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PACLITAXEL-OCTREOTIDE CONJUGATES INHIBIT GROWTH OF HUMAN NON-SMALL CELL LUNG CANCER CELLS *IN VITRO*

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Aim: **To evaluate the effects of paclitaxel-octreotide conjugates on the growth of cultured non-small cell lung cancer cells.** ***Methods:*** **RT-PCR was performed to detect mRNA for the subtypes of the human somatostatin receptor (SSTR) using specific primers. MTT-based cytotoxicity assay was used to evaluate the cell viability after treatment with paclitaxel and the conjugates. Cell cycle perturbations were determined using a Fluorescence-Activated Cell Sorter.** ***Results:*** **Non-small cell lung cancer A549 and Calu-6 cells expressed mRNA for SSTR2 and SSTR5. Paclitaxel and the conjugates effectively inhibited the growth of A549 and Calu-6 cells in a concentration- and time-dependent manner. In SSTR-negative fibroblasts, the conjugates were less cytotoxic than paclitaxel. The conjugates and paclitaxel could induce the increase of G_2/M phase ratio in A549 cells.** ***Conclusion:*** **The paclitaxel-octreotide conjugates can be used as selective-targeted chemotherapeutic agents for treating non-small cell lung cancer.**
Key Words: **non-small cell lung cancer, paclitaxel, octreotide.**

Death from lung cancer is one of the most common types of cancer-related death. Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung tumors. All the currently available treatment options for NSCLC, including surgery, radiation, and chemotherapy, have limited efficacy [1]. Surgery is not an option for treatment because approximately 65% of these patients have advanced-stage (IIIB/IV) disease at diagnosis [1]. In addition, NSCLC is more resistant to chemotherapy than other forms of cancer [2]. Although some progress has been made in the management of patients with NSCLC, there is still a need to develop more efficacious methods of treatment. Targeted chemotherapy is a modern approach for the treatment of cancers because it is more efficacious and less toxic than usual systemic chemotherapy [3].

Somatostatin (SST) is a peptide hormone, the cellular actions of which are mediated by a family of G-protein-coupled receptors (SSTR) that has five subtypes: SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 [4]. Some investigators have reported that cells of human small cell lung cancer and NSCLC overexpress SSTRs [5, 6]. The precise nature of the expression of SSTRs by NSCLC cell lines remains controversial. Ferone et al [7] detected SSTRs in Calu-6 cells, although numerous investigators have reported that many NSCLC cell lines do not express SSTRs [8, 9]. SST analogs may be potential vehicles for chemotherapeutic drugs used to treat SSTR-positive tumors because the binding of SST to its receptor is followed by its internalization. Therefore, the binding of an SST conjugate to cancerous cells that express SSTRs could result in the accumulation of the chemotherapeutic drug malignant cells [10]. Although this putative mechanism of action has not yet been demonstrated for SST analogs carrying cytotoxic drugs, the localization of primary tumors and their metastases by scintigraphy using radiolabeled SST analogs lend strong support for such a of this mechanism of action [10, 11].

Paclitaxel is a diterpenoid taxane derivative that was first isolated from *Taxus brevifolia* by Wani in 1971 [12]. It possesses excellent antitumor activity in a wide variety of tumor models, especially in NSCLC [13]. Its antitumor actions are attributed to its ability to promote tubulin assembly into microtubules [14]. In the presence of paclitaxel, depolymerization of the microtubules is inhibited, thereby interfering with the G_2 and M phases of the cell cycle [15]. In spite of its excellent antitumor activity, paclitaxel is not cell specific.

Octreotide (SMS 201-995, Sandostatin™) is an octapeptide analog of endogenous SST and binds to SSTR-2, SSTR-3 and SSTR-5 [16]. By virtue of these properties, we thought that octreotide had the potential be a suitable vehicle for delivering paclitaxel to its intracellular target. Therefore, we developed a series of cytotoxic octreotide conjugates that contain paclitaxel and evaluated their cytotoxicity in two NSCLC cell types, namely, Calu-6 cells, which are known to express SSTRs and A549 cells, whose expression of SSTRs is considered to be low [17].

MATERIALS AND METHODS

Materials. The human NSCLC A549 cell line was obtained from the Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai. The human NSCLC cell line Calu-6 was purchased from Tianjin

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Abbreviations used: DEPC – diethylpyrocarbonate, HPLC – high-performance liquid chromatography, NSCLC – non-small-cell lung cancer, PyBOP – benzotriazol-1-yloxy-tris-pyrrolidinophosphonium, SST – somatostatin, SSTR – somatostatin receptor, WP-06-1 – 2'-succinyl-paclitaxel.

Medical University Cancer Institute (China). Cultured human fibroblast cells were obtained from human scar tissue and were supplied by Dr. Bin Xu, of the Central Laboratory of Qilu Hospital (China); and Dr. Bin Xu had got the permission of Ethical committee and patients' agreement for the cultured human fibroblast cells. Roswell Park Memorial Institute Medium 1640 (RPMI), fetal bovine serum, and typsin were purchased from Invitrogen; TRIzol reagent and diethylpyrocarbonate (DEPC) were purchased from Sangon, Shanghai; RT-PCR Kit and DNA Marker DL2000 were purchased from TaKaRa Biotechnology Co. Ltd. (China); The five *SSTR* subtypes and *β-actin* primers were made by Invitrogen. Paclitaxel was purchased from Manfangyuan Chemical Industry Co., Ltd., China; Octreotide was purchased from Zillion Co. Ltd. (China); and benzotriazol-1-yloxy-tris-pyrrolidinophosphonium (PyBOP) was purchased from Shanghai Medpep Co. Ltd. (China).

Synthetic chemistry. The conjugates were synthesized by the Pharmaceutical Chemistry Institute of Pharmacy College, Shandong University. Many researchers have reported that the 2' position of paclitaxel is a suitable site for reversible derivatization [18–20]. Structure-activity studies on pacliatxel revealed that the C-13 ester side chain and its 2'-hydroxl group appear essential for tubulin binding [13]. This information suggests that the 2' and 7' position are the most suitable sites for reversible derivatization [21]. 2'-succinyl-paclitaxel (WP-06-1) was synthesized by the procedure described by Cavallaro et al [20]. It was activated by PyBOP and then coupled to octreotide. Two kinds of conjugate were purified by high-performance liquid chromatography (HPLC). WP-06-2A was the broad singlet product purified by HPLC (HPLC. 15.67 min.; MS. 1998.7; MW. 1996.27) and WP-06-2B was a pure singlet product purified by HPLC (HPLC. 20.85min.; MS. 2892.8; MW. 2890.19).

Cell culture. A549 cells were cultured in RPMI-1640 that contained 10% FBS. Calu-6 cells were cultured in 15% FBS. Fibroblast cells were cultured in RPMI-1640 medium that contained 20% fetal bovine serum. All culture media were replaced with fresh media every two to three days. The cells were cultured at 37 °C in 5% CO_2/95% air and were used when they were in their growth phase.

The detection of SSTR mRNA by RT-PCR. The expression of SSTR mRNA using RT-PCR was performed according to the manufacturer's instructions. Total RNA was extracted using TRIzol reagent. An aliquot (1 μg) of total RNA was reverse transcribed using AMV-reverse transcriptase and then amplified using specific primers for SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5 (Table 1). β-Actin was used as the internal control. The PCR conditions were as follows: (I) denaturing for 40 s at 94 °C; (II) annealing for 40 s at 55 °C for SSTR2 and SSTR5 or for 40 s at 57 °C for SSTR1, SSTR3 and SSTR4; (III) extension for 1 min at 72 °C; and (IV) final extension for 5 min at 72 °C cycled 30 times. The PCR products were visualized by ethidium bromide staining and electrophoresis in 2% agarose. The optical density (OD) of the target band was corrected for the corresponding β-actin band. The results were expressed as the OD ratio.

Table 1. RT-PCR Primers

Index	Primers	Length(bp)
SSTR-1	Forward 5'-ATGGTGGCCCTCAAGGCCGG-3'	
	Reverse 5'-CGCGGTGGCGTAATAGTCAA-3'	318
SSTR-2	Forward 5'-TCCTCTGGAATCCGAGTGGG-3'	
	Reverse 5'-TTGTCCTGCTTACTGTCACT-3'	332
SSTR-3	Forward 5'-GGAGAAGACTGAGGAGGAGG-3'	
	Reverse 5'-TTTCCCCAGGCCCTACAG-3'	235
SSTR-4	Forward 5'-ATCTTCGCAGACACCAGACC-3'	
	Reverse 5'-ATCAAGGCTGGTCACGACGA-3'	321
SSTR-5	Forward 5'-CGTCTTCATCATCTACACGG-3'	
	Reverse 5'-GGCCAGGTTGACGATGTTGA-3'	223
β-actin	Forward 5'-ATCATGAAGTGTGACGTGGAC-3'	
	Reverse 5'-AACCGACTGCTGTCACCTTCA-3'	461

Cell proliferation assay. Cell proliferation was assessed by the MTT-based cytotoxicity assay. Cells were seeded at 4000 cells/well in 96-well plates, and the protocol of the MTT assay was the same as that described by Rivera et al. [22].

To investigate whether WP-06-1 retains the toxicity of paclitaxel, we first treated A549 cells with different concentrations (0.01, 1, 100, 1000 and 10 000 nmol/L) of WP-06-1 and paclitaxel for 24 h. The cytotoxicity of the conjugates in A549 cells and Calu-6 cells was then assessed using concentrations of 0.01, 1, 100 and 1000 nmol/L conjugates for 24 h, 48 h and 72 h.

To determine whether WP-06-2A and WP-06-2B cause cytotoxicity by binding to SSTRs, A549 cells were pretreated with 10μmol/L octreotide for 30min before 1μmol/L conjugates were added. It is known that fibroblasts are low-SSTR-expressing cells [23, 24]. Therefore, we chose these cells as the SSTR-negative control cells. The fibroblasts were treated by different concentrations (0.01, 1, 100, and 1000 nmol/L) of conjugates and paclitaxel for 24 h.

Cell-cycle analysis. Cell cycle perturbations were determined after a 24 h treatment of 1 μmol/L paclitaxel, WP-02-A, WP-02-B by flow cytometry using a Fluorescence-Activated Cell Sorter (FACS) (FC500, Beckman Coulter Co. Ltd., USA).

Statistical analysis. SPSS statistical software (version 12.0) was used for analyses. Statistical significance was determined using the analysis of variance (ANOVA). Data are expressed as mean ± standard deviation (SD). Data were deemed statistically significant at $p < 0.05$.

RESULTS

Expression of SSTRs in A549 cells, Calu-6 cells and fibroblasts. The expression of mRNA for SSTR1, SSTR2, SSTR4 and SSTR5 was detected in A549 and Calu-6 cells. In the A549 cell line, the expression of SSTR2 mRNA was conspicuous, whereas the expression of SSTR5 mRNA was weak. The expression of SSTR5 mRNA in Calu-6 cells was obvious, but the expression of SSTR2 mRNA was not marked (Fig. 1). Neither cell line expressed SSTR3 mRNA nor mRNA was detected in fibroblasts for any subtype of SSTR.

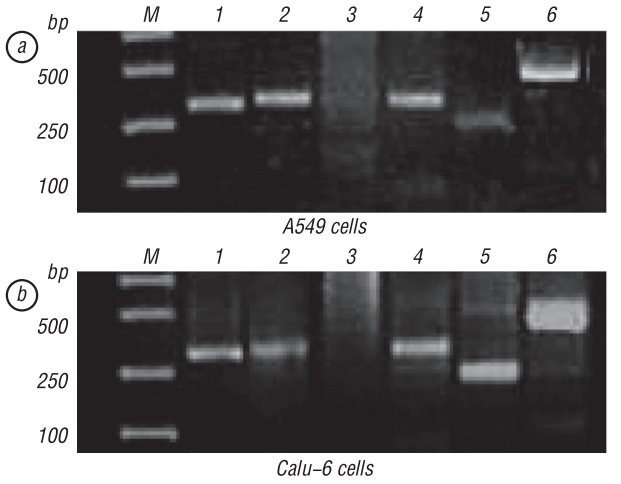

Fig. 1. The detection of mRNA for SSTRs in A549 (*a*) and Calu-6 (*b*) cells by RT-PCR. Calu-6 and A549 cells did not express the mRNA for SSTR-3. Lane M, marker; Lane 1, SSTR-1; Lane 2, SSTR-2; Lane 3, SSTR-3; Lane 4, SSTR-4; Lane 5, SSTR-5; Lane 6, β-actin

Toxicity of the WP-06-1. There were no differences in the cytotoxic activity of WP-06-01 and placlitaxel in A549 cells (Table 2). This result established that the succinyl group on the 2' position of paclitaxel is not essential for its toxicity. WP-06-1 retains the toxicity of paclitaxel.

Table 2. Cell viability of A549 cells after a 24 h treatment of WP-06-1 and paclitaxel (%, mean ± SD)

	Concentration (nmol/L)					
	0	0.01	1	100	1000	10 000
Paclitaxel	100	84.4 ± 5.3	82.5 ± 3.1	73.6 ± 6.7	64.9 ± 6.3	69.2 ± 5.6
WP-06-1	100	85.3 ± 1.3	82.5 ± 6.2	70.3 ± 4.8	72.9 ± 5.1	65.2 ± 2.2

Toxicity of the conjugates in SSTR-positive cells. The conjugates inhibited the growth of A549 and Calu-6 cells in a concentration-dependent manner (Fig. 2, *a* and *b*). WP-06-2B was significantly more cytotoxic than WP-06-2A and paclitaxel at low concentrations (0.01, 1 and 100 nmol/L) in A549 cells ($p < 0.05$). At 10 μmol/L, all the drugs caused precipitates in the culture media. There were no differences in the viability of A549 cells when treated with 1 μmol/L or 10 μmol/L paclitaxel. However, 10 μmol/L WP-06-2B and WP-06-2A were more cytotoxic than that observed at 10 μmol/L paclitaxel in A549 cells ($p < 0.05$). At this concentration, the viability of A549 cells was 45.7 ± 6.9% with WP-06-2A, 46.7 ± 9.0% with WP-06-2B treatment whereas for paclitaxel, viability was 69.2 ± 5.6% (see Fig. 2, *a*). In Calu-6 cells, the two conjugates and paclitaxel caused concentration-dependent cytotoxicity to the same degree (see Fig. 2, *b*).

The conjugates also inhibited the growth of A549 and Calu-6 cells in a time-dependent manner (Fig. 2, *c* and 2, *d*). In A549 cells, 100 nmol/L WP-06-2B showed higher cytotoxicity than WP-06-2A and paclitaxel at 24 h. When the exposure times to the conjugates and paclitaxel were extended to 48–72 h, there were no differences in the relative viability or cytotoxicity in A549 cells (see Fig. 2, *c*). In Calu-6 cells, 100 nmol/L WP-06-2B showed less cytotoxicity than WP-06-2A and paclitaxel at all exposure times (see Fig. 2, *d*).

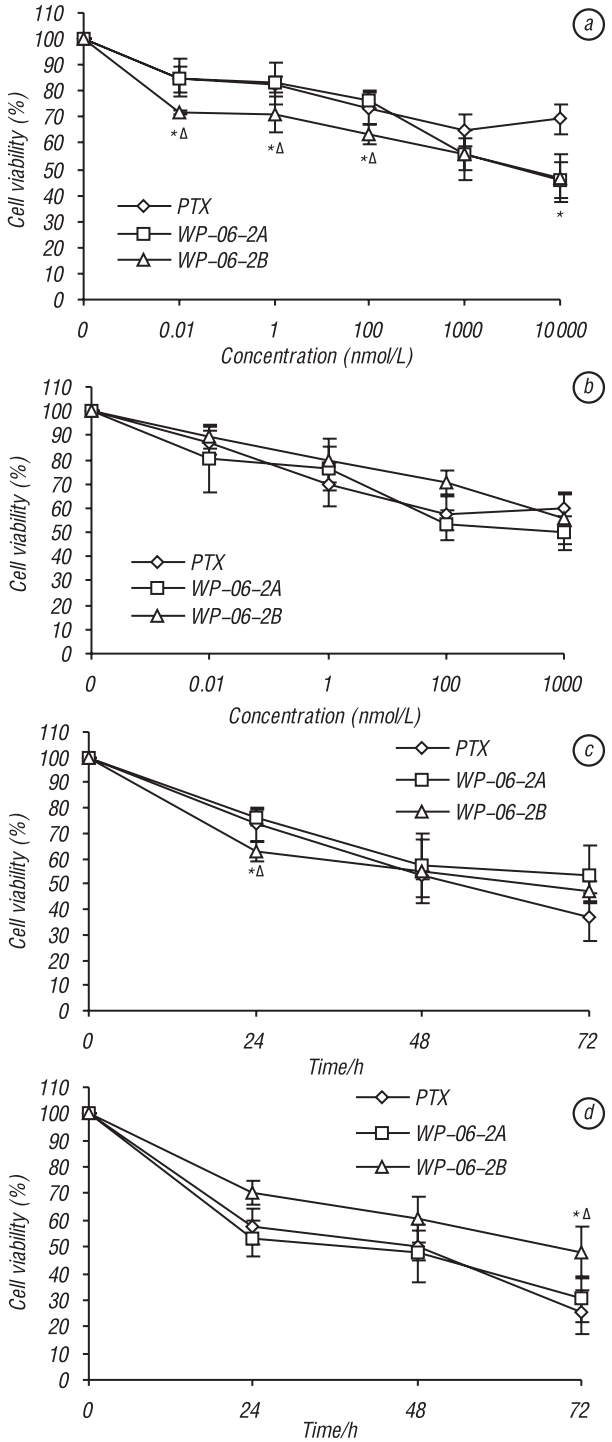

Fig. 2. The conjugates inhibited the growth of A549 and Calu-6 cells. Figures *a* and *b* show that 24 h exposure of A549 cells (*a*) and Calu-6 cells (*b*) to the conjugates inhibited cell growth in a concentration-dependent manner. Data of treatment with higher concentrations are not shown, due to precipitation in cell media. Figures *c* and *d* show the time-dependent inhibitory effect of 100 nmol/L conjugates on the growth of A549 (*c*) and Calu-6 (*d*) cells. (Mean ± SD. $^{*}p < 0.05$ *vs* PTX; $^{\Delta}p < 0.05$ *vs* WP-06-2A)

Octreotide modified the cytotoxicity of WP-06-2A and WP-06-2B, but ameliorate the cytotoxicity of paclitaxel. Following 24 h exposure to 1 μmol/L WP-06-2A, the viability of A549 cells was 55.4 ± 9.8%. Pretreatment for 30 min with 10 μmol/L octreotide increased the viability to 63.7 ± 5.4%. A similar result was seen when 1 μmol/L WP-06-2B was used. Pretreatment with octreotide increased cell viability from 55.8 ± 6.1% to 71.8 ± 9.6%. In contrast,

pretreatment with octreotide exacerbated the cytotoxic effects of 1 μmol/L paclitaxel (59.2 ± 6.4% vs 64.9 ± 6.3%; $p < 0.05$) (Table 3). Pretreatment of octreotide therefore ameliorates the cytotoxicity of the conjugates but potentiates the cytotoxicity of paclitaxel.

Table 3. Cell viability of A549 cells after a 24h treatment with/without 10 μmol/L octreotide pretreated for 30 min (%, mean ± SD)

	Control	Paclitaxel	WP-06-2A	WP-06-2B
Non-pretreated	100	64.9 ± 6.3	55.4 ± 9.8	55.8 ± 6.1
OCT pretreated	87.9 ± 9.9	59.2 ± 6.4*	63.7 ± 5.4*	71.8 ± 9.6*

*$p < 0.05$, *vs* Non-pretreated.

Toxicity of the conjugates in fibroblasts (SSTR-negative) cells. Changes in cell morphology were observed in fibroblasts following 24 h exposure to 1 μmol/L paclitaxel (data is not shown). These changes were associated with a reduction in cell viability (64.7 ± 8.6%). Exposure to 1 μmol/L conjugates for 24 h caused no overt changes in cell morphology, but was associated with moderate reductions in cell viability (WP-06-2A, 86.1 ± 1.8%; WP-06-2B, 90 ± 5.6%). The toxicity of the conjugates on fibroblast cells was significantly lower ($p < 0.05$) than that of paclitaxel.

Analysis of cell cycle. The G_2/M ratio increased from 13.4% in untreated A549 cells to 44.9% in A549 cells exposed to 1 μmol/L paclitaxel for 24 h (Fig. 3). Exposure of these cells to 1 μmol/L of two conjugates for 24 h increased this ratio further (WP-06-2A, 55.8%; WP-06-2B, 75.4%) (see Fig. 3).

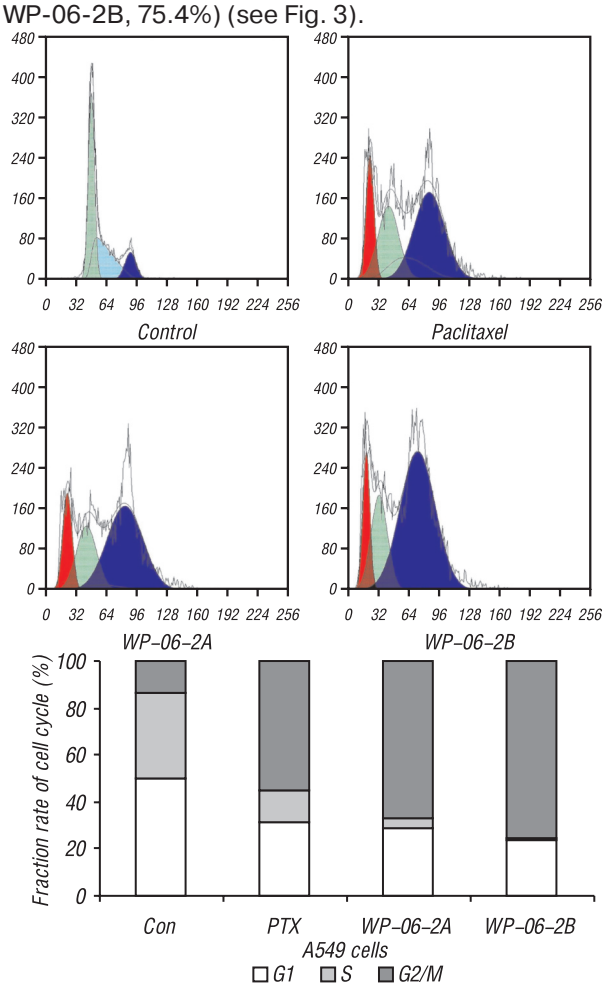

Fig. 3. The cell cycle perturbations of A549 cells determined using FACs Scan flow cytometry after a 24 h exposure to 1 μmol/L paclitaxel, WP-06-2A and WP-06-2B. Control (Con) represents the results of A549 cells that were not exposed to any drugs

DISCUSSION

Over the past decade, several analogs of somatostatin have been developed for the targeted delivery of chemotherapeutic agents and antisense peptide nucleic acids [25–28]. In doing so, these recent advances in the synthesis and evaluation of such compounds have contributed to the establishment of the concept of targeted drug therapy. Remarkable progress has also been made on the identification of tumors and their metastases that express somatostatin receptors. Current preclinical data provide good evidence that SSTR-positive tumors can be targeted successfully *in vivo* using somatostatin analogs coupled to chemotherapeutic agents, which are more effective and considerably less toxic than unconjugated cytotoxic radicals [29]. The anti-tumor drug, paclitaxel is therapeutically beneficial for NSCLC. However, it is not cell-specific, which is a major drawback. Therefore, conjugates of octreotide and paclitaxel may be useful for targeted drug therapy for NSCLC.

Several investigators have reported that human NSCLC may overexpress SSTRs [5, 6]. However, the expression of SSTRs by NSCLC cell lines remains controversial. In agreement with the results of Ferone et al [7], we detected mRNA for SSTR-2 and SSTR-5 in Calu-6 cells and the expression of SSTR-5 was greater than that of SSTR-2. We found mRNA for SSTR1 and SSTR4 in Calu-6 cells. Nayak et al [17] reported that A549 cells do not express SSTRs. Given this result, we intended to use A549 cells as a SSTR-negative control cell line. However, we established that these cells expressed all the subtypes of SSTR except SSTR-3. Furthermore, we found that the expression of SSTR-2 was more pronounced than that of SSTR-5. As a result, we had two cells that we could use to evaluate the targeted delivery of paclitaxel using an octreotide carrier.

In our experiment, WP-06-2A and WP-06-2B inhibited the growth of A549 and Calu-6 cells in a concentration- and time-dependent manner and the suppression of cell growth was potentiated at the higher concentrations. When the exposure time was extended to 72 h, the viabilities of A549 and Calu-6 cells were extremely low. FACS analysis showed that the G_2/M ratio in A549 cells in the presence of 1 μmol/L paclitaxel or the conjugates for 24 h increased. The result indicated that both WP-06-2A and WP-06-2B maintained the cytotoxicity of paclitaxel. Within our experiment, we showed that SSTR-negative fibroblasts, WP-06-2A and WP-06-2B were less cytotoxic than paclitaxel. When A549 cells were pretreated with excess octreotide, the cytotoxicities of both WP-06-2A and WP-06-2B decreased and the cytotoxicity of paclitaxel increased. These results show that WP-06-2A and WP-06-2B can bind selectively to SSTRs and cause cell death specially [25, 29]. Because WP-06-2A and WP-06-2B were cytotoxic in tumor cells expressing SSTRs, we suggest that the development of paclitaxel-octreotide conjugates may be valuable for targeted therapy of NSCLC.

The different expressions of SSTRs influenced the cytotoxicity of WP-06-2B. In A549 cells, which overex-

press SSTR-2, the cytotoxic potency of WP-06-2B was greater than that of paclitaxel at low concentrations. In Calu-6 cells, which overexpress SSTR-5, 100 nmol/L WP-06-2B was less cytotoxic than paclitaxel. However, the different expressions of mRNA for SSTR-2 and SSTR-5 have little influence on the cytotoxicity of WP-06-2A. When compared to the cytotoxic effects of free paclitaxel, the cytotoxic effects of WP-06-2A were similar in A549 and Calu-6 cells, but were less toxic in fibroblasts. Culler et al [30] reported that the affinity of octreotide for SSTR-2 is higher than its affinity to SSTR-5. Therefore, the affinity of WP-06-2B for SSTR-2 might be greater than its affinity for SSTR-5. This difference in affinity could account for the different cytotoxicity of WP-06-2B in A549 and Calu-6 cells because of the different expressions of mRNA for SSTR-2 and SSTR-5 in the two cell lines. When tumor tissue over-expresses mRNA for SSTR-2, one might expect that WP-06-2B would have more potent antitumor effects and less toxic side effects than WP-06-2A. Further investigations are needed to assess the biological properties of WP-06-2B *in vivo*.

There was an interesting result in our experiment. All the drugs caused precipitates in cell culture media when 10 μmol/L concentrations were used. The viability of A549 cells that were exposed to 10 μmol/L paclitaxel was the same as that of A549 cells treated with 1 μmol/L paclitaxel. Yet, the viabilities of A549 cells that were exposed to 10 μmol/L WP-06-2A and WP-06-2B progressively decreased and were lower than those of cells exposed to 10 μmol/L paclitaxel. It is known that the aqueous solubility of paclitaxel is extremely low [20] and octreotide is water-soluble [20, 31]. Therefore, the higher cytotoxicity of the conjugates might be due to their being more water- solubility than paclitaxel in aqueous cell culture medium.

Schally et al. [10, 32] have developed a cytotoxic analog of somatostatin, AN-238, in which the somatostatin carrier peptide RC-121 was linked to 2-pyrrolino-doxorubicin (AN-201), which is a potent derivative of doxorubicin. When compared to AN-201, they found that AN-238 was more effective and less toxic in a NSCLC H-838 xenogenic graft in nude mice. Moody et al [8] synthesized camptothecin-somatostatin conjugate by linking camptothecin to the amino terminal of somatostatin analog and reported that the conjugate inhibited the growth of human small cell lung cancer cells. Huang et al. [25] synthesized octreotide-conjugated paclitaxel by coupling paclitaxel succinate to the amino terminal of octreotide. When comparing the effects of free paclitaxel in human breast MCF-7 carcinoma cells, they showed that octreotide-conjugated paclitaxel retained the biological activity of paclitaxel by inducing the formation of tubulin bundles and eventually causing apoptosis. All of our experimental results were obtained using cultured cell systems. Given our results, further research on *in vivo* cell selectivity and cytotoxicity of WP-06-2A and WP-06-2B is warranted.

In conclusion, the results of this study show that NSCLC cell lines, such as A549 and Calu-6 cells, express SSTRs. Irrespective of whether paclitaxel succinate was coupled to the amino acid end and/or the free amino terminus of lysine of octreotide, WP-06-2A and WP-06-2B were potent inhibitors of cell growth of NSCLC cells *in vitro*. These results suggest strongly that conjugates of somatostatin analogs and paclitaxel could be used as efficacious agents for selective targeted cancer chemotherapy *in vitro* and could be a promising therapeutic modality for the treatment of NSCLC.

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КОНЪЮГАТЫ ПАКЛИТАКСЕЛА-ОКТРЕОТИДА ИНГИБИРУЮТ РОСТ КЛЕТОК НЕМЕЛКОКЛЕТОЧНОГО РАКА ЛЕГКОГО *IN VITRO*

Цель: **оценить эффект конъюгатов паклитаксела-октреотида на рост культивированных клеток немелкоклеточного рака легкого человека.** ***Методы:*** **для определения мРНК подтипов рецептора соматостатина человека (SSTR) применяли ОТ-ПЦР. Анализ цитотоксичности в МТТ-тесте применяли для оценки выживаемости клеток после их инкубации с паклитакселом и конъюгатами. Нарушения клеточного цикла определяли с применением FACS — клеточного сортера.** ***Результаты:*** **установлено, что клеточные линии немелкоклеточного рака легкого A549 и Calu-6 экспрессируют SSTR2 и SSTR5 мРНК. Отмечено эффективное дозо- и времязависимое угнетение роста клеток A549 и Calu-6 паклитакселом и конъюгатами. Для SSTR-негативных фибробластов конъюгаты менее цитотоксичны, чем паклитаксел. Конъюгаты и паклитаксел могут индуцировать повышение соотношения фаз G_2/M в клетках A549.** ***Выводы:*** **конъюгаты паклитаксел-октреотида могут быть использованы как селективные химиотерапевтические агенты для воздействия на немелкоклеточный рак легкого.**

Ключевые слова: **немелкоклеточный рак легкого, октреотид, паклитаксел.**