Improving Combination Cancer Therapy by Acetaminophen and Romidepsin in Non-small Cell Lung Cancer Cells

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Combination chemotherapy is more effective than mono-chemotherapy and is widely used in clinical practice for enhanced cancer treatment. In this study, we investigated the potential synergistic effects of acetaminophen, a common component in many cold medicines, and romidepsin, a histone deacetylase (HDAC) inhibitor, in the A549 non-small cell lung cancer (NSCLC) cell line. The combination of acetaminophen and romidepsin also exerted significant cytotoxicity and apoptosis induced by activation of caspase-3 on tumor cells in vitro. Moreover, combination therapy significantly induced increased production of chemokines that stimulate migration of activated T-cells into tumor cells. This mechanism can lead to active T-cell mediated anti-tumor immunity in addition to the direct cytotoxic chemotherapeutic effect. Activated T-cells led to enhanced cytotoxicity in drug-treated A549 cells through interaction with tumor cells. These results suggested that the interaction between the two drugs is synergistic and significant. In conclusion, our data showed that the use of romidepsin and low concentrations acetaminophen could induce effective anti-tumor effects via enhanced tumor immune and direct cytotoxic chemotherapeutic responses. The combination of acetaminophen with romidepsin should be considered as a promising strategy for the treatment of lung cancer.

Key Words: Chemotherapy, Acetaminophen, Romidepsin, Histone deacetylase inhibitor, A549 cells

INTRODUCTION

Lung cancer is one of the most common of cancer worldwide. There are multiple subtypes, but lung cancers can be categorized into the following two major subtypes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) (Rivas-Fuentes et al., 2015). According to studies, NSCLC accounts for approximately 80–85% of all lung cancer cases. Depending on the staging of lung cancer, patients are eligible for certain treatments ranging from surgery to radiation to chemotherapy, as well as targeted therapy (Provencio et al., 2011; Liu et al., 2018).

Recently, it was demonstrated that a cold medicine used to alleviate pain and reduce fever was effective in cancer therapy. Additionally, many other researchers exhibited that another cold medicine was effective in inhibiting bladder cancer (Matsumoto et al., 2016). Most medicines used to ease symptoms of cold consist of non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are frequently used as analgesic and antipyretic drugs that most probably exert their anti-fever effect by inhibiting cyclooxygenase (COX)-2 (Jozwiak-
Bebenista and Nowak, 2014). Several studies have demonstrated that acetaminophen in particular, induces apoptosis and necrosis in a variety of cells, including cancer cells. Acetaminophen is an antipyretic and analgesic agent, similar to NSAIDs, and has been shown to exert significant anticancer effects in tumor cells. However, long-term acetaminophen administration can lead to serious hepatotoxicity as a main side effect (Liang et al., 2012; Posadas et al., 2012; Yu et al., 2014). Therefore, determining the appropriate acetaminophen treatment concentration should be the main consideration in therapeutic decisions.

Romidepsin is one of a depsipeptide small molecule (MW=540.7) belonging to histone deacetylase (HDAC) inhibitors (Valdez et al., 2015). Several HDAC inhibitors have been reported to act as tumor suppressors that either indirectly contribute to tumor cell death by inducing changes in cell cycle distribution or directly induce apoptosis in various cancer cells (Vinodhkumar et al., 2008; Gao et al., 2014). Interestingly, HDAC inhibitors are known to induce expression of multiple T cell chemokines such as C-C motif chemokine ligand 5 (CCL5) and C-X-C motif chemokine ligand 10 (CXCL10), thus recruiting effectors T-cells to tumor cells. Therefore, expression of these T cell chemokines can lead to effective active immunity (Zheng et al., 2016). Despite these advantages, most of the known HDAC inhibitors when used as a single agent in treatment protocols failed to show any clinical benefits in nearly all types of solid tumors tested, including renal and breast cancer (Slingerland et al., 2014). Therefore, many researchers have explored the combination of HDAC inhibitors with other anticancer drugs as a potential treatment scheme that might result in an optimal effect (Suraweera et al., 2018). In this study, we investigated the antitumor effect of the combined acetaminophen and romidepsin drugs in the A549 human non-small-cell lung carcinoma (NSCLC) cell line. In particular, we confirmed that combination therapy increased the expression of T cell chemokines, which in turn led to the effective migration of Jurkat cells, a human T-cell lymphoma. These results are promising precursors that might eventually lead to better immunotherapy based on the added interaction between T-cells and tumor cells.

MATERIALS AND METHODS

Reagents

Cold medicine, Pancold-S Oral Solution, was purchased from Dongwha Pharm Co Ltd (Seoul, Korea). Acetaminophen and romidepsin were purchased from Sigma-Aldrich (St. Louis, MO, USA) Acetaminophen was dissolved in 0.5 M ethyl alcohol and romidepsin was dissolved in dimethyl sulfoxide (DMSO). PMA (phorbol 12-myristate 13-acetate) and Ionomycin were purchased from Sigma-Aldrich.

Cell culture

Human non-small-cell lung cancer (NSCLC) A549 cells and Jurkat T cells (clone E6-1) were purchased from American Type Culture Collection (ATCC, Manassas, VA, USA). The cells were maintained in RPMI1640 medium (Hyclone, Logan, UT, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Gibco/Invitrogen, Carlsbad, CA, USA), 1% penicillin/streptomycin (Hyclone, Logan, UT, USA) in a humidified atmosphere with 5% CO₂ at 37°C.

Cell viability assay

A549 cells (2 × 10⁴ cells/well) were seeded in 96-well plates and incubated 24 h. The cells were then treated with various concentration of cold medicine, acetaminophen and romidepsin for 24 and 48 h. After incubation for 24 and 48 h, the medium was exchanged with a fresh medium containing EZ-Cytox reagent 10 μL (Daeil lab service, Seoul, South Korea) and incubated for 2 h at 37°C. The absorbance was measured at 450 nm by using a VersaMax microplate reader (Molecular Device, Sunnyvale, CA, USA).

Cell cycle analysis

A549 cells (2 × 10⁴ cells/well) were seeded in 24-well plates and incubated 24 h. A549 cells were treated with the indicated dose of cold medicine for 48 h were harvested and washed with PBS, and then fixed with 70% ice-cold ethanol at -20°C overnight. After incubation overnight, the cells were washed and then stained by adding 200 μL of propidium iodide for 30 min at room temperature in the
dark. The DNA content was analyzed by NovoCyte Flow Cytometer (ACEA Bioscience, San Diego, CA, USA). All tests were performed in triplet.

**Apoptosis assay**

To determine the effect of combined treatment with acetaminophen and romidepsin, A549 cells (9 × 10^4 cells/well in 24-well plates) were determined using annexin V apoptosis kit. The cells were treated with the indicated concentration of acetaminophen (3 nM) or/and romidepsin (7 nM) for 48 h. Control cells were combined treatment with EtOH and DMSO. After 48 h, the cells were washed twice with PBS and the cells were counted and 1 × 10^5 cells were resuspended in 100 μL of binding buffer. And then, addition of 5 μL Annexin V-FITC and 5 μL PI (BD Biosciences, San Jose, CA, USA) and incubation for 15 min at room temperature in the dark. Subsequently, 400 μL of binding buffer were added and the early and late apoptotic cells were analyzed by flowcytometry. All tests were performed in triplet.

**Western blotting**

A549 cells (2 × 10^5 cells/well in 6-well plates) treated with acetaminophen and/or romidepsin for 48 h were harvested and washed with cold PBS. Cell pellets were lysed using a RIPA lysis buffer for 10 min on ice. Lysates were centrifuged at 10,000 ×g for 10 min at 4°C, and protein supernatant was measured by BCA protein assay reagent (Thermo Fisher Scientific, Waltham, MA, USA). The protein lysates (15 μg) were separated by either 10% or 12% sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The proteins were transferred onto PVDF membrane (GE Healthcare, Freiburg, Germany) and were blocked with 5% skimmed milk for 1 h. Then, incubated overnight with appropriate primary antibodies against anti-β-actin antibody (1:1,000) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) and caspase-3 antibody (1:1,000) (Cell signaling Technology, Beverly, MA, USA). After incubation with primary antibody, the membranes were incubated for 1 h at room temperature with horse radish peroxidase (HRP) conjugated secondary antibody (1:2,000, anti-mouse antibody or anti-rabbit antibody) (Cell signaling Technology, Beverly, MA, USA). The protein signals were developed using an enhanced chemiluminescence detection system (ECL) (Thermo Fisher Scientific, Waltham, MA, USA).

**Enzyme-linked immunosorbent assay**

A549 cells (2 × 10^5 cells/well in 6-well plates) were treated with acetaminophen and/or romidepsin for 48 h. The cell culture supernatants were harvested and the secretion levels of CCL5 and CXCL10 in cell culture were assayed using a human CCL5/RANTES and CXCL10/IP-10 DuoSet ELISA kit (R&D systems, Minneapolis, MN, USA) following the manufacturer's protocols. The absorbance was measured at 450 nm by using a microplate reader. All assays were performed as three independent experiments.

**Co-culture experiments**

A549 cells were pretreated with acetaminophen (3 mM) and romidepsin (7 nM) for 24 h and washed twice with PBS. Jurkat cells were activated with PMA and Ionomycin and then co-cultured with A549 cells at effector to target (E-T) ratio of 5:1 for 48 h. Plates were wash with PBS twice and the living cells were stained with crystal violet solution for 5 min. After drying, the colonies were observed and intensity was quantified.

**Statistical analysis**

Data are presented as means ± standard error (SD). Statistical significance of differences was examined by t-test or one-way ANOVA. The results with P < 0.05 was considered as statistically significant.

**RESULTS**

**Inhibition of proliferation and induction of cell cycle arrest by cold medicine in A549 cells**

The inhibitory effect of cold medicine on cell growth and proliferation was determined using the WST cell viability and proliferation assay in A549 cells. Cells were treated with the indicated concentration of cold medicine for 24 or 48 h. Proliferation of A549 cells was inhibited in a dose- and time-dependent manner (Fig. 1A). To determine whether the anti-proliferative effect was due to cell cycle arrest, cells were treated with 10% (v/v) cold medicine at half maximal
inhibitory concentration (IC₅₀) value for 48 h. Cell cycle distribution and nuclear DNA content were determined by flow cytometric analysis. As shown in Fig. 1B and 1C, the cold medicine treatment group showed the increasing population of cells in G0/G1 phase of cell cycle compared to control group. These findings indicated that cold medicine induces cell cycle arrest and inhibits cell proliferation of A549 cells.

Inhibition of A549 cell viability by acetaminophen-romidepsin administration

We evaluated the cytotoxicity of acetaminophen or romidepsin, or both, using the WST cell viability and proliferation assay in A549 cells. When treated with acetaminophen alone (1–10 mM), proliferation of A549 cells was inhibited in a dose- and time-dependent manner. The mean IC₅₀ value of acetaminophen was 7 mM for a 48 h incubation (Fig. 2A). In addition, romidepsin showed anti-proliferation effects in A549 cells. The IC₅₀ value of romidepsin was 10 nM following a 48 h incubation (Fig. 2B). In order to study the synergistic effect of acetaminophen and romidepsin, A549 cells were treated with acetaminophen (IC₂₅: 3 mM) and romidepsin (IC₂₅: 7 nM) for 24 or 48 h. As shown in Fig. 2C, the combination of acetaminophen (3 mM) and romidepsin (7 nM) significantly decreased cell viability (28%) compared with when cells were treated for 48 h with acetaminophen (75%) or romidepsin (75%) alone. These results revealed that the combination of acetaminophen and romidepsin is a more effective anti-cancer agent in A549 cells.

Synergistic induction of apoptosis in A549 cells by combined treatment of acetaminophen and romidepsin

We examined the apoptosis induced by administration of acetaminophen (3 mM) or romidepsin (7 nM), or both, using flow cytometry. The combination treatment induced an increase of apoptotic cells compared with when acetaminophen
or romidepsin was administered alone. As shown in Fig. 3A and 3B, the percentage of apoptotic cells in A549 cultures treated with acetaminophen (3 mM) and romidepsin (7 nM) for 48 h, was 29% and 10%, respectively. However, the percentage of apoptotic cells following combination treatment for 48 h was 63%. To determine whether cell death by apoptosis was associated with caspase 3 activity, western blot analysis of caspase 3 was performed to confirm caspase activity. The combination treatment remarkably induced caspase 3 activation compared with treatment with acetaminophen (3 mM) or romidepsin (7 nM) alone (Fig. 3C). These results suggested that combination treatment with acetaminophen and romidepsin effectively induced apoptosis through activation of caspase 3.

Induction of chemokines in A549 cells by combination treatment with acetaminophen and romidepsin

Romidepsin has the characteristic property of inducing the production of chemokines, which induce in turn homing of T-cells. To determine whether acetaminophen would be able to induce a significant increase of CCL5 and CXCL10 production through combination with romidepsin, we evaluated the levels of CCL5 or CXCL10 secreted in the supernatants of A549 cells treated with these drugs (IC_{50} values) by ELISA. Treatment with acetaminophen (3 mM) or romidepsin (7 nM) alone induced little change in the expression of chemokines (CCL5 and CXCL10) but the combination of the 2 drugs resulted highly 2 or 3 folds compared to the group by treatment alone in the production of chemokines (Fig. 4A and 4B). These results suggested that combination treatment induced the synergistic effect of these drugs on regulating the expression of chemokines.

Cell growth inhibition of A549 cells co-cultured with Jurkat T-cells

We previously identified an increased expression of che-
Fig. 3. Enhancement of apoptosis-induction in A549 cells by combination treatment with acetaminophen and romidepsin. (A) A549 cells were treated with acetaminophen (3 mM) or/and romidepsin (7 nM) for 48 h, then early and late apoptosis was analyzed by flow cytometry. (B) Bar charts showed quantitative data for total apoptosis rate at each the treated group. (C) A549 cells were treated with acetaminophen (3 mM) or/and romidepsin (7 nM) for 48 h, then the caspase-3 was determined by western blot analysis. The data are presented as means ± SD for triplicate experiments. B; **P<0.01 compared with acetaminophen, ***P<0.001 compared with romidepsin.

Fig. 4. Induction of T-cell chemokines in A549 cells by combined-treatment of acetaminophen and romidepsin. (A) A549 cells were treated with acetaminophen (3 mM) or/and romidepsin (7 nM) for 48 h, and then the levels of CCL5 secretion was determined by ELISA. (B) The secreted levels of CXCL10 was determined by ELISA following the treatment with acetaminophen (3 mM) or/and romidepsin (7 nM) for 48 h. Three independent experiments were performed and results shown as means ± SD. A; ***P<0.001 compared with acetaminophen, ***P<0.001 compared with romidepsin. B; *P<0.01 compared with acetaminophen, **P<0.01 compared with romidepsin.
mokines in A549 cells due to the combined administration of the tested drugs. To determine whether these induced chemokines exhibit a similar cytotoxicity effect on A549 cells as the one shown by activated Jurkat cells, A549 cells were treated with acetaminophen and romidepsin for 24 h and then co-cultured with activated Jurkat cells for 48 h. As shown Fig. 5, co-culturing of activated Jurkat cells with drug-treated A549 cells at effector (E) to target (T) cell ratio of 5:1 (E:T ratios) showed 21% reduction of cell viability compared with drug-treated A549 cells alone.

**DISCUSSION**

Cancer therapy has developed from general chemotherapy to combination chemotherapy. Although general chemotherapy is the main therapeutic approach used to treat cancers, there are limitations in treatment due to chemoresistance as well as due to the fact that it has been shown to be less effective than combination chemotherapy. In many types of research, combination therapies have focused on synergistic effect exerted in cancer therapy because each individual agent tested targets a different mechanisms (Bayat Mokhtari et al., 2017; Li et al., 2018; Saputra et al., 2018). Therefore, we tried to identify the potential cancer therapeutic effects exhibited between the 2 drugs tested here through a combination approach. We also confirmed the synergistic effect displayed by the released-cytokines (CCL5 and CXCL-10) induced by the administered combination of these 2 drugs.

Recently, the studies examining the anticancer effect of drug components used to alleviate cold symptoms have been steadily increasing, and thus the range of agents applied to cancer therapy is getting wider. Acetaminophen, one of the components of cold medicine, is known to exhibit anticancer effects on a variety of cancer cells, but caution is needed in the case that high doses might be required because of its potential side effects that might even lead to hepatoma (Sayour et al., 2016).

Thus, we expected that combination of a low concentration of acetaminophen and other anticancer agents could be synergistic in cancer therapy and effective in minimizing these side effects. Especially, romidepsin, histone deacetylase (HDAC) inhibitor, is known to be more effective in combination therapy than mono-therapy (Suraweera et al., 2018). As such, many recent studies have focused primarily on examining the effects of the combination of romidepsin with other anticancer drugs (Petrich and Nabhan, 2016).

In our study, in order to select the appropriate concentrations for the combined administration of acetaminophen and romidepsin, the IC$_{50}$ of both acetaminophen and romidepsin were determined (Fig. 2). Consecutively, synergistic administration of the IC$_{50}$ value of each drug induced lower cell viability in A549 cells than when treated with the IC$_{50}$ value of each drug alone. Although combination of the IC$_{50}$...
values of each drug induced less than 20% cell death, combination of the IC\textsubscript{25} values was considered sufficient.

Apoptosis, as a process of programmed cell death, induces DNA damage in the cancer site and inhibits tumor growth. This can be initiated by 2 different mechanisms, an intrinsic pathway and an extrinsic pathway, which induces activation of caspase 3 and 7 (Pistritito et al., 2016; Bundscherer et al., 2018). This stimulated caspase activity results in the induced final apoptotic cell death (Stennicke and Salvesen, 2000). This stimulated caspase activity results in the induced final apoptotic cell death. We found that combination treatment with acetaminophen and romidepsin induced increased levels of apoptosis in A549 cells leading to the activation of caspase 3 (Fig. 3). Therefore, these results showed that combination of acetaminophen and romidepsin synergistically induces apoptosis by caspase 3 in A549 cells (Qin et al., 2002).

In addition, HDAC inhibitors are known to stimulate the expression of chemokines that induce leukocyte homing into tumors. Chemokines, such as CCL5 and CXCL10, induce lymphocyte migration through binding to specific receptors in a concentration-dependent manner (Stein and Nombela-Arrieta, 2005; Liu et al., 2015). T-cell infiltrating into tumor microenvironment can improve patient survival (Ward and Westwick, 1998; Hopewell et al., 2013). Based on these, we assumed that combination of acetaminophen with romidepsin would lead to the increased expression of more effective chemokines in A549 cells than when treated with a single drug (Fig. 4). Moreover, we predicted that increased production of chemokines would induce activated T-cells into the tumor microenvironment. when drug-treated A549 cells where co-cultured with activated T-cells, this resulted in increased induced T-cell mediated tumor killing compared to the drug-treated mono-cultured A549 cells (Fig. 5).

In conclusion, our results implied that combination treatment with acetaminophen and romidepsin synergistically induced cell death and apoptosis in A549 cells, through an increase in chemokine production and activation of caspase 3. We conducted the co-culture system to identify the interaction of tumor cells with T-cells in the tumor microenvironment. Although the synergistic mechanism between these 2 drugs remains unclear, our results demonstrated that combination chemotherapy is more effective than single drug administration in human non-small-cell lung cancer (NSCLC) A549 cells.

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**CONFLICT OF INTEREST**

The authors have no conflict of interest to declare.

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