, USA) and data were analyzed using the BD FACStation™ software version 6.0 (BD Biosciences). Experiments were performed in triplicate.

SP analysis of MCF-7 cells. MCF-7 cells ($5x10^5$) were seeded in DMEM supplemented with 10% FBS. Following 24 h incubation, cells were washed twice with PBS, and fresh media were added. The cells were then treated with ethanol (CTL), dexamethasone (100 nM), RU486 (1 μM), or RU486 (1 μM) and dexamethasone (100 nM) for 72 h. SP analysis was performed as previously described (11). To detach cells, cultures were trypsinized for 3 min and detachment was monitored under a phase-contrast microscope. The number of viable cells was estimated using trypan blue staining. Cells were centrifuged at 25˚C for 3 min at 150 x g and resuspended in 5 ml PBS. To detect SP cells, cells at a density of $1x10^6$ cells/ml were incubated with Hoechst 33342 dye (5 μg/ml) in DMEM supplemented with 10% FBS for 90 min at 37˚C, with vortexing every 10 min. At the end of the incubation, cells were centrifuged at 4˚C for 3 min at 150 x g and transferred to microcentrifuge tubes. PI (1 μg/ml) was added to the tube for 15 min at 37˚C prior to fluorescence-activated cell sorting for the identification and exclusion of dead cells. Samples were analyzed using the BD FACSAria™ system and the FACSDiva™ software version 6.1 (BD Biosciences). In order to confirm that cells belonging to the SP were expressing the ABCG2 transporter, Hoechst 33342 staining was also performed in cells additionally treated for 90 min with the ABCG2 inhibitor verapamil (50 μM; Merck KGaA).

Flow cytometric analysis of ABCG2 expression. Cells were detached using trypsin as aforementioned, and 5 ml DMEM supplemented with 10% FBS were added to the culture for trypsin inactivation. Cells were collected by centrifugation for 3 min at 150 x g at 25˚C, resuspended in 5 ml PBS and centrifuged again. Cell pellets were resuspended in 500 μl total volume of PBS containing FITC-conjugated anti-ABCG2 antibody (cat. no. 332014; 1:50; BioLegend, Inc., San Diego, CA, USA). Following incubation for 25 min at room temperature, cells were rinsed three times with PBS and flow cytometric analyses were performed in triplicate using the FACSCalibur™ system (BD Biosciences).

Statistical analysis. The statistical significance of the differences between groups was assessed using Student's t-test using Microsoft Excel software version 2016 (Microsoft Corporation, Redmond, WA, USA). Data are expressed as the mean ± standard error of the mean of at least three independent experiments. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Dexamethasone decreases MCF-7 cell viability. The present study evaluated the effects of dexamethasone on the viability of human MCF-7 breast adenocarcinoma cells using trypan blue staining. Following treatment with various concentrations of dexamethasone for 72 h, MCF-7 cell viability was reduced to 92, 81, 54 and 45% of the control levels by 1, 10, 100 nM and 1 μM dexamethasone, respectively (Fig. 1A). Following 72 h of treatment, 100 nM dexamethasone significantly reduced the numbers of viable MCF-7 cells compared with control (Fig. 1B). Therefore, a dose of 100 nM dexamethasone was used in all subsequent experiments. To confirm that the observed reduction in MCF-7 cell viability was due to dexamethasone, the glucocorticoid inhibitor RU486 was employed. The inhibitory effects of dexamethasone on MCF-7 proliferation were abolished following treatment with 1 μM RU486 (Fig. 1C).

Dexamethasone does not affect cell cycle distribution of MCF-7 cells. To determine whether the observed decrease in MCF-7 cell viability was the result of cell cycle arrest or apoptosis, the DNA contents of the surviving cells were assessed using PI staining followed by flow cytometry. The fraction of MCF-7 cells in the G_0/G_1 phase demonstrated an upward

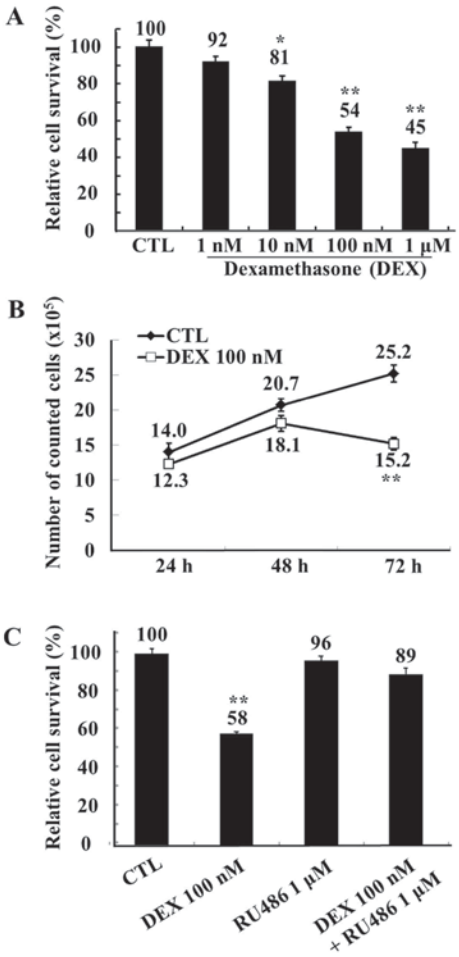

Figure 1. Viability of MCF-7 cells following treatment with DEX, assessed by trypan blue staining. (A) Human MCF-7 breast adenocarcinoma cells were treated with ethanol (CTL) or with DEX (1, 10, 100 nM and 1 μM) for 72 h. Relative cell survival rate is presented as percentage survival vs. the survival of control cells following treatment with DEX. (B) MCF-7 cells were treated with ethanol (CTL) or with DEX (100 nM) for 24, 48, and 72 h. Cell survival is presented vs. the survival of control cells following treatment with DEX. (C) MCF-7 cells were treated with ethanol (CTL), the glucocorticoid inhibitor RU486 (1 μM), DEX (100 nM), or RU486 in combination with DEX for 72 h. Relative cell survival rate is presented as percentage survival vs. the survival of control cells following treatment with DEX. Data are expressed as the mean ± standard error of the mean. *P<0.05 and **P<0.01 vs. the CTL group. DEX, dexamethasone; CTL, control.

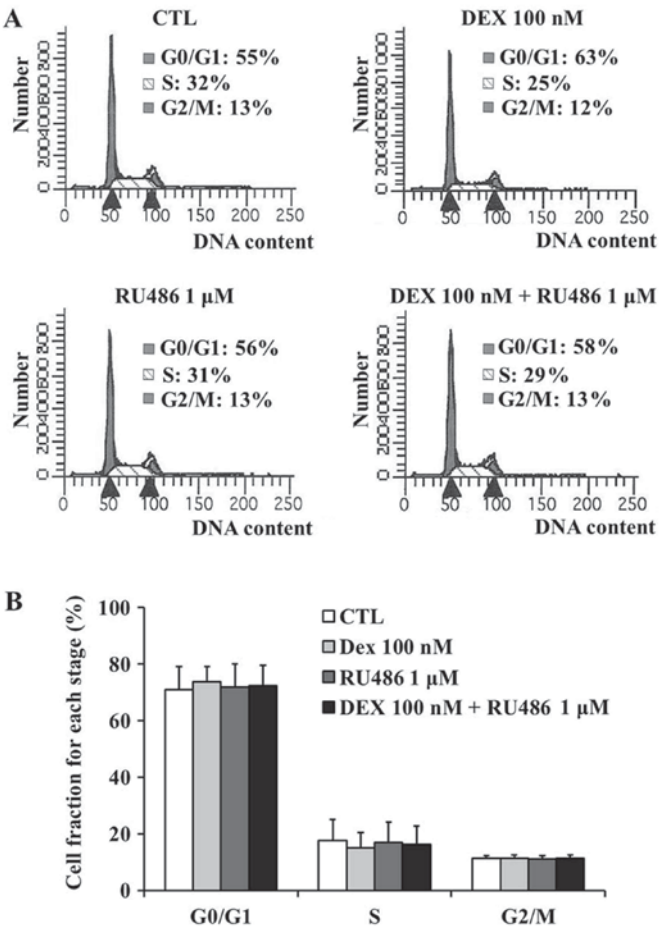

Figure 2. Alterations in cell cycle distribution of MCF-7 cells following treatment with DEX. Human MCF-7 breast adenocarcinoma cells were treated with ethanol (CTL), the glucocorticoid inhibitor RU486 (1 μM), DEX (100 nM), or RU486 in combination with DEX for 72 h. Cell cycle analysis was then performed using flow cytometry, following DNA staining with propidium iodide. (A) Representative results of flow cytometric analysis of cell cycle distribution. (B) Quantification data from three independent experiments. Data are expressed as the mean ± standard error of the mean. DEX, dexamethasone; CTL, control.

trend (~8% increase) following treatment with 100 nM dexamethasone compared with untreated control cells; however, no statistical significance was detected (Fig. 2A and B). In detail, the G_0/G_1 fraction was 71.00±9.45% in untreated cells, 73.67±6.19% in cells treated with 100 nM dexamethasone, 72.00±9.33% in cells treated with 1 μM RU486 and 72.33±8.28% in cells treated with RU486 and dexamethasone. The results of the apoptosis assay demonstrated that dexamethasone did not produce any statistically significant effects on MCF-7 cell apoptosis (Fig. 3A and B).

Dexamethasone decreases the SP fraction of MCF-7 cells. To investigate the effects of dexamethasone treatment on the SP fraction of MCF-7 cells, cells were treated with 100 nM dexamethasone and 1 μM RU486 as aforementioned. SP cells were detected using Hoechst 33342 staining followed by flow cytometry. The size of the SP fraction was 1.6±0.1% in untreated cells, 0.6±0.1% in cells treated with 100 nM dexamethasone, 1.6±0.1% in cells treated with 1 μM RU486 and 1.1±0.2% in cells treated with RU486 and dexamethasone (Fig. 4A and B). The SP fraction was significantly decreased following dexamethasone treatment (P<0.01) compared with untreated cells, whereas co-administration of RU486 attenuated the effects of dexamethasone (P<0.05 compared with dexamethasone-treated cells). Following treatment with verapamil, the SP fraction was not detected.

Dexamethasone downregulates ABCG2 expression in MCF-7 cells. To investigate whether the effects of dexamethasone on the SP of MCF-7 cells may be associated with the ABCG2 transporter, the expression of ABCG2 was assessed using flow cytometry. The present results demonstrated that ABCG2 expression was significantly downregulated following treatment with dexamethasone compared with untreated cells (P<0.01; Fig. 5). Furthermore, RU486 co-administration appeared to restore the dexamethasone-induced ABCG2 downregulation in MCF-7 cells (P<0.01 compared with dexamethasone-treated cells; Fig. 5). ABCG2-positive cells

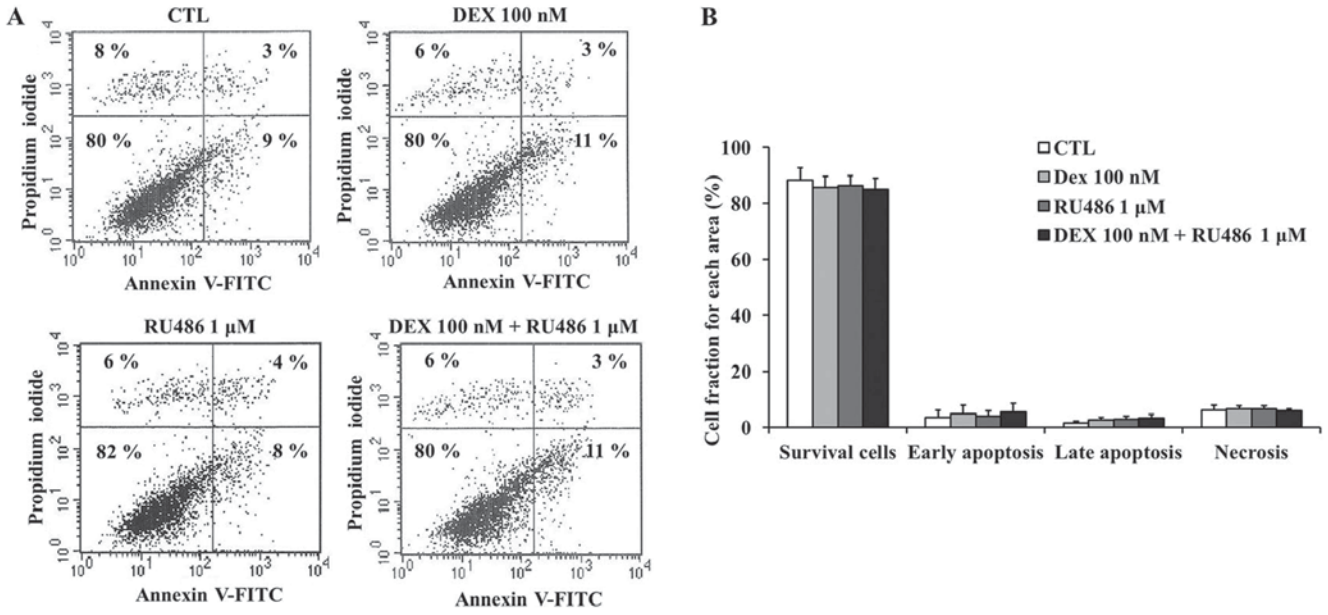

Figure 3. Alterations in apoptosis of MCF-7 cells following treatment with DEX. Human MCF-7 breast adenocarcinoma cells were treated with ethanol (CTL), the glucocorticoid inhibitor RU486 (1 μM), DEX (100 nM), or RU486 in combination with DEX for 72 h. Cells were then stained with FITC-conjugated Annexin V and propidium iodide, and analyzed using flow cytometry. (A) Representative results of flow cytometric analysis of apoptosis. Surviving cells are presented in the lower left quadrant, where Annexin V-FITC and propidium iodide levels are low. (B) Quantification data from three independent experiments. Data are expressed as the mean ± standard error of the mean. DEX, dexamethasone; CTL, control; FITC, fluorescein isothiocyanate.

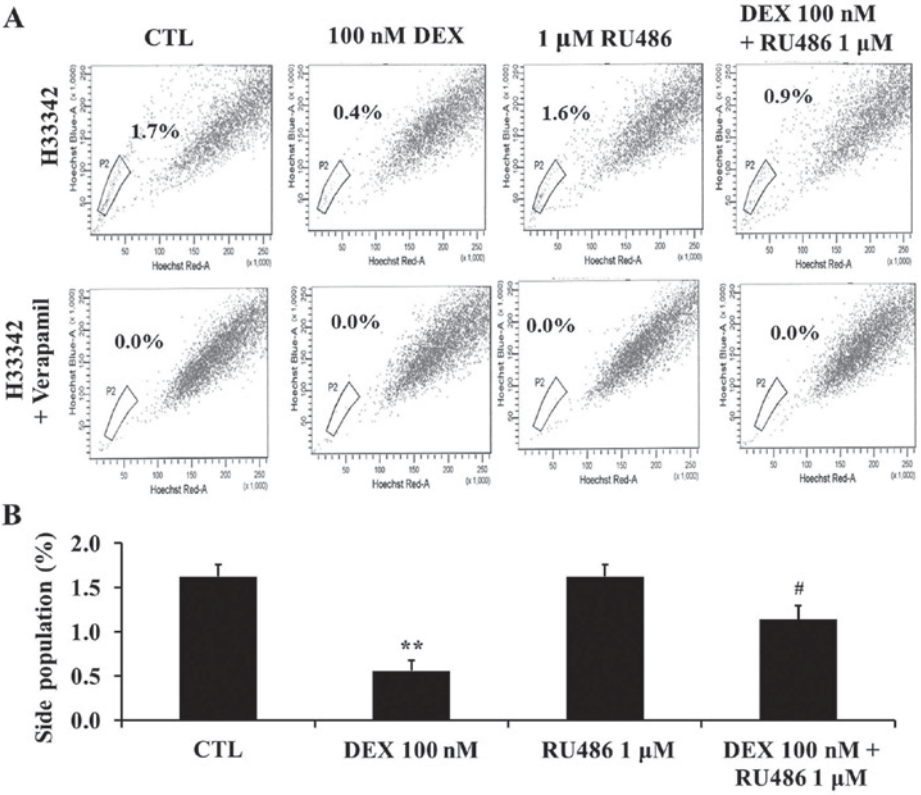

Figure 4. SP analysis of MCF-7 cells following treatment with DEX. Human MCF-7 breast adenocarcinoma cells were treated with ethanol (CTL), the glucocorticoid inhibitor RU486 (1 μM), DEX (100 nM), or RU486 in combination with DEX for 72 h, and then incubated with Hoechst 33342. SP cells were analyzed using flow cytometry with a 515-nm side population filter (Hoechst blue). (A) Representative results of SP flow cytometric analysis. (B) Quantification data from three independent experiments. Data are expressed as the mean ± standard error of the mean. **P<0.01 vs. CTL group; $^{\#}$P<0.05 vs. DEX 100 nM group. SP, side population; DEX, dexamethasone; CTL, control; H33342, Hoechst 33342.

were detected as 6.8±0.06% in untreated cells, 6.7±0.17% in the presence of 1 μM RU486, 3.7±0.32% in the presence of 100 nM dexamethasone, and 5.5±0.24% in the presence of both 1 μM RU486 and 100 nM dexamethasone.

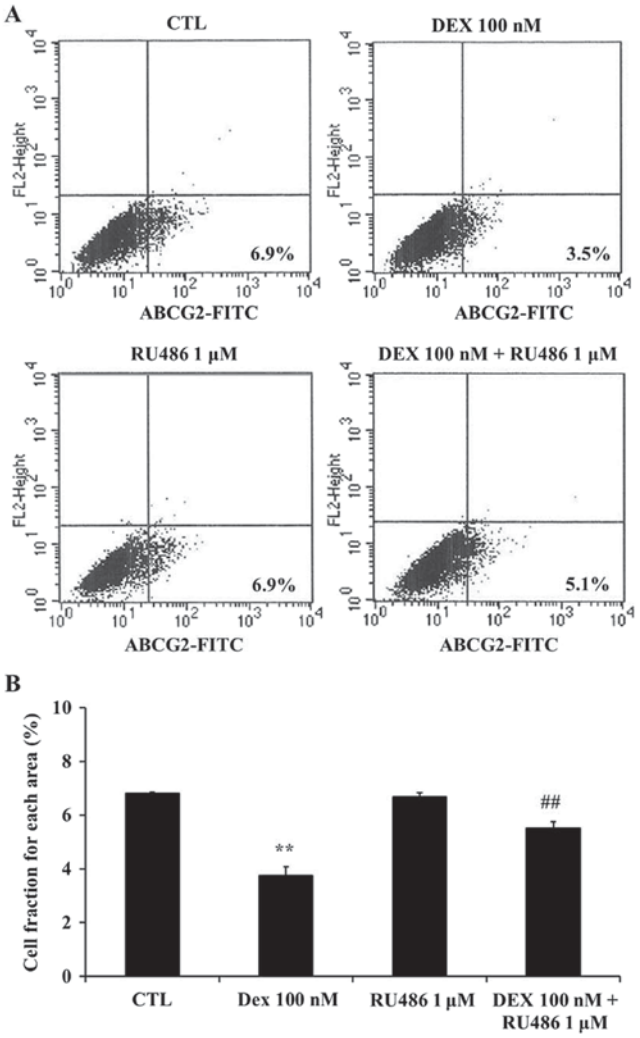

Figure 5. Alterations in ABCG2 expression in MCF-7 cells following treatment with DEX. Human MCF-7 breast adenocarcinoma cells were treated with ethanol (CTL), the glucocorticoid inhibitor RU486 (1 μM), DEX (100 nM), or RU486 in combination with DEX for 72 h. Cells were then stained with a FITC-conjugated anti-ABCG2 antibody and analyzed using flow cytometry. (A) Representative results of flow cytometric analysis of ABCG2 expression. The percentage of ABCG2 expression is presented in the lower right quadrant. (B) Quantification data from three independent experiments. Data are expressed as mean + standard error of the mean. **P<0.01 vs. CTL group; $^{\#\#}$P<0.01 vs. DEX 100 nM group. DEX, dexamethasone; ABCG2, ATP-binding cassette subfamily G member 2; FITC, fluorescein isothiocyanate; CTL, control.

Discussion

The inhibitory effects of dexamethasone on breast cancer cell growth remain controversial, as dexamethasone has been demonstrated to inhibit cell growth (2) and induce apoptosis (3,4), whereas it has also been reported to prevent cell death (5) and promote cellular proliferation (6). These contradictory results may, in part, be attributed to alterations in protein expression due to variations in the cell culture environment among the various studies (21). Dexamethasone has been demonstrated to enhance the efficacy of anticancer drugs on breast cancer cells *in vitro* (4), whereas it has also been reported to downregulate the expression of the ABCG2 transporter in breast cancer cells (9,22-24). Therefore, it may be hypothesized that dexamethasone inhibits cancer cell growth via targeting cancer stem-like cells. The results of the present study revealed that dexamethasone targeted cells in the SP of MCF-7 breast cancer cells and downregulated the expression of ABCG2, whereas its effects were abolished by the glucocorticoid inhibitor RU486. Traditional chemotherapeutic agents, including doxorubicin and docetaxel, have not been reported to affect the SP fraction; however, the plant alkaloid berberine has been demonstrated to decrease the SP fraction among breast cancer cells, and this effect was associated with ABCG2 downregulation (11). These results suggested that the molecular mechanisms underlying the SP-suppressing actions of dexamethasone may involve the downregulation of ABCG2 in cancer cells.

The pharmacological profile of dexamethasone is diverse and has been reported to include antiemetic (25), anti-inflammatory (26) and pro-differentiating properties (27,28). In addition, dexamethasone has been reported to enhance the sensitivity of cancer cells to the effects of chemotherapy *in vitro* (7) and *in vivo* (8). Furthermore, dexamethasone increased the survival of patients with multiple myeloma in a phase II clinical trial when used as an adjuvant treatment in combination with anticancer drugs (29), and enhanced the effects of prostate cancer chemotherapy *in vitro* and *in vivo* (30). The present results demonstrated that dexamethasone inhibited the growth and decreased the SP fraction in human MCF-7 breast cancer cells, possibly through the downregulation of ABCG2 expression.

In conclusion, the results of the present study suggested that the inhibitory effects of dexamethasone on cancer cell growth may be associated with a decrease in the SP fraction or the number of cancer stem-like cells. Therefore, it may be hypothesized that dexamethasone can target breast cancer cell SPs and increase the sensitivity of tumor cells to chemotherapy, thus holding potential as a chemosensitizer in the adjuvant treatment of patients with breast cancer.

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