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Gartanin Enhances TRAIL-Mediated Liver Cancer Cell Death Through DR5 Upregulation and Autophagy Activation

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ABSTRACT

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) has no effect on normal cells, but can induce apoptosis selectively in tumor cells. Gartanin, a xanthone compound in mangosteen, has been shown to inhibit cancer cell growth by arresting the cell cycle and inducing autophage. In this study, we revealed that gartanin can sensitize TRAIL-induced human liver cancer cell death. We have found that gartanin enhances DR5 expression, a death receptor for TRAIL. This effect appears to be related to CHOP activation associated with the response of endoplasmic reticulum (ER) stress. Gartanin treatment also inhibited p62 protein expression and cleaved LC3 to activate autophagy flux, which is related with TRAIL-induced cell death. Pretreatment with autophagy flux inhibitor, LY294002, inhibited gartanin-induced DR5 expression. In summary, our results reveal that the combined treatment of gartanin and TRAIL can be a valuable tool for cancer treatment.

Keywords: Gartanin; TRAIL; DR5; Autophagy; Liver Cancer Cell

Introduction

TRAIL has been actively developed for clinical cancer treatment because TRAIL selectively induces apoptosis in cancer cells without showing cytotoxicity in normal cells [1-3]. TRAIL binds to its receptors DR4 and DR5 in cancer cells and transmits apoptotic signals. Upon initiation of TRAIL-mediated cell signaling, FADD (Fas-associated protein with death domain) is recruited to DR4 and DR5 and sequentially caspase-8 is activated to induce apoptotic pathway [4,5]. Caspase-9 is also activated by TRAIL and initiates the caspase cascade and subsequent apoptosis [4,5]. However, many cancer cells, including human liver cancer cells, have resistance to TRAIL-induced apoptosis, which limits the use of TRAIL alone [6]. Therefore, it is very necessary to develop a therapeutic agent capable of overcoming TRAIL resistance or sensitizing liver cancer cells to TRAIL. Gartanin isolated from mangosteen fruit has been known to be a member of the class of isoprenylated xanthones [7]. Gatanin has been shown to have anti-inflammatory, antioxidant and anti-cancer abilities in many studies [8,9]. In addition, gartanin can activate autophagy in several cell types [10,11]. Despite these observations, the molecular mechanisms by which gartanin induces tumor cell death in liver cancer cells have not yet been elucidated. Recent reports have shown that DR5 plays an important role in the cancer cell death by TRAIL [12,13]. Regulation of transcriptional DR5 expression is mediated by C/EBP homologous transcription factor (CHOP) [14,15], that is activated when cells undergo endoplasmic reticulum (ER) stress [16]. PERK/eIF2α signaling is activated in ER stress conditions to improve transcription of CHOP [17,18]. ROS are produced as a by-product of cellular respiration, induce apoptosis, and are also used as signaling substances for cell growth [19]. Accumulated ROS can induce DR5 expression through ER stress induction and chop activation [20]. However, the

mechanisms by which gartanin induces ER stress in liver cancer cells and its effect on DR5 expression have not been known to date.

Autophagy uses lysosomes to convert damaged cells and cellular debris that are no longer useful into other proteins and amino acids to create healthier, newer cells. Autophagy is considered to be necessary for cell death as well as for cell survival [21]. During autophagy, the dual membrane autophagosome is developed to swallow a variety of cellular components including the cytoplasmic organelle [22]. Promoting the formation of autophagic vesicle is mediated by microtubule associated protein light chain 3 (LC3-I), that is transformed into LC3-II by phosphatidylethanolamine (PE) [23]. This process involves the formation of ubiquitinated forms mediated by Atg7, Atg3 and Atg16L complex. Another autophagy marker, p62, serves as a ubiquitin-binding protein that protects protein aggregates in lysosomes or proteasomes for degradation by autophagy [24]. Activation of autophagic flux has been found to inhibit TRAIL-induced apoptosis through activation of AMPK [25,26]. Conversely, activation of autophage flux has been shown to improve TRAIL-mediated tumor cell death via down-regulation of c-FLIP and upregulation of DR5 [27,28]. The aim of this study is to find at the molecular level how gartanin-induced autophagy affects TRAIL-induced apoptosis of liver cancer cells.

Materials and Methods

Cell Culture

Human liver cancer cell lines Hep3B and HepG2 were purchased from the American Type Culture Collection. Cells were cultured in DMEM supplemented with 10% fetal bovine serum (FBS) and antibiotics (100 Unit/ml penicillin and 100 µg/ml streptomysin; Thermo Fisher Scientific, Inc., Waltham, MA, USA) and maintained at 37°C with 5% CO_2 in a humidified atmosphere.

Reagents

Gartanin extracted from mangosteen was obtained from Prof. Young-Won Chin (Dongguk University). Anti-p62 (cat no. sc-28359) and Anti-LC3 (cat no. sc-398822) antibodies were purchased from Santa Cruz Biotechnology. Other antibodies including anti-caspase-3 (cat no. AB1899), anti-caspase-8 (cat no. 06-775), and anti-caspase-9 (cat no. AB16969) were purchased from Calbiochem (La Jolla, CA, USA). Antibodies directed against FADD (cat no. 2782), PARP (cat no. 9542), and GAPDH (cat no. 5174) were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Primary antibodies were diluted at a ratio of 1: 500 to 1: 2000 before use. 6-carboxy-2′,7′-dichlorodihydrofluorescein diacetate (DCFDA) and Hydroethidine (HE) were purchased from Molecular Probes (Eugene, OR, USA).

Cell Viability (MTT)

Human liver cancer cell lines Hep3B and HepG2 cells were seeded in a 96-well culture plates at density of 5 × 10^4 cells/well. Cells were treated with gartanin and TRAIL. After 24 h, cells were incubated with MTT solution (Sigma-Aldrich Corp., MO, USA), and then absorbance was measured at 570 nm using a microplate reader (BioTek Instruments, VT, USA).

Observation of Morphologic Changes

Hep3B cells were seeded into 6-well culture plates at density of 5 × 10^4 cells/well and treated with gartanin and TRAIL for 24 h. Cell morphology changes were analyzed using a phase contrast microscope (Leica, Nussloch, Germany).

DAPI Staining

Hep3B cells were seeded and supplemented with gartanin and TRAIL. After 24 h, cells were stained with 300 nM DAPI solution, and then incubated for 5 min. The nuclei were imaged and observed using a fluorescence microscope (Carl Zeiss Meditec AG, Jena, Germany).

Transmission Electron Microscopy

The Karnovsky's solution (pH 7.4) was treated for 2 hours to pre-fix the cells. Next, cells were washed with cacodylate buffer. Then, the cells were treated 1% osmium tetroxide and 1.5% potassium ferrocyanide for 1 hour for post fixation. Cells were dehydrated from 50% to 100% alcohol, and the cells were fixed with Poly / Bed 812 resin (Pelco), and observed with an electron microscope (EM 902A, Zeiss).

GFP-LC3 Translocation

Plasmids encoding the GFP-LC3 gene were transfected into Hep3B cells, and then cell were treated with gartanin for 24h. The degree of recruitment of GFP-LC3 to autophagosome was measured by fluorescence microscopy.

Western Blot

Total protein extracts were obtained using PRO-PREP protein extraction solution (iNtRON Biotechnology, Sungnam, Republic of Korea). Protein was quantitated and 20 ug of protein was separated by SDS-PAGE and transferred to the nitrocellulose membranes. After the membrane is treated with antibodies, then the membrane was developed using an ECL reagent (Amersham, Arlington Heights, IL, USA).

Flow Cytometric Analysis

Cells were collected and fixed with 70% ethanol. Then, cells were treated 50 µl of a 100 µg / ml stock of RNase and added 200 µl PI (Propidium iodide). To analyze the amount of phosphatidylserine in the cell membrane outer layer, the cells were stained with FITC conjugated annexin-V (R&D Systems) for 1 hour. Sub-G1 DNA content and fluorescence level of annexin-V were analyzed by flow cytometer (BD FACS Calibur, Becton Dickinson, USA).

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Measurement of ROS

Cells were plated into a 6-well plate at density of 5 × 10^4 cells/well and then treated to 20 μM of gartanin for indicated time. To measure H_2O_2 and O_2^- in the cells, 5 μM DCFDA and 4 μM HE were treated and stained for 20 min at 37 °C, respectively. The fluorescence intensities of intracellular DCFDA and HE were analyzed by flow cytometer.

In Vitro Caspase Activity Assay

The activity of caspase-type protease was measured using caspase activity kit (R & D Systems) according to the manufacturer's instructions.

Statistical Analysis

Data analysis was performed using SPSS version 14.0 (SPSS, Inc., Chicago, IL, USA). Values are represented as the mean ± standard deviation of triplicate data. Statistical comparisons were conducted using a two-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. Statistical significance was set at $P < 0.05$ and $P < 0.01$.

Results

Gartanin Sensitizes TRAIL-Induced Apoptosis in Liver Cancer Cells

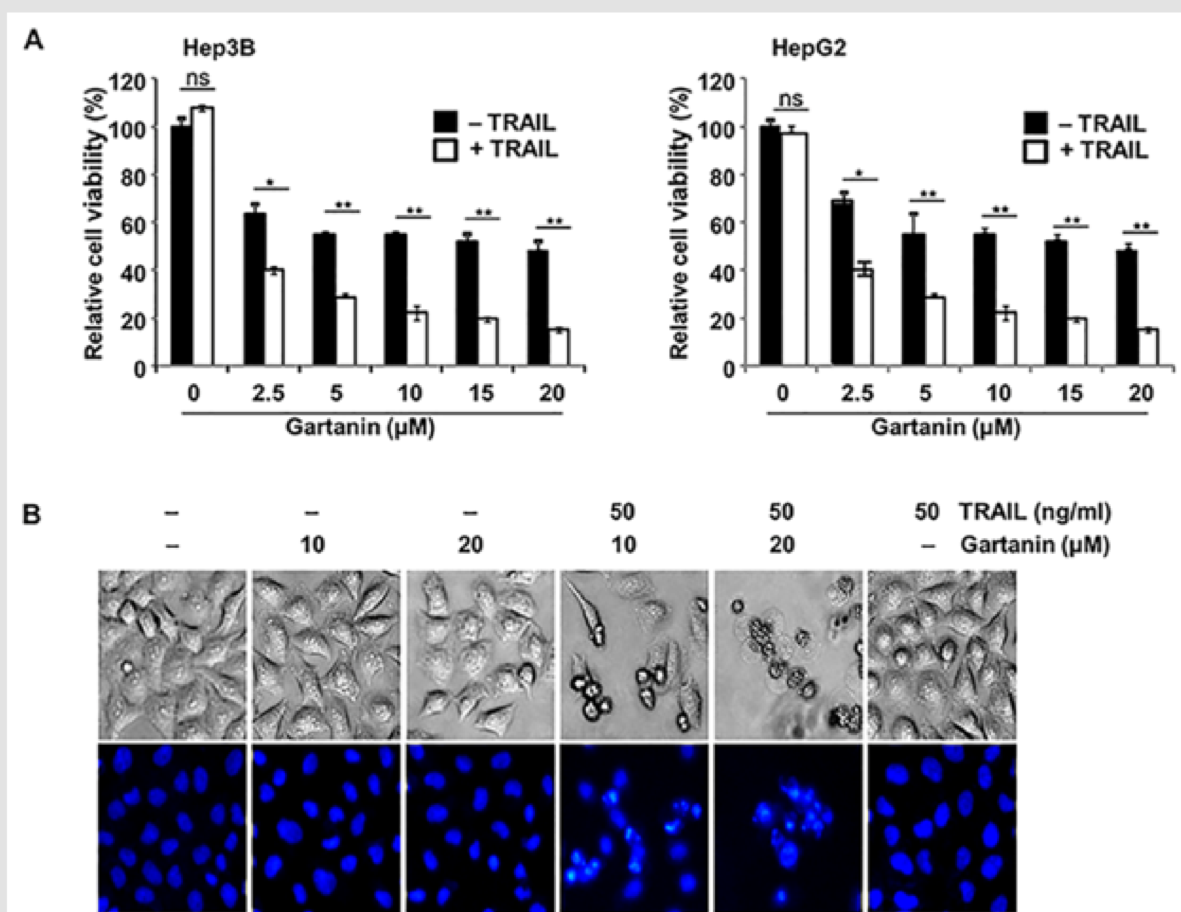

Figure 1: Gartanin enhances TRAIL-mediated liver cancer cells death. Hep3B and HepG2 cells were pretreated with 0 to 20 μM of gartanin for 1 h and then treated with or without 50 ng/ml TRAIL for 24 h.

A. To analyze cellular viability, cells were treated with MTT solution.

B. The cells morphology was observed under an optical microscope (×400) (upper panel). To confirm the degree of condensation and cleavage of chromosomes, DAPI staining was performed and analyzed by fluorescence microscopy (lower panel). Data represent the mean (± standard deviation, SD) of three independent experiments. *P < 0.05 and **P < 0.01 vs. Control cells. NS represents no significance.

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We evaluated cell viability to find the concurrent therapeutic effect of gartain and TRAIL on Hep3B and HepG2 cells using the MTT assay. When treated with 50 ng/ml TRAIL alone for 24 hours, there was no significant change in cell growth in Hep3B and HepG2 cells. (<5%), indicating that these cells are resistant to TRAIL. The single gartanin treatment of the indicated concentration groups showed about 40% inhibition of cell growth. However, the combined treatment of gartanin and 50 ng/ml TRAIL strongly reduced cell survival to about 80% (Figure 1A). Using phase contrast microscopy, we found that cells co-treated with gartanin and TRAIL significantly reduced cell numbers compared to cells supplemented with gartanin or TRAIL alone (Figure 1B), upper panel. And also, the combined treatment of gartanin and TRAIL induced a significant change in the chromatin that was destroyed and condensed in the nucleus (Figure 1B) lower panel. From these results, we demonstrate that co-treatment with gartanin and TRAIL can significantly inhibit the growth of TRAIL-resistant liver cancer cells.

Gartanin Enhances TRAIL-Mediated Apoptosis

We examined whether the decrease in cell viability induced by gartanin and TRAIL combination treatment was associated with the activation of apoptotic signals. Our results show that sub-G1 cells (Figure 2A) upper panel in Hep3B cells is significantly increased by approximately 25% or more by concurrent treatment with combined treatment of 20 μM gartanin and 50 ng/ml TRAIL. We also found that the annexin-V positive cell population increased about 2.5-fold over the TRAIL alone-treated group (Figure 2A, lower panel). Our results also show that caspase-8, -9, -3, and PARP are cleaved only in the group treated with gartanin and TRAIL (Figure 2B). Similarly, caspase-8, -9, -3 activities were significantly increased with gartanin and TRAIL combined treatment (Figure 2C).

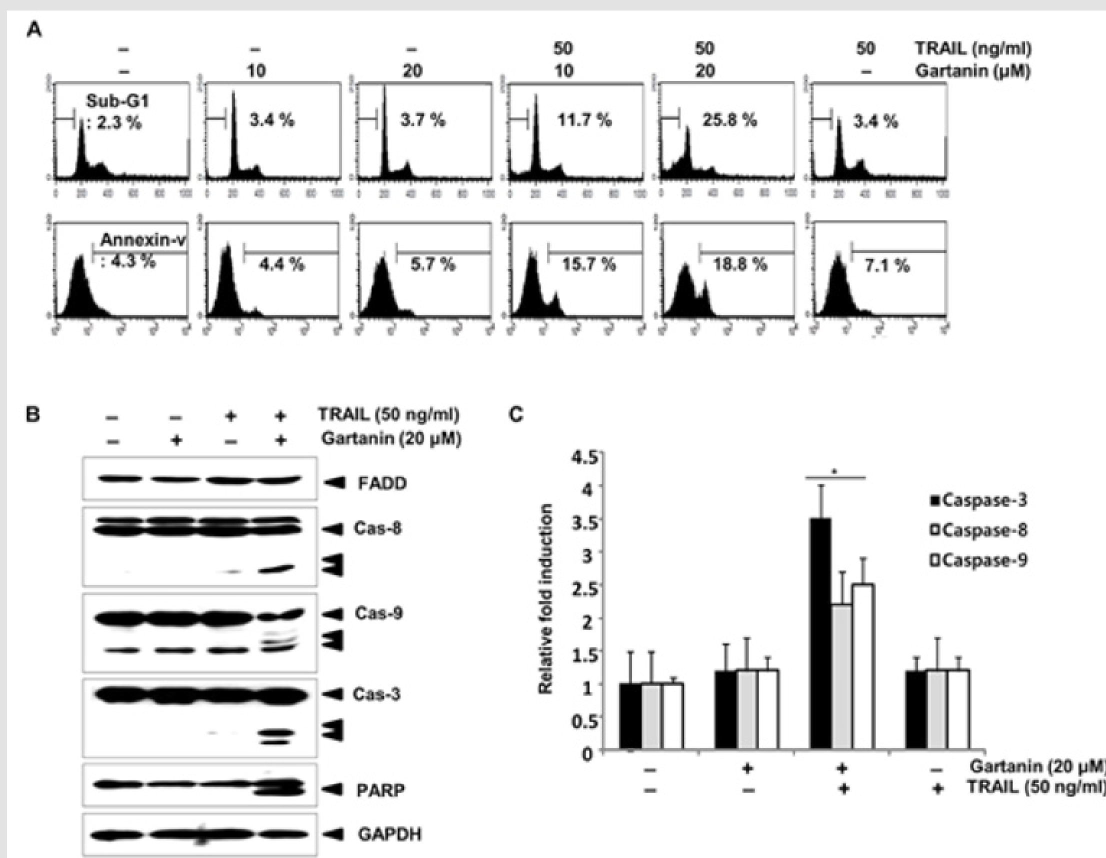

Figure 2: Gartanin sensitizes TRAIL-induced apoptosis. Hep3B cells were pretreated with 10 to 20 μM of gartanin for 1 h and then treated with or without 50 ng/ml TRAIL for 24 h.

A. To analyze apoptosis, we measured the amount of sub-G_1 cell population and Annexin-V positive cells using flow cytometry.
B. Cells were subjected to Western blotting using the indicated antibodies. GAPDH was used as loading control.
C. Relative activities of caspase-3, -8, and -9. Data represent the mean (± standard deviation, SD) of three independent experiments. *P < 0.05 vs. Control.

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Gartanin Induces ER Stress-Dependent DR5 Expression

Recent reports indicate that ROS-induced DR5 upregulation is crucial to the susceptibility of TRAIL-induced apoptosis [29,30]. Therefore, we investigated whether gartanin could induce ROS production in Hep3B cells. As shown (Figure 3A), we observed that gartanin treatment increase O_2^- and H_2O_2 amounts in the cells detected by HE and DCFDA based flow cytometry. Recently, Hayashi et al. have shown that ROS increase ischemic neuronal cell death via activation of ER stress [31]. Therefore, we determined whether gartanin could activate ER stress. We found that gartanin treatment upregulated protein expression levels of XBP-1, GRP78 and phosphorylation levels of eIF-2α (Figure 3B). Collectively, these results indicate that gartanin can induce ER stress in Hep3B cells. CHOP is activated in ER stress conditions and acts as a transcription factor that induces DR5 expression [14,15]. We next investigated whether gartanin could induce CHOP expression. We confirmed by Western blotting that Gartanin increases CHOP expression in Hep3B cells in a time-dependent manner (Figure 3C). Indeed, we investigated that gartanin treatment strongly increased DR5 protein levels (Figure 3C). To demonstrate the functional role of DR5 in sensitizing TRAIL-mediated cell death by gartanin, we used DR5-specific blocking chimeric antibodies. Treatment of DR5- blocking antibody completely blocked sub-G_1 cells increased by gartanin and TRAIL combined treatment in Hep3B cells (Figure 3D).

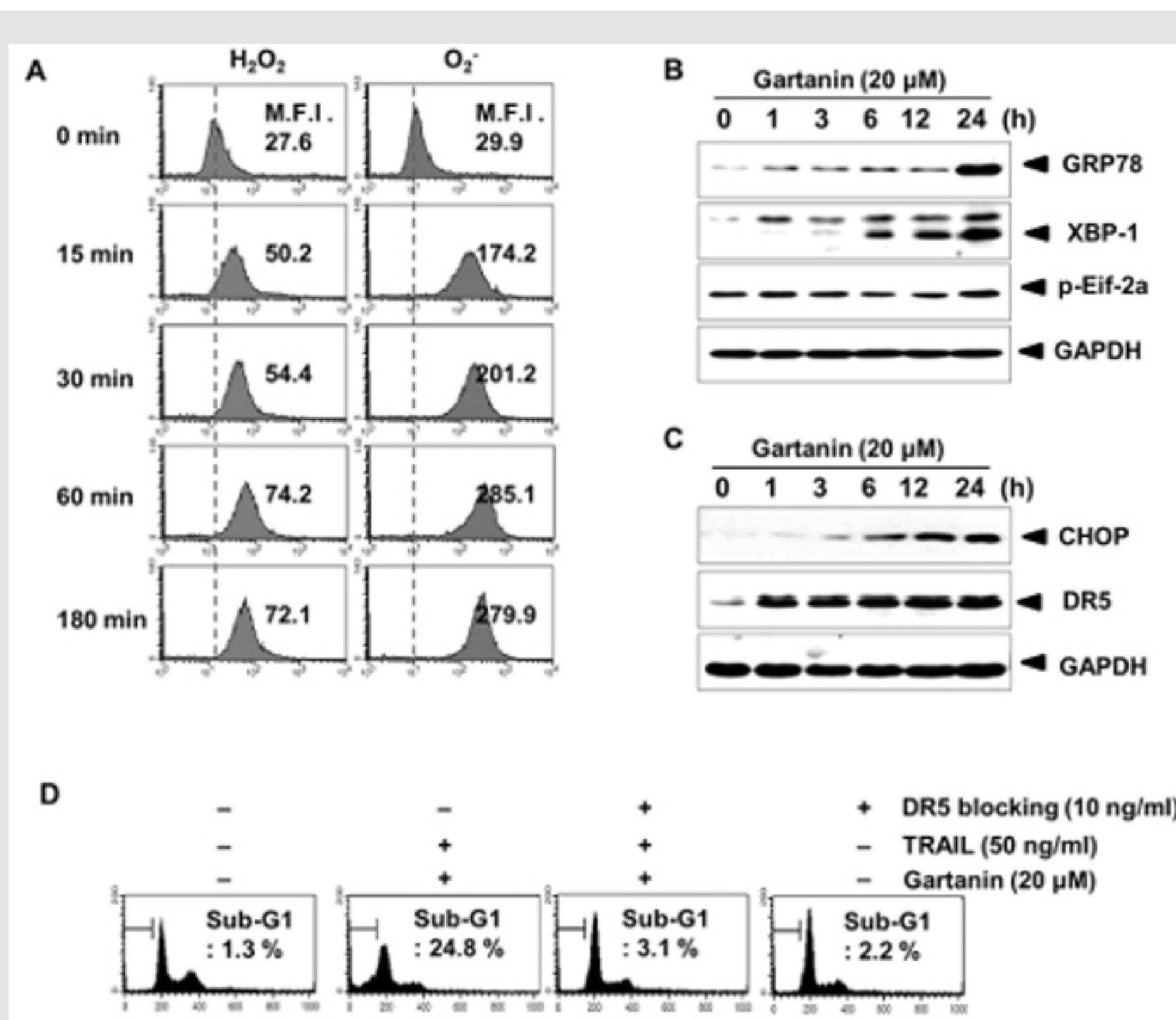

Figure 3: Gartanin induces DR5 expression via CHOP.

A. Hep3B cells were added with 20 μM gartanin and stained with DCFDA and HE. Fluorescence values of DCFDA and HE were detected by flow cytometry.

B. B and C: Hep3B cells were treated with 20 μM gartanin for 24 h, then cell lysis was performed to subject to western blotting.

C. D: DR5-specific blocking antibody was pre-treated with Hep3B cells for 30 min, and then treated with gartanin and TRAIL. Flow cytometry was used to analyze sub-G_1 cell population.

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Gartanin Stimulates Activation of Autophagic Flux

A recent study has implicated that induction of autophagic flux can sensitize TRAIL-mediated apoptosis via induction of DR5 [28]. Therefore, we evaluated whether gartanin could induce autophagy flux by estimating LC3-II transformation and p62 expression using western blotting assay. Our results revealed that gartanin decreased p62 expression but increased LC3-II expression in a time-dependent manner (Figure 4A). We transfected Hep3B cells with GFP-LC3 plasmid to analyze autophagy induced by gartanin. Untreated cells showed diffuse expression of GFP-LC3 whereas cells treated with gartanin showed highly-intense dotted expression (Figure 4B). Next, we verified electron microscopy to more accurately analyze gutanin-induced autophagy. Our results showed that treatment of gartanin increases autophagic and empty vacuoles. The vacuoles appeared to increase in size, which means the continuous fusion of autologous autoantibodies with lysosomes after gartanin treatment (Figure 4B) lower panel. Next, we investigated whether LY294002, an autophagy inhibitor, could affect gartanin-mediated autophagy and TRAIL-sensitivity. Pretreatment with LY294002 reduced LC3-II conversion and DR5 expression induced by gartanin treatment (Figure 4C). Consistently, LY294002 pretreatment reduced the extent of gartanin/TRAIL-induced caspase-3 cleavage and annexin-V positive cell population (Figures 4D & 4E).

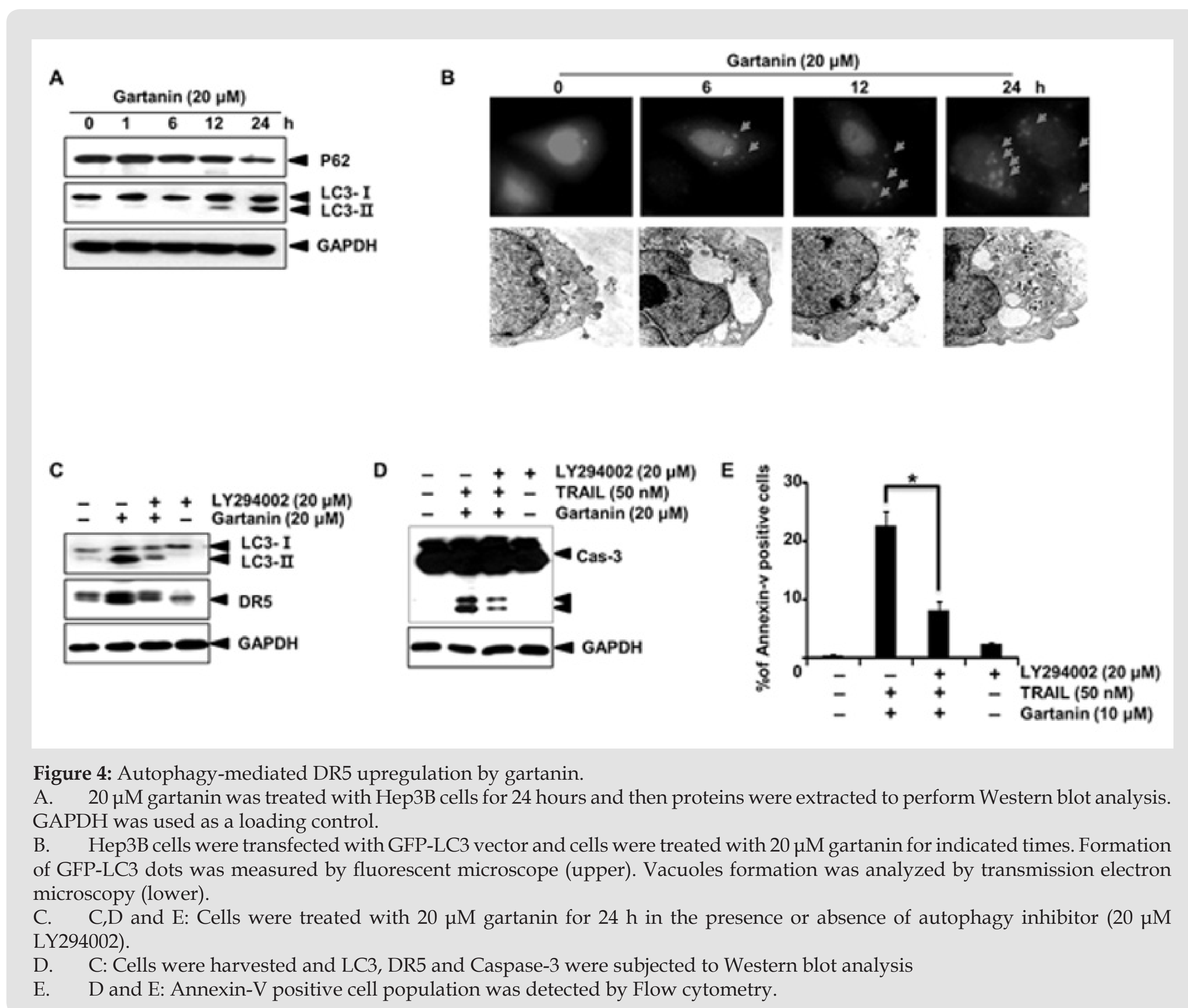

Figure 4: Autophagy-mediated DR5 upregulation by gartanin.

A. 20 µM gartanin was treated with Hep3B cells for 24 hours and then proteins were extracted to perform Western blot analysis. GAPDH was used as a loading control.

B. Hep3B cells were transfected with GFP-LC3 vector and cells were treated with 20 µM gartanin for indicated times. Formation of GFP-LC3 dots was measured by fluorescent microscope (upper). Vacuoles formation was analyzed by transmission electron microscopy (lower).

C. C,D and E: Cells were treated with 20 µM gartanin for 24 h in the presence or absence of autophagy inhibitor (20 µM LY294002).

D. C: Cells were harvested and LC3, DR5 and Caspase-3 were subjected to Western blot analysis

E. D and E: Annexin-V positive cell population was detected by Flow cytometry.

Discussion

TRAIL is being studied for use in clinical trials because of its high anticancer specificity. However, since many human cancer cells show tolerance to TRAIL, it is necessary to develop an adjuvant [2,3]. Therefore, the development of a combined treatment agent that enhances the apoptosis effect by TRAIL is an important task in TRAIL-based cancer treatment. The purpose of our study was to find whether gartanin could increase sensitivity to TRAIL in liver cancer cells. Through this study, it was found that gartanin induces apoptosis of liver cancer cells by effectively increasing TRAIL-induced activation of caspases and cleavage of PARP. Since caspase-9 plays an important role in the induction of cytochrome c-dependent apoptosis, efforts are needed to identify which mitochondrial pathway is involved in gartanin and TRAIL-induced apoptosis. As seen through the results of (Figure 1), HepG2 liver cell line expressing wild type p53 is not more sensitive than p53 null Hep3B cell line in combination treatment of gartanin and TRAIL. Thus, the combination of gartanin and TARIL may induce apoptosis in a manner independent of p53. But for a more accurate mechanism, further studies are needed to investigate whether similar results are obtained in other liver cancer cell lines. Indeed, this study found that gartanin induces upregulation of DR5, which enhances sensitivity to TRAIL in liver cancer cells. Our results demonstrated that DR5/Fc chimeric treatment can effectively inhibit the apoptosis induced by combination therapy, suggesting that the caspase-dependent apoptosis signal is due to increased interactions between DR5 and TRAIL. We also investigated that gartanin treatment increased GRP78 and CHOP expression and eIF2α phosphorylation. This result implies that gartanin might cause ER stress. And we found that siRNA for CHOP resulted in down-regulation of DR5 induced by gartanin (data not shown). This data indicates that gartanin-mediated CHOP expression induces upregulation of DR5, which in turn sensitizes TRAIL-induced apoptosis.

Autophagy regulates key processes in TRAIL-mediated cell death. Our experiments showed that the autophagosome formation inhibitor, LY294002, suppressed cell death through inhibition of gartanin-induced LC3-II and DR5 expression. This means that increased DR5 expression by gartain is associated with autophagy activation. Taken together, our results show that gartanin can lead to enhanced TRAIL -mediated apoptosis through activation of ER stress and autophagy-dependent DR5 upregulation. Further studies using xenograft animal models are required to investigate whether gartanin has potential effect for TARAIL induced apoptosis in vivo.

Competing Interests

The authors declare no conflicts of interest.

Authors Contributions

Conceptualization, Funding acquisition, Investigation, Methods development, Supervision, Writing, review, and editing: Dong-Oh Moon.

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