ONXY-015 Works Synergistically with Chemotherapy in Lung Cancer Cell Lines and Primary Cultures Freshly Made from Lung Cancer Patients

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ABSTRACT

p53 mutations and loss of heterozygosity (LOH) have been detected in >50% of lung cancers. Wild-type p53 can prevent replication of damaged DNA and promote apoptosis of cells with abnormal DNA. A human adenovirus, ONYX-015, which has a deletion in the E1B region, has shown tumor-specific cytolytic effect in tumor cells with nonfunctional p53 and antitumor efficacy that can be augmented by chemotherapeutic agents. A recent report from an independent group, however, indicates that wild-type p53 is necessary for the infection of this replicating virus, and it is in direct contradiction to previous observations of the ONYX group. In this study, we carried out cytopathic effect (CPE) assays using ONYX-015 on five human lung cancer cell lines with known p53 status. Two of these cell lines, NCI-H522 and NCI-H1703, have mutations and LOH in their p53 gene. Both lines were lysed in a dose-dependent manner and showed 100% cytotoxicity at a multiplicity of infection of 0.1. Two additional cell lines, NCI-H2347 and NCI-H838, both of which have wild-type p53 gene, showed near complete lysis at a multiplicity of infection of 1. We demonstrate here that the lung cancer cells with nonfunctional p53 are at least 10 times more sensitive to ONYX-015 cytolyis than the lung cancer cells with wild-type p53. In addition, standard chemotherapeutic agents (paclitaxel and cisplatin) showed a synergistic effect when combined with ONYX-015, and this effect was p53 mutant dependent. Furthermore, we tested the cytolytic effect of ONYX-015 on a panel (n = 7) of primary first-passage cultures made from freshly resected lung cancers. ONYX-015 lysed primary lung cancer cells in six of seven (86%) primary cultures. Two of four primary cultures treated with chemotherapeutic agents had a synergistic effect with ONYX-015. Our data indicate that wild-type p53 is not required for the infection of this replicating virus, and also we demonstrate that ONYX-015 is effective alone and works synergistically with chemotherapeutic agents in lung cancer cell lines and primary cultures. This study suggests that ONYX-015 may be effective, especially in combination with conventional chemotherapy, in the treatment of patients with lung cancer.

INTRODUCTION

Lung cancer is the leading cause of cancer deaths in the United States among both men and women, with >170,000 newly diagnosed cases each year (1). Despite aggressive approaches made in the therapy of lung cancer in the past decades, the 5-year survival rate for lung cancer remains <15% (1). Surgery, chemotherapy, and radiation have been used with generally unsatisfactory results in advanced disease. Improvement in the efficacy of lung cancer treatment is a major public health goal. New therapies based on better understanding of the biology of lung cancer are needed for the treatment of patients with lung cancer. Lung cancers are divided into two major histological classes: NSCLC2 and SCLC. NSCLC (75% of all lung cancers) consists of three major types: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (2). Lung adenocarcinomas and squamous cell carcinomas represent 60–70% of all lung cancers.

Extensive studies have revealed several types of genetic alterations that contribute to lung cancer: ras gene mutation, myc gene amplification, Her-2/neu overexpression, and LOH in chromosome regions 3p, 5q, 8p, 11p, 13q, 17p, and 18q. LOH is highly suggestive of the presence of a tumor suppressor gene at the deleted chromosome site (3). p53, Rb, and the pathways in which they are involved have been described in lung cancer. There are a number of chromosome regions, e.g., 3p, 5q, 9p, and others, thought to harbor currently undiscovered tumor suppressor genes (2). p53 mutations and LOH have been detected in >50% of lung cancers (4). Loss or mutation of p53 tumor suppressor gene is a very common genetic abnormality in many human cancers (5). Germ-line inheritance of one defective p53 gene is responsible for a cancer family syndrome, the Li-Fraumeni syndrome, associated with a greatly increased risk of developing a wide range of cancers (6). The human p53 protein is a 393-amino acid nuclear phosphoprotein. It binds both specifically and nonspecifically to DNA and has specific interactions with a number of viral and cellular proteins that can affect its activity as a transcription factor. The viral proteins include viral oncogene products, SV40 large T antigen, the adenovirus E1B 55K protein, and the human papilloma virus E6 protein (5). The host proteins include the TATA box-binding protein and the MDM-2 protein. The p53 protein is a tumor suppressor that responds to DNA damage. The protein activates one of the two pathways in a cell with DNA damage: either the growth-arrest pathway in which cell division is halted until the DNA damage has been repaired, or the apoptotic pathway in which heavily damaged cells undergo programmed cell death (7). When p53 genes are deleted or mutated, these two protective pathways in the cells become nonfunctional, and the cells become prone to DNA damage and unregulated cell growth.

The better understanding of the p53 protein and its role in lung cancer development has made p53-based gene therapy possible. Clinical studies of adenovirus- and retrovirus-mediated wild-type gene transfer to lung cancer patients have resulted in tumor regression in some patients (7, 8). More recently, ONYX Pharmaceuticals, Inc. (Richmond, CA) has genetically designed a tumor-targeting adenovirus, ONYX-015, that only replicates in cells that lack functional p53 gene and therefore kills tumor cells specifically (9). This genetic design takes advantage of the fact that adenovirus E1B 55K binds (and inactivates) wild-type p53 protein. This binding is essential to virus replication. The newly designed mutant adenovirus ONYX-015 contains an 827-bp deletion in the E1B region and a point mutation at codon 2022 that generates a stop codon. ONYX-015 cannot replicate in normal cells but can replicate in tumor cells lacking functional p53 (9). ONYX-015 has been shown to kill cervical carcinoma cells, colon carcinoma cells, glioblastoma cells, and pancreatic adenocarcinoma cells lacking functional p53 with an efficiency comparable with that of wild-type adenovirus (9). The virus has no effect on normal cells with functional p53 at a MOI of up to 1 pfu/cell, whereas the cells with nonfunctional p53 were killed at MOI of 0.01 pfu/cell. Thus, p53 inactivation increases sensitivity to ONYX-015 by a factor of 100 (10). It was also demonstrated that this virus caused a significant reduction in tumor size and complete regression of 60% of the tumors...
induced by p53-deficient human cervical carcinoma cells in nude mice (10). This virus has entered Phase II clinical trials for the treatment of squamous cell cancers of the head and neck and adenocarcinomas of the pancreas (11).

Recently, Hall et al. (12) showed that d11520 (or ONYX-015) can only generate a CPE in cells with wild-type p53 but not in the cells with mutant p53. They claimed that the virus can only kill cells with wild-type p53, and the cells with nonfunctional p53 are resistant to virus-induced cell death. Their data raised serious questions on the usefulness of ONYX-015 to kill tumor cells.

To determine the potential therapeutic role of ONYX-015 on lung cancer patients, primary human lung cancer cultures and lung cancer cell lines with known p53 status were treated with the virus in this study. Additional experiments testing the potential efficacy of ONYX-015 and conventional chemotherapy (cisplatin and paclitaxol) to lyse these NSCLC cell lines. We tested the cytotoxicity of ONYX-015 against five NSCLC cell lines (NCI-H522, NCI-H1703, NCI-H157, NCI-H838, and NCI-H2347) were obtained from American Type Culture Collection. NCI-H1703 is a lung adenocarcinoma cell line with a missense mutation at codon 285 (GAG→AAG), and NCI-H522 is a lung adenocarcinoma cell line with a single base deletion at codon 191 (CCT→CTT) of p53 gene. LOH of the p53 gene was found in both NCI-H522 and NCI-H1703 cells. NCI-H157 is a lung squamous carcinoma cell line with a nonsense mutation at codon 298. NCI-H838 and NCI-H2347 are lung adenocarcinoma cell lines with wild-type p53 gene sequence. The p53 status of all five cell lines was independently confirmed by DNA sequencing at the University of California and San Francisco Cancer Center core facility.

**Primary Tumor and Normal Peripheral Lung Cell Cultures.** Lung tumors and adjacent normal lung tissues of patients with lung cancer were taken from the operating room at room temperature immediately after resection. The experiments were performed after approval by the Committee of Human Research at the University of California and in accordance with an assurance filed with and approved by the Department of Health and Human Services. The specimens were dissected with scalpels into <5-mm cubes. The pieces of tumor were placed in triple enzyme medium (1× collagenase, 1× hyaluronidase, and 1× DNase; Sigma, St. Louis, MO; Ref. 13) in HBSS (Life Technologies, Inc., Gaithersburg, MD) with a magnetic bar and were then spun on a stir plate at room temperature for 2–3 h, until most of the solid tumor or normal tissue was dissociated. The cells were filtered through a 70-micron nylon cell strainer (Becton Dickinson, Lincoln Park, NJ) and suspended in RPMI 1640 with 10% fetal bovine serum (HyClone Laboratories, Inc., Logan, UT).

**Adenovirus.** ONYX-015 and wild-type adenovirus were supplied by ONYX Pharmaceuticals. ONYX-015 is a chimeric human group C adenovirus that does not express the Mr 55,000 product of the E1B region encoding the Mr 55,000 protein (9). The virus contains a deletion between nucleotides 2496 and 3323 in the E1B region encoding the Mr 55,000 protein. In addition, a C→T transition at codon 2022 in E1B generates a stop codon, preventing expression of a truncated protein from the deleted gene. Wild-type adenovirus is identical to ONYX-015 except in the E1B Mr 55,000 gene region, where the original wild-type sequence is present.

**CPE Assay.** In replicate six-well plates, cells (5 × 10^5) were grown to 90–90% confluence and infected with either ONYX-015 or with wild-type adenovirus for 90 min at increasing MOIs, i.e., 0, 0.01, 0.1, and 1 100 pfu/cell (10). Plates were monitored daily for CPE, and the assay was terminated when essentially total cytolysis was observed at an MOI of 0.01 (MOI of 0.1 for primary cultures) with wild-type adenovirus. In experiments testing combined efficacy of chemotherapy and ONYX-015, cisplatin and paclitaxol (10 nM each) were added to test plates for 24 h immediately after 90-min ONYX-015 treatment. The plates were stained with crystal violet and then analyzed.

**Cell Viability Assay.** Cells were inoculated at densities of 5 × 10^4 in 60-mm culture dishes 24 h before treatments and treated with ONYX-015 at MOI of 0.1, 0.01, and 0.001 with or without cisplatin and paclitaxol (10 nM for each). Culture medium alone was used for mock infection. Cell viability was evaluated at day 8 by trypan blue, followed by cell counting using a standard hemacytometer (12). All experiments were performed in triplicate.

**p53 Mutation Analysis.** SSCP of the p53 gene was carried out on all lung cancer cell lines and tumor samples. A 5.5-μl loading mixture was prepared with 1 μl of the PCR product, 0.5 μl of Genescan 500 size standards (Perkin-Elmer, ABI), a 0.5-μl loading dye (Perkin-Elmer, ABI), 0.5 μl of 100 mM NaOH, and 3.0 μl of deionized formamide. All gels consisted of 0.5× Mutation Detection Enhancement gel (FMC, Rockland, ME) with 2.5–10% glycerol (Sigma) and 1× TBE (Life Technologies). All gels were run at a constant 60 W, and the SSCP results were analyzed using Genescan software (ABI) with analysis procedures and settings as described by the manufacturer. The direct DNA sequencing was carried out by University of California and San Francisco Cancer Center core facility.

**Immunohistochemistry.** Immunohistochemistry was done using snap-frozen, OCT (Tissue-Tek, Torrance, CA)-embedded tumors that had been cut into 6-μm sections, hydrated, and digested with Pronase. The primary antibody (DO-7; DAKO Corp.), which reacts with the wild and mutant types of the intracellular p53 protein (14), was applied at 1:500 dilution, and tissues were incubated at room temperature for 1 h. Universal DAKO Labeled Streptavidin-Biotin kit (LSAB+) and the secondary antibody was then applied. Diamobenzidine was used as the chromogen, and the slides were counterstained with hematoxylin.

**RESULTS**

Primary normal human peripheral lung culture cells and C33A (p53-deficient) cervical carcinoma cells were used as controls for the sensitivity study of ONYX-015 and wild-type adenovirus. Complete cytolysis was seen in normal cells treated with wild-type adenovirus at a MOI of 0.01 within 10 days. No significant CPE was observed at the same time points with a MOI of 1, 0.1, and 0.01 in ONYX-015-treated normal cells. Cytolysis equivalent to that of the wild-type virus was only evident when a much higher titer was used (MOI >10) in these cells. C33A, with an inactivating mutation at codon 273 of the p53 gene, was used as positive control cell line. When monitored for an extended period of 1–2 days (i.e., 11–12 days), C33A cells were completely lysed by the wild-type virus at a MOI of 0.001 and by ONYX-015 at a MOI of 0.01.

We tested the cytotoxicity of ONYX-015 against five NSCLC cell lines (NCI-H522, NCI-H1703, NCI-H157, NCI-H2347, and NCI-H838) using CPE assays. Both NCI-H1703 and NCI-H522 are lung adenocarcinoma cell lines containing only a mutated p53 gene (Table 1). NCI-H157 is a squamous cell lung cancer cell line with a nonsense mutation at p53 codon 298. Both NCI-H2347 and NCI-H838 have wild-type p53 gene. In triplicate experiments, ONYX-015 lysed NCI-H522 and NCI-H1703 cells (Fig. 1) in a dose-dependent manner (Fig. 2A). Complete cytolysis was evident at a MOI of 1 and 0.1 pfu/cell 10 days after infection. In three other lung cancer cell lines NCI-H157, NCI-H838, and NCI-H2347, complete cytolysis was observed at a MOI of 1 (Table 1).

To determine the synergistic effect of ONYX-015 with conventional NSCLC chemotherapy, a sensitivity study was carried out on these NSCLC cell lines. We tested the cytotoxicity of cisplatin and paclitaxol at a concentration of 10 μM, 1 μM, 100 nM, 10 nM, 1 nM, and 0.1 nM. Cells were killed completely by both agents at 10 μM, 1 μM, and 100 nM. At 10 nM cisplatin and paclitaxol, cells were able to grow to complete confluence, and minimal cytotoxicity was seen. The results are comparable in all these NSCLC cell lines. This chemotherapy (10 nM cisplatin and 10 nM Taxol) was combined with the ONYX-015 treatment for all five NSCLC cell lines (Table 2). Synergistic effects were evident in three NSCLC cell lines with p53 mutations, i.e., NCI-H522, NCI-H1703, and NCI-H157.

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ONYX-015 AND LUNG CANCER

Table 1  CPE of wild-type adenovirus (WT) and ONYX-015 on lung cancer cell lines and lung cancer primary cultures

<table>
<thead>
<tr>
<th>Cells</th>
<th>CPE</th>
<th>p53 status</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3IA (cervical carcinoma)</td>
<td>+ 0.01</td>
<td>CGT→TGT codon 273</td>
<td>(25)</td>
</tr>
<tr>
<td>Normal lung primary culture</td>
<td>+ 0.1</td>
<td>CCA→CT codon 191</td>
<td>(26)</td>
</tr>
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<td>NSCLC cell lines</td>
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<td></td>
</tr>
<tr>
<td>NCI-H522</td>
<td>+ 0.1</td>
<td>NM: p53 IHC+</td>
<td>(27)</td>
</tr>
<tr>
<td>NCI-H1703</td>
<td>+ 0.1</td>
<td>NM: p53 IHC+</td>
<td>(28)</td>
</tr>
<tr>
<td>NCI-H157</td>
<td>+ 0.1</td>
<td>NM: p53 IHC+</td>
<td>(29)</td>
</tr>
<tr>
<td>NCI-H2347</td>
<td>+ 0.1</td>
<td>Wild-type</td>
<td>(29)</td>
</tr>
<tr>
<td>NC1-H838</td>
<td>+ 0.1</td>
<td>Wild-type</td>
<td>(29)</td>
</tr>
<tr>
<td>Primary tumor cultures</td>
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<tr>
<td>NSCLC patient 1</td>
<td>+ 1</td>
<td>TAC→TGC codon 163</td>
<td>(27)</td>
</tr>
<tr>
<td>NSCLC patient 2</td>
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<td>(28)</td>
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<td>LS patient 7</td>
<td>+ 1</td>
<td>NM: p53 IHC+</td>
<td>(29)</td>
</tr>
</tbody>
</table>

* Lowest MOI giving complete lysis was presented.
* No mutation detected.
* Immunohistochemical staining status of p53.
* Primary lung sarcoma.

Combined with chemotherapy, the CPE of ONYX-015 was augmented by at least 10-fold (Fig. 3A). Complete cell lysis was shown at a MOI of 0.001, 0.01, and 0.1 on NCI-H522, NCI-H1703, and NCI-H157, respectively, in synergistic fashion. These three cell lines were sensitized by ONYX-015 to this low-dose chemotherapy, which does not work effectively on these cells when used alone. No significant synergistic effect was observed in the two NSCLC cell lines with intact p53 sequence, i.e., NCI-H2347 and NCI-H838.

Seven primary lung cancer cultures, including five NSCLCs and two primary lung sarcomas, were studied for the CPE of ONYX-015. In all seven lung cancer primary cultures tested, 90–100% cells were killed at a MOI of 1. Complete cell lysis in one primary tumor culture and partial lysis (30–50%) in the other three primary lung cancer cultures were evident at a MOI of 0.1. Wild-type adenovirus served as a control for effective infection in all experiments.

In one NSCLC case, we were able to establish primary cultures from both normal lung and lung tumor tissues. ONYX-015 lysed most of the tumor cells at a MOI of 1 and 0.1, whereas no significant cytolytic effect was noticed in normal culture at a MOI of 1. Synergistic effects of ONYX-015 with standard chemotherapy were studied in four of these primary lung cancer primary cultures (Table 2). At a MOI of 0.1, ONYX-015 showed synergistic effect (5–10-fold) with low-dose standard NSCLC chemotherapy in two of the four tumors, whereas no significant synergistic effect was observed in the other two tumors, despite an effect seen with the ONYX-015 virus alone.

A cell viability assay was carried out using NCI-H1703 at 8 days after infection; dose-dependent cytolysis is shown (Fig. 2B). A synergistic effect with chemotherapeutic agents (10 nM cisplatin and 10 nM paclitaxol) was also evaluated on day 8 (Fig. 3B). The treatment variable (with two levels: Mock and Mock+Chem0) was not significant ($P = 0.2471$ by the F test). The MOI 0.001 versus MOI 0.001 + Chem0 was significantly different, however ($P = 0.0024$ by the Student t test).

The p53 status of these lung cancer cell lines and lung tumors was determined by SSCP and direct sequencing of the 5–8 exon of the p53 gene. The p53 status of all five NSCLC cell lines was confirmed by our own SSCP and sequencing analysis. One p53 exon 5 mutation was detected in the DNA from a lung cancer tumor tissue by SSCP and direct sequencing (Table 1). In addition, immunohistochemical staining of p53 was performed on all lung cancer tissues (Table 1).

**DISCUSSION**

These experiments demonstrate that ONYX-015 can infect and lyse effectively NSCLC cell lines, and more clinically relevant, these data indicate that the ONYX-015 virus kills fresh human primary lung cancer cells and work synergistically with standard NSCLC chemotherapy. In this study, no significant cytolytic effect was noticed in primary normal lung cultures prepared from freshly resected specimens. ONYX-015 did not cause significant CPEs in normal human small airway epithelial cells, as shown in an earlier report (10). This virus has been genetically designed to replicate specifically in cells that lack functional p53 gene, causing tumor cell lysis. Because NSCLC is, in part, a genetic disease, gene-based therapy is both a logical and attractive strategy. More than half of all lung cancers have p53 mutations and LOH. It is likely that a much higher percentage of lung cancers have some defects in p53-dependent growth regulation pathway (15, 16). Therefore, lung cancer is a very good target for the ONYX-015 virus (3). ONYX-015 has the potential to offer a new form of therapy based on the molecular genetics and biology of lung cancer cells. This virus has already been shown to be safe and has entered Phase II clinical trials for the treatment of patients with head and neck squamous cell carcinoma and adenocarcinomas of the pancreas (11).

We think that primary tumor cultures may provide more clinically relevant information, in addition to other preclinical studies. Originally, nude mice were used to study the antitumor efficacy of ONYX-015 in some cancer cell lines; immunocompetent rodent tumor models are not applicable for studying the antitumor efficacy of ONYX-015 because adenoviruses can only replicate effectively in human cells. The synergistic effect shown in 50% primary lung cancer cultures tested with conventional chemotherapy makes ONYX-015 more at-
tractive for treatment of lung cancer. It is possible that in the clinical setting ONYX-015 will enhance standard chemotherapy to a greater extent, because the virus will be administrated at higher titers.

There is increasing evidence that other possible defects in p53 signal pathway may be involved in the development of lung cancer. Overexpression of MDM-2 protein was found in 70% of the NSCLCs tested (16). Recently, it was reported that the expression of p14-ARF is altered in ~40% of NSCLCs (16). The p14-ARF, which links tumor suppressors Rb and p53 (17), promotes MDM-2 degradation and stabilizes p53 (18). Thus, the p53 protein maybe indirectly inactivated by mechanisms other than p53 mutations in the rest of lung cancers. This, we believe, may explain in part why ONYX-015 effectively lyses those tumor cells with intact p53 gene, as described in some other studies (12, 19). In theory, ONYX-015 should kill most, if not all, lung cancers, along with many other types of cancers. Nevertheless, other unknown mechanisms by which ONYX-015 can replicate independently of the cell cycle have been suggested (20).

The combination of ONYX-015 and conventional NSCLC chemotherapy had greater antitumor efficacy than ONYX-015 alone in most lung cancer cell lines and primary cultures tested here. The effect appears to be synergistic, because minimal cytotoxicity was observed when either of these chemotherapeutic agents was used alone at identical concentrations. The mechanism of this synergistic effect is under study. The possibility that each agent works independently on different cell populations cannot be ruled out, although it is unlikely to be the case here. It has been reported that the adenovirus E1A gene expression can activate the cell cycle (21) and/or increase the cellular sensitivity to chemotherapy in a p53-independent manner (22). This may be a possible mechanism by which the synergistic effect occurs in some NSCLC cells, because all three p53-mutant NSCLC cell lines showed a synergistic effect whereas no significant effect was noticed in the other two cell lines with the wild-type p53 gene. There is a possibility that p53 function may not be completely lost in these two cell lines with wild-type p53 gene, and it might explain why these two cell lines were less sensitive to ONYX-015 when compared with the two with nonfunctional p53 genes. Other unknown functions of p53 in viral replication or cell cycle control may play a role in this synergistic effect.

Adenovirus- and retrovirus-mediated wild-type gene transfer to lung cancer patients has entered Phase I clinical trials (7, 8). Wild-type p53 was delivered to tumor cells by direct intratumoral injection. Wild-type p53 can induce apoptosis in tumor cells, therefore causing tumor regression. Like other gene replacement strategies, the problems of gene transfer remain, e.g., efficient gene transfer requires a high-titer recombinant retrovirus; adenovirus can achieve high-efficiency transduction but can bind and inactivate wild-type p53. The replacement of wild-type p53 might not affect some of those tumors with a nonfunctional p53 pathway.

One of the major problems for wild-type gene replacement therapy is immune-mediated clearance. Because ONYX-015 is a replicating virus, cell-mediated immunity directed toward infected tumor cells may actually enhance the efficacy of ONYX-015 in patients with tumor. Antibody-mediated immune response may not affect ONYX-015 significantly because of the relatively poor penetration of antibodies into...
solid tumor masses. ONYX-015 is a tumor-targeting recombinant adenovirus because it takes advantage of both the normal function of the p53 protein and the properties of adenoviral proteins. ONYX-015 replicates, selectively, in any tumor cell with nonfunctional p53. However, efficacy of ONYX-015 therapy may be restricted, in part, by a host immune response to adenoviral proteins. ONYX-015 replicates, selectively in p53-deficient human tumor cells [see comments]. Science (Washington DC), 274: 373–376, 1998.

Fig. 3. Synergistic effect with conventional chemotherapy in NSCLC cells. A. Synergistic CPE with chemotherapeutic agents paclitaxel (10⁻⁸ M) and cisplatin (10⁻⁸ M) in both NCI-H522 and NCI-H1703 cells. B. Synergistic effect was shown in NCI-H1703 cells by cell viability assay. The MOI 0.001 versus MOI+Chemo 0.001 is significantly different (P = 0.0024, Student t test). Bars, SD.

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