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Original scientific article

CHEMOSENSITIZING EFFECTS OF METHYL JASMONATE ON PACLITAXEL-RESISTANT ANDROGEN-DEPENDENT AND INDEPENDENT PROSTATE CANCER CELL LINES

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The taxane-based therapy provides survival benefit in patients with metastatic prostate cancer; however, the average survival is less than 20 months due to the partial taxane-related chemoresistance. Innovative strategies are needed to overcome the chemoresistance for improved patient survival. In this project, paclitaxel-resistance was developed on androgen-independent *PC3* and androgen-dependent *22Rv1* and *LNCaP* human prostate cancer (PCa) cell lines to investigate the efficacy of methyl jasmonate (MeJa), an anti-cancer drug, in overcoming the chemoresistance. The PCa cell lines were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) at 37°C under 5% CO_2. The cell lines were exposed to the gradually increasing doses of paclitaxel. Since the resistance on *LNCaP* could not be achieved, the study was continued with *22Rv1* cell line. It was demonstrated that paclitaxel-resistant cell lines overexpress *ABCB1*. Resistance levels of cells and MeJa activity in all resistant and parental lines were measured using CellTiter-Glo® luminescent assay. Test results were compared with Student's t-test or analysis of variance (ANOVA). $P \leq 0.05$ (two-tailed) was considered to be significant. In conclusion, MeJa showed more cytotoxicity on paclitaxel resistant *PC3 (PC3-Ptx^R)* cells than resistant *22Rv1 (22Rv1-Ptx^R)* cells. Detection of cytotoxic effects of MeJa in overcoming paclitaxel resistance may contribute to the development of alternative new compounds for the prevention or chemosensitization of resistance to chemotherapeutics such as paclitaxel.

Keywords: Prostate cancer, Paclitaxel resistance, Methyl Jasmonate, *PC3*, *22Rv1*

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INTRODUCTION

Paclitaxel, which has been widely used in prostate cancer (PCa) chemotherapy is obtained from the bark of Pacific yew tree, *Taxus brevifolia*. Paclitaxel has the molecular formula of $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9 g/mol. It was found to be effective against breast, lung, ovary, larynx, and prostate cancers in the first clinical trials initiated in 1981. Paclitaxel binds to the β-tubulin subgroup of microtubules during mitosis and prevents the conversion of microtubules into tubulins, thus destructing the spindle strands during mitosis and stops cell division (LI *et al.*, 2011; SCHIFF *et al.*, 1980; FITZPATRICK *et al.*, 2003). While this mechanism of action of paclitaxel is expected to exhibit anti-neoplastic activity in tumor cells with multi-drug resistance, chemoresistance is frequently observed. Laboratory studies described a variety of paclitaxel resistance mechanisms including overexpression of multidrug resistance gene (MDR-1), molecular changes in the target molecule β-tubulin, changes in apoptotic regulatory and mitosis control point proteins, and changes in lipid composition and potentially in the overexpression of *interleukin 6 (IL-6)* (LI *et al.*, 2011). Innovative strategies are required to sensitize paclitaxel resistance for improved patient survival.

Methyl jasmonate (MeJa), a plant stress hormone, is natural cyclopentanone oil from the jasmonate family, which is the oxidized fatty acids (CESARI *et al.*, 2014). MeJa is made from linolenic acid and has been shown to induce apoptosis in cancers due to the excessive similarity to lipoxygenase products, and because of these properties, jasmonates are considered as a new potential anticancer drug family (LIECHTI *et al.*, 2002). MeJa and other jasmonates containing the related synthetic analogs were found to inhibit cancer cell proliferation by inducing cell death in human and murine (FLESCHER, 2005; 2007; GOLDIN *et al.*, 2007; COHEN and FLESCHER, 2009; REISCHER-PELECH and FLESCHER, 2012; ELIA and FLESCHER, 2013; RAVIV *et al.*, 2013), breast (YERUVA *et al.*, 2008a; KNIAZHANSKI *et al.*, 2008), cervix (ZHAO *et al.*, 2010; MILROT *et al.*, 2012; 2013; GOLDIN *et al.*, 2008), colon (ÁVILA-ROMÁN *et al.*, 2012; RAVIV *et al.*, 2011), colorectal (ZHENG *et al.*, 2013), stomach (PARK *et al.*, 2010), hepatoma (KIM *et al.*, 2004), lung (YERUVA *et al.*, 2006; ROTEM *et al.*, 2005), lymphoma (FINGRUT *et al.*, 2005; REISCHER *et al.*, 2007), melanoma (PEREIRA LOPES *et al.*, 2010; TONG *et al.*, 2008), neuroblastoma (SAMAILA *et al.*, 2004), prostate (KNIAZHANSKI *et al.*, 2008; EZEKWUDO *et al.*, 2007; ELIA and FLESCHER *et al.*, 2008), and sarcoma (EZEKWUDO *et al.*, 2008) cancers. However, the mode of action of MeJa on paclitaxel resistance is unknown. Only one study reported that MeJa inhibits the anti-apoptotic Bcl-2 protein and increases some pro-apoptotic proteins in the radio-resistant *PC3* cell line (JIANG *et al.*, 2008).

The aim of this study was to determine the mode of action of MeJa in sensitizing the paclitaxel resistance in PCa. Thus, this study on *PC3* and *22Rv1* PCa cell lines will contribute to the development of alternative new compounds to prevent or overcome the resistance of cancer cells to chemotherapeutics. These results may help the development of new therapy regimes. Overcoming the drug resistance will increase the success of cancer treatment in clinic.

MATERIALS AND METHODS

Material

Paclitaxel (Cat#T7402) was purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in dimethyl sulfoxide (DMSO). MeJa (Cat#392707) also purchased from Sigma-

Aldrich was dissolved in sterile distilled water and filter sterilized. Both stock solutions were stored at -20°C until use.

Cells Lines and Maintenance

Androgen-independent *PC3* and androgen-dependent *LNCaP* and *22Rv1* human PCa cell lines were generously gifted by Prof. Dr. William Gmeiner from Wake Forest University, NC, USA. Human PCa cell lines were maintained in RPMI-1640 media (Gibco, Grand Island, NY, USA) with 10% FBS (Gemini Bio-Products, West Sacramento, CA, USA) at 37°C in the presence of 5% CO_2 in a humidified incubator. Cells were passaged using Trypsin-EDTA twice a week when they reach 80-90% confluence.

Development of Paclitaxel-Resistant Cell Lines

Cells were treated with gradually increasing doses of paclitaxel (starting from 0.1 nM to 350 nM) to gain resistance over a period of about 3 months as described by TAKEDA *et al.* (2007). Paclitaxel resistance in *LNCaP* was not accomplished. Paclitaxel resistant cell lines, *PC3-Ptx*^{R} and *22Rv1-Ptx*^{R}, were maintained in RPMI-1640 supplemented with 10% FBS and 200 nM paclitaxel at 37°C under teh presence of 5% CO_2.

Verification of Paclitaxel-Resistant Cell Lines

The cells were seeded at 3000 cells/well in 96-well plates. Next day, paclitaxel treatment was started and continued for 72 h. The cell viabilities were measured with CellTiter-Glo® luminescent cell viability assay (Promega, Madison, WI, USA) according to the manufacturer's instructions. An LMAXII 384 microplate reader (Molecular Devices, Toronto, ON, Canada) was used to measure luminescence.

Determination of ABCB1 gene expression

Clinical paclitaxel resistance is often associated with *ABCB1* (*MDR1*) overexpression, and *in vitro* paclitaxel resistance also demonstrates overexpression of the *ABCB1* gene. In this study, overexpression *ABCB1* gene in parental, and paclitaxel-resistant cell lines were measured by Real-Time PCR. RNA isolation from the cells was performed by the RNeasy Mini Kit (Qiagen, Hilden, Germany) and cDNA synthesis was performed by RT^2 First Strand Kit (Qiagen) according to the manufacturer's protocol. Real-Time PCR was performed using the RT^2 qPCR primer assays (Qiagen) for *ABCB1* and *ACTB* (as housekeeping) genes using SYBR Green Master Mix (Qiagen). Data analysis of the CT values of *ABCB1* and *ACTB* was performed online using the software obtained through https://www.qiagen.com/tr/shop/genes-and-pathways/data-analysis-center-overviewpage/.

Determination of Paclitaxel Cytotoxicity

At this stage, only paclitaxel was administered to the parental and paclitaxel resistant *PC3-Ptx*^{R} and *22Rv1-Ptx*^{R} cells at increasing concentrations ranging between 0-350 nM. Cytotoxicity was determined by CellTiter-Glo® luminescent cell viability assay.

Determination of MeJa Cytotoxicity

At this stage, only MeJa was administered to the parental and resistant *PC3-Ptx^R* and *22Rv1-Ptx^R* cells at increasing concentrations from 0 to 5 mM. Cytotoxicity was determined by CellTiter-Glo® luminescent cell viability assay.

Statistical Analysis

All experiments were performed in triplicates and repeated 3 times. Results were compared with Student's t-test or variance analysis (ANOVA). $P \leq 0.05$ (two-tailed) value was considered to be significant.

RESULTS AND DISCUSSION

Resistance to paclitaxel in the PCa cell lines was verified by comparing the resistant lines to the parental *PC3* and *22Rv1* lines (Figure 1 and 2, respectively). The paclitaxel resistance in *PC3-Ptx^R* and *22Rv1-Ptx^R* cells was confirmed by statistically significant overexpression of *ABCB1* gene (P=0.002 and P=0.035, respectively) (Figure 3).

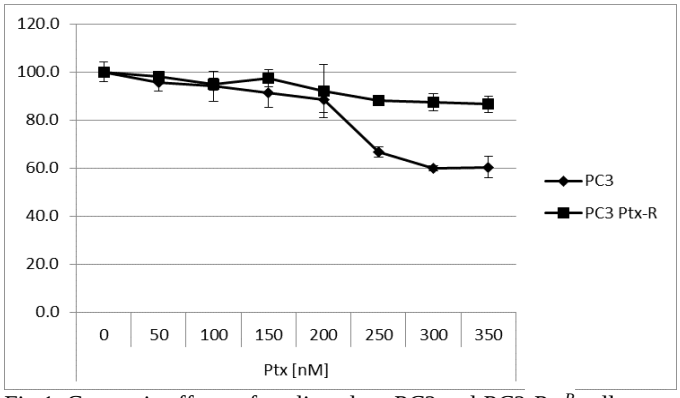

Fig.1. Cytotoxic effects of paclitaxel on *PC3* and *PC3-Ptx^R* cells.

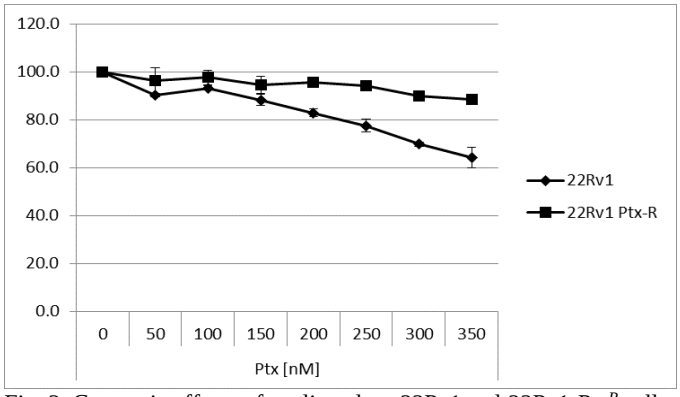

Fig. 2. Cytotoxic effects of paclitaxel on *22Rv1* and *22Rv1-Ptx^R* cells.

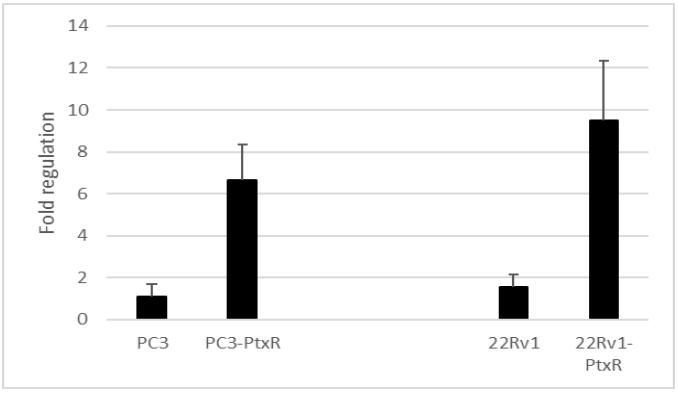

Fig. 3. *ABCB1* expression in parental and paclitaxel-resistant PCa cell lines.

After administration of MeJa, paclitaxel-resistant cell lines died more than the parental cell lines. MeJa showed more cytotoxicity on *PC3-Ptx^R* cells than *22Rv1-Ptx^R* cells (Figure 4 and 5).

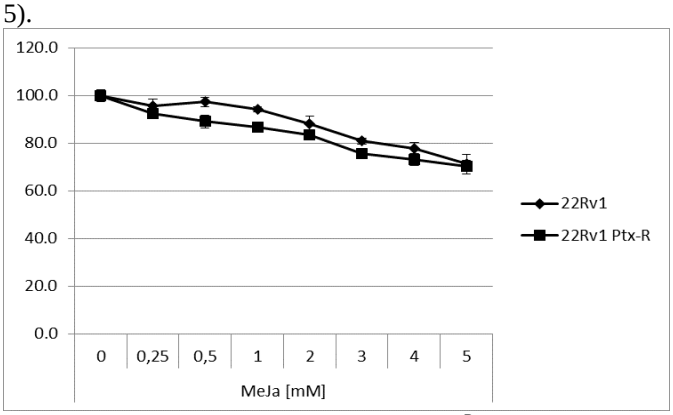

Fig.4. Effects of MeJa on *22Rv1* and *22Rv1-Ptx^R* cells.

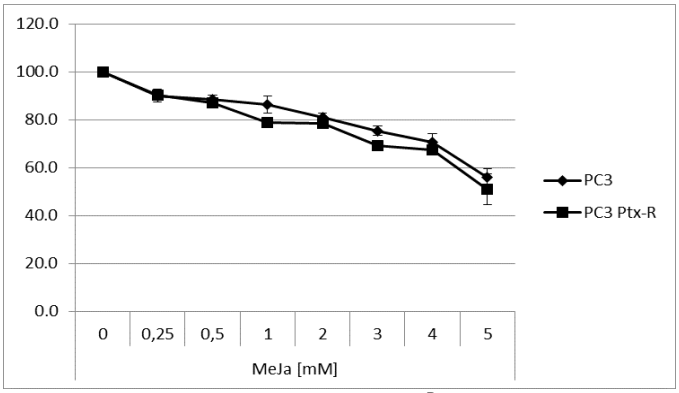

Fig.5. Effects of MeJa on *PC3* and *PC3-Ptx^R* cells.

Paclitaxel is often used as a chemotherapeutic agent for PCa. However, acquired drug resistance due to prolonged use of paclitaxel poses as an obstacle in the treatment of PCa patients (LI *et al.*, 2011; KREIS *et al.*, 2001). Therefore, many approaches towards developing small molecules have been actively studied to overcome paclitaxel resistance in PCa. In this study, it was aimed to determine the effect of MeJa against paclitaxel resistance. It has been demonstrated for the first time that MeJa may be an option to overcome paclitaxel chemoresistance.

Taxane class compounds (paclitaxel and docetaxel) are among the most important cancer chemotherapeutics of recent years. The microtubule polymerization and stabilization thus stopping the cell cycle in G2/M phase are among the multiple effects of paclitaxel. These effects cause antiproliferation and apoptosis of tumor cells in solid tumors and leukemia patients. However, it is controversial whether taxol-mediated apoptosis is a secondary result of mitotic pause or an alternative mechanism of action against tumor cells (LI *et al.*, 2011; KREIS *et al.*, 2001).

In our study, resistance was not obtained in *LNCaP* cell line, therefore *22Rv1* PCa cell line was used instead. Each of the two cancer cell lines (*PC3* and *22Rv1*) gained paclitaxel resistance at different periods. This diversity may be due to whether the cells are metastatic, sensitive to androgen, or arisen from different cancer cell sources. The IC_{50} dose of paclitaxel in PCa cell lines shows a wide range in the studies. In some studies, the IC_{50} dose is in the nM range while in some studies it is in the µM range. In our study, the IC_{50} doses of paclitaxel in *PC3* and *22Rv1* cell lines were determined to be 3.08 µM and 8.85 µM, respectively. JIANG *et al.* (2008) determined the 48-hour IC_{50} dose of paclitaxel on *PC3* cell line as 5 µM, while KREIS *et al.* (2001) determined the 72-hour IC_{50} dose on *PC3* as 12.35 nM and on *DU-145* as 15.73 nM. In both studies, paclitaxel was obtained from Sigma as in our study. In this respect, the observed cytotoxic activities of paclitaxel were evaluated in a similar way.

Several mechanisms have been reported for the formation of paclitaxel resistance including *ABCB1* overexpression, point mutations in β-tubule, and changes in microtubule dynamics. In our study, the overexpression of *ABCB1* gene in paclitaxel resistant PCa cells was shown. In addition, studies have shown that paclitaxel resistance in PCa is associated with a more aggressive and invasive phenotype (LI *et al.*, 2011; KREIS *et al.*, 2001). Therefore, alternative strategies for the treatment of paclitaxel-resistant PCa are urgently needed to improve the survival rates of PCa patients.

MeJa and related jasmonates have been reported to inhibit cancer cell proliferation by inducing cell death in human and mouse breast, cervix, colon, colorectal, stomach, hepatoma, lung, lymphoma, melanoma, neuroblastoma, prostate, and sarcoma cancers (RAVIV *et al*, 2012).

MeJa was shown to exert its antiproliferative effect by promoting S-phase arrest in PC3 while inducing G0/G1 cell cycle arrest in DU-145 (YERUVA *et al*, 2008b). Both PC3 and DU-145 cell lines are known to have mutant P53 gene and overexpress Bcl2, an anti-apoptotic protein (COHEN and FLESCHER, 2009). Intrinsic induction of apoptosis due to mitochondrial damage bypasses Bcl-2 overexpression driving the cell to apoptosis (COHEN and FLESCHER, 2009). However, MeJa treatment was reported to activate caspase 3 and DNA fragmentation indicating extrinsic apoptosis induction in PC3 and DU-145 c PCa cell lines (YERUVA *et al*, 2008b). In recent studies, the anti-carcinogenic effects of MeJa in combination with various molecules and

novel synthetic MeJa analogues in various cancers have been demonstrated (YOUSEFI *et al.*, 2020; SUCU *et al.*, 2019). However, in the literature, there is no study showing the effect of MeJa on paclitaxel resistant cells. Only one study reported that MeJa inhibits the anti-apoptotic Bcl-2 protein in the radio-resistant *PC3* cell line and increases some pro-apoptotic proteins (LI *et al.*, 2011). In our study, MeJa has overcome the paclitaxel resistance by causing more deaths in the Ptx^R Pca cell lines compared to the parental cell lines.

CONCLUSIONS

In this study, two human PCa cell lines were made resistant to paclitaxel and the cytotoxic effects of MeJa on these cell lines were studied. This study is the first preliminary study showing that MeJa can be effective in overcoming chemoresistance. However, there is a need for extensive studies to determine the mechanism of action of MeJa in chemoresistance. The results of this study may contribute to the rearrangement of chemotherapeutic drug regimens for cancer patients who are difficult to treat effectively due to drug resistance problems. This report suggests the possibility of using MeJa as an option to sensitize paclitaxel chemoresistance in PCa. However, the results presented here needs further verification by future in vitro studies with cancer cell lines treated by taxane-group chemotherapeutics and by animal studies. Future studies may help to explain the mechanisms underlying paclitaxel resistance in PCa cells.

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EFEKTI HEMOSENSITIZACIJE METIL JASMONATA NA PANDITAKSEL-OTPORNE ANDROGEN-ZAVISNE I NEZAVISNE ĆELIJSKE LINIJE PROSTATE

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Izvod

Terapija zasnovana na taksanu obezbeđuje korist za preživljavanje kod pacijenata sa metastatskim karcinomom prostate, međutim, prosečno preživljavanje je manje od 20 meseci usled parcijalne hemorezistencije povezane sa taksanom. Potrebne su inovativne strategije za prevazilaženje hemorezistencije za poboljšanje preživljavanja pacijenata. U ovom projektu, rezistencija paklitaksela na stanične linije *22Rv1* i *LNCaP*-a, nezavisnih od androgena *PC3* i androgen-zavisnih humanih prostate (PCa), razvijena je da istraži efikasnost metil jasmonata (MeJa), visokog antikancerogenog leka, u prevazilaženju chemoresistance. Linije PCa ćelija su održavane u RPMI-1640 mediju dopunjenom sa 10% fetalnog goveđeg seruma (FBS) na 37° C pod 5% CO2. Ćelijske linije su bile izložene postepeno povećavajućim dozama paklitaksela. Pošto se rezistencija na *LNCaP* ne može postići, studija je nastavljena sa linijom *22Rv1* ćelija. Pokazano je da ćelijske linije otporne na paklitaksel ekspresionišu *ABCB1*. Nivoi otpornosti ćelija i MeJa aktivnosti u svim rezistentnim i roditeljskim linijama su mereni korišćenjem CellTiter-Glo® Luminescent Assai. Rezultati testa su upoređeni sa Studentovim t-testom ili analizom varijanse (ANOVA). Smatra se da je $P \leq 0.05$ (dvosmerni) značajan. U zaključku, MeJa je pokazala veću citotoksičnost na *PC3 (PC3-PtkR*) ćelijama rezistentnim na paklitaksel nego rezistentne *22Rv1 (22Rv1-PtkR)* ćelije. Detekcija citotoksičnih efekata MeJa za senzibilizaciju rezistencije na paklitaksel može doprineti razvoju alternativnih novih jedinjenja za prevenciju ili preokretanje otpornosti na hemoterapeutik kao što je paklitaksel.

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