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FADD-dependent apoptosis induction in Jurkat leukemia T-cells by the resveratrol analogue, 3,4,5-trihydroxy-*trans*-stilbene

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Abstract

The plant-produced compound, resveratrol (3,5,4′-trihydroxy-*trans*-stilbene, 3,4,5-THS), induces apoptosis in various human leukemia cell types in vitro, and thus appears to be a promising anti-leukemia agent. In this study, we observed that treatment of resveratrol-resistant Jurkat cells with the resveratrol analogue, 3,4,5-trihydroxy-*trans*-stilbene (3,4,5-THS), rapidly induced extensive apoptosis, indicating that the apoptotic activity of the analogue differed from that of the parental compound resveratrol. Indeed, we found that treatment of Jurkat cells with 3,4,5-THS, unlike treatment with resveratrol, induced activation of caspase-8 and apoptosis by a Fas-associated death domain (FADD) protein-dependent mechanism without involving the known death ligands CD95 ligand (CD95L), tumor necrosis factor α (TNFα) and TNF-related apoptosis-inducing ligand (TRAIL). Therefore, 3,4,5-THS induced activation of a FADD-dependent apoptotic mechanism that was unresponsive to the parental compound resveratrol. Therefore, the ability of 3,4,5-THS, but not resveratrol, to induce apoptosis demonstrates a structure-associated apoptotic activity of the resveratrol analogue.

Keywords: Resveratrol; Analogues; Apoptosis; FADD; Caspase-8; PARP

1. Introduction

Human epidemiological and animal studies have furnished information indicating that the plant-produced compound, resveratrol, which is abundantly present in various human dietary sources, such as grape and red wine, may be a useful natural drug that reduces incidences of inflammation, coronary heart diseases, degenerative neurological disorders, and cancer [1–3]. The anti-cancer activity of resveratrol was initially demonstrated by its ability to inhibit the development of carcinogen-induced pre-neoplastic lesions in cultured mouse breast tissue and growth of skin cancer in a mouse model [4]. It has been since demonstrated that resveratrol induces apoptosis in various cultured cancer cells, especially leukemia cells [5–13]. A recent study showed that resveratrol had no toxicity in normal blood cells [12] and was a potent ex vivo bone marrow purging agent, because it induced selective apoptosis of leukemia cells contaminating the bone marrow [11]. Therefore, resveratrol appears to be a promising anti-leukemia agent. However, it should be noted that the dose of resveratrol and the duration of treatment required to induce a significant degree of apoptosis in leukemia cells depends on the cell type [12].

There have been contradictory reports on the involvement of CD95 in cells treated with resveratrol. Thus, resveratrol induced expression of CD95L, which in turn triggered CD95-dependent apoptosis in human promyelocytic leukemia and breast cancer cells [5]. On the other hand, it has been argued that the apoptotic effect of resveratrol on human promyelocytic leukemia cells is unlikely to be mediated by the CD95-dependent mechanism, but rather by a mechanism that involves mitochondria

Abbreviations: Resveratrol, 3,5,4′-trihydroxy-*trans*-stilbene; 3,4,5-THS, 3,4,5-tihydroxy-*trans*-stilbene; FADD, Fas-associated death domain; DN-FADD, dominant-negative FADD; PARP, poly(ADP-ribose) polymerase; CD95L, CD95 ligand; TNFα, tumor necrosis factor α; TRAIL, TNF-related apoptosis-inducing ligand

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[12]. More recently, it has been reported that a mitochondrion-dependent mechanism(s) is required to mediate the apoptotic effect of resveratrol on numerous leukemia cell types [8,12,14].

While studying the apoptotic activity of resveratrol and various synthetic resveratrol analogues [15], we observed that human Jurkat T-cell leukemia cells were relatively resistant to apoptosis induction by resveratrol, but very sensitive to the apoptotic effect of the resveratrol analogue, 3,4,5-THS. This finding indicated that the compound 3,4,5-THS was capable of inducing apoptosis by a mechanism that was unresponsive to resveratrol. In this study, we investigated the process activated upon induction of apoptosis by 3,4,5-THS in the resveratrol-resistant Jurkat cells.

2. Materials and methods

2.1. Materials

Rabbit polyclonal antibodies to human caspases-8 (clone GD13) and TNFα (Cat# T-8300) were purchased from Sigma-Aldrich, Inc.; mouse monoclonal antibodies to human PARP (clone C-2-10) and CD95 (clone CH-11) from BIOMOL, Inc.; rabbit polyclonal antibody to human TRAIL (Cat# sc-7877) from Santa Cruz Biotechnology, Inc.; mouse monoclonal antibody to human CD95L (clone NOK-1) from BD-Pharmingen, Inc. ECL-Western blot reagents were purchased from Amersham Pharmacia Biotech, Inc. Synthetic resveratrol and 3,4,5-THS (Fig. 1A) have been described elsewhere [16]. The structures and purities (>99%) of the compounds were confirmed by high-resolution mass spectroscopy, ^{1}H NMR and HPLC analyses. Each compound stock was prepared in dimethylsulfoxide at 100 mM and stored at 4 °C.

2.2. Cell stocks

Wild type, dominant-negative FADD (DN-FADD), and FADD-null Jurkat cell lines have been described [17-19]. DN-FADD Jurkat cells constitutively express a high level of FADD that lacks the death effector domain (DED) and thus acts as dominant-negative FADD [17], whereas FADD-null Jurkat cells do not express FADD [19]. The cells were cultured in RPMI 1640 medium supplemented with non-essential amino acids (1 mM), and sodium pyruvate (1 mM). The human colon carcinoma HCT116 cell line was cultured in McCoy's 5a medium supplemented with L-glutamine (2 mM). The human breast carcinoma MCF-7 cell line was cultured in DME medium. All culture media were also supplemented with with fetal bovine serum (10%), penicillin (100 units/ml), and streptomycin (50 units/ml). The cell cultures were incubated in a humidified 37 °C incubator in 5% CO_2 atmosphere.

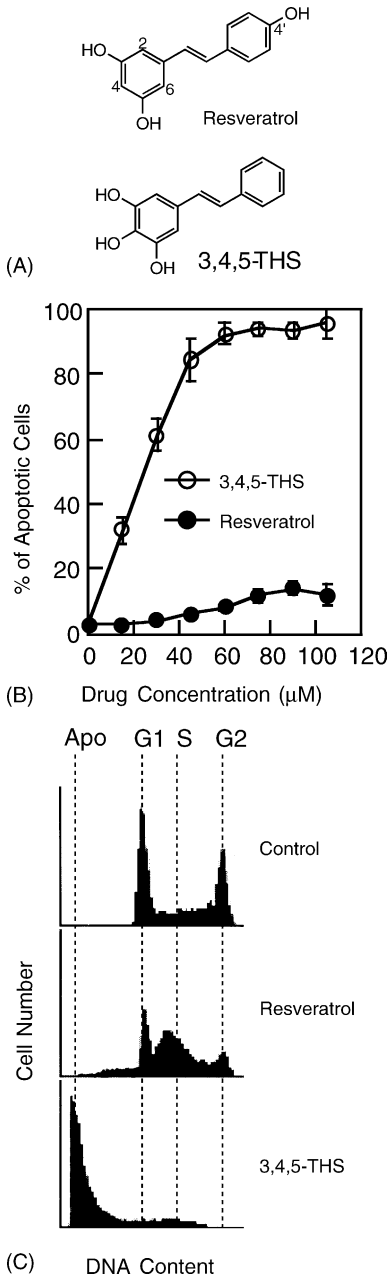

Fig. 1. 3,4,5-THS, but not resveratrol, induces apoptosis of Jurkat cells. (A) Structures of resveratrol and 3,4,5-THS. (B) Jurkat cells were treated for 48 h with resveratrol, or 12 h with 3,4,5-THS at various concentrations. Then the cells were fixed, stained with DAPI, and apoptotic cells were scored under a fluorescence microscope. (C) Jurkat cells were untreated (control) or treated for 48 h with 50 μM resveratrol, or 12 h with 50 μM 3,4,5-THS. Then the cells were fixed, stained with propidium iodide and analyzed in a flow cytometer. Apo, G1, S, and G2 denote cell fractions in apoptosis, G1, S and G2 phases of the cell cycle, respectively.

2.3. Determination of apoptosis by DAPI staining

Untreated or compound-treated Jurkat cells were fixed in 2% paraformaldehyde for 30 min at room temperature, and subsequently gently pelleted onto a glass slide using a Cytospin centrifuge. The slide was incubated for 10 min in phosphate-buffered saline containing 500 ng/ml DAPI at

room temperature, and the cells on the slide were examined under a fluorescence microscope equipped with a DAPI filter. Apoptotic cells were identified by the presence of densely stained granular nuclear apoptotic bodies [18]. Five hundred to 600 cells were randomly scored to determine the percentage of the apoptotic cell population.

2.4. Determination of apoptosis and cell cycle profile by FACS

Jurkat cells in cultures, untreated or treated with a compoud, were pelleted by centrifugation at 700 × *g* for 10 min, and fixed in 100% methanol for 1 h. Then, the cells were pelleted again, resuspended in propidium iodide solution (50 mM propidium iodide, 150 mM NaCl, 10 mM Tris, 10 μg/ml DNase-free RNase A, pH 8.0), and incubated for 1 h at 37 °C before they were analyzed by flow cytometry using a Beckman EPICS-XL Flow Cytometer. Cells with sub-G1 DNA content were considered to be apoptotic.

2.5. Analysis of protein by Western blot

Whole cell extracts were prepared under reducing conditions according to a published protocol [20], and aliquots containing 50 μg protein were subjected to SDS-PAGE (10%) and Western blot analysis using ECL reagents [18].

3. Results

3.1. Apoptosis induction in Jurkat cells by resveratrol and 3,4,5-THS

Upon DAPI staining, the apoptotic cells were easily identified and quantified by fluorescence microscopy [18]. We consistently observed that treatment of Jurkat leukemic T-cells for 48 h with resveratrol, at concentrations up to 100 μM, induced approximately 12% apoptosis, whereas a 12-h treatment of the cells with 50 μM 3,4,5-THS induced 80–90% apoptosis (Fig. 1B). To confirm these observations, Jurkat cells were untreated or treated with 50 μM 3,4,5-THS and 50 μM resveratrol for 12 and 48 h, respectively, and then stained with propidium iodide and analyzed by flow cytometry. The results showed that resveratrol induced very little apoptosis but significant S-phase arrest, whereas virtually all of the 3,4,5-THS-treated cells were apoptotic as indicated by their sub-G1 DNA content (Fig. 1C). Apparently, these Jurkat cells were relatively resistant to the apoptotic effect of resveratrol but very responsive to the apoptotic effect of 3,4,5-THS. It should be mentioned that a recent study showed that treatment of Jurkat cells with 50 and 100 μM resveratrol induced approximately 30 and 50% apoptosis, respectively [12]. Presently, the reason unclear for the discrepancy is unclear. Nevertheless, the fact that the Jurkat cells in our study responded differently to the apoptotic effect of resveratrol and 3,4,5-THS indicated that 3,4,5-THS induced activation of an apoptotic mechanism that was unresponsive to resveratrol. Therefore, we investigated the reasons 3,4,5-THS, but not resveratrol, induced apoptosis in these Jurkat cells.

3.2. Induction of FADD-dependent activation of caspase-8 and apoptosis by 3,4,5-THS

By monitoring caspase-catalyzed cleavage of the nuclear protein PARP as a biochemical end-point of apoptosis, we investigated the effect of 3,4,5-THS in Jurkat cells. Our results repeatedly showed that treatment with 50 μM of 3,4,5-THS for 3.5, 7, 12, and 16 h induced progressive apoptotic cleavage of the PARP protein, and that complete PARP cleavage occurred at approximately 12 h (Fig. 2A), The results also showed that the progression of PARP cleavage in the 3,4,5-THS-treated cells was nearly concurrent with activation of caspase-8, that is, appearance of the p18 subunit of the active caspase-8 (Fig. 2A). In contrast, treatment of Jurkat cells for up to 24 h with 50 μM resveratrol actually increased the level of the inactive pro-caspase-8 in the cells (Fig. 2B), but it did not induce conversion of pro-caspase-8 into active caspase-8, and apoptotic cleavage of the PARP (Fig. 2B).

The FADD protein is essential for caspase-8 activation in various cell types, including Jurkat cells, treated with compounds such as non-steroidal anti-inflammatory drugs and cycloheximide [17–19]. Therefore, caspase-8 activation in the 3,4,5-THS-treated Jurkat cells suggested the possibility that 3,4,5-THS induced activation of a FADD-dependent mechanism. Previously, it was demonstrated that a DN-FADD Jurkat cell sub-line expressing a DN-FADD, and a FADD-null Jurkat cell sub-line were specifically defective in the FADD-dependent apoptotic

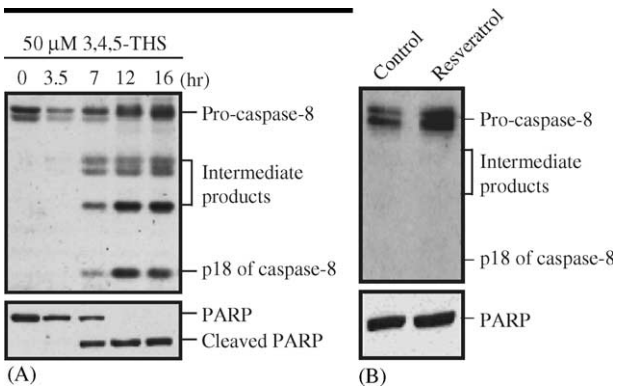

Fig. 2. 3,4,5-THS, but not resveratrol, induces activation of caspase-8. (A) Jurkat cells were treated with 50 μM of 3,4,5-THS for 0, 3.5, 7, 12, and 16 h, and then subjected to Western blot analysis to detect intact PARP (116 kDa), cleaved PARP (85 kDa), and conversion of pro-caspase-8 into active caspase-8, as indicated by the production of the p18 subunit of active caspase-8. (B) Jurkat cells were left untreated (control) and treated with 50 μM of resveratrol for 24 h, and then analyzed for PARP and caspase-8.

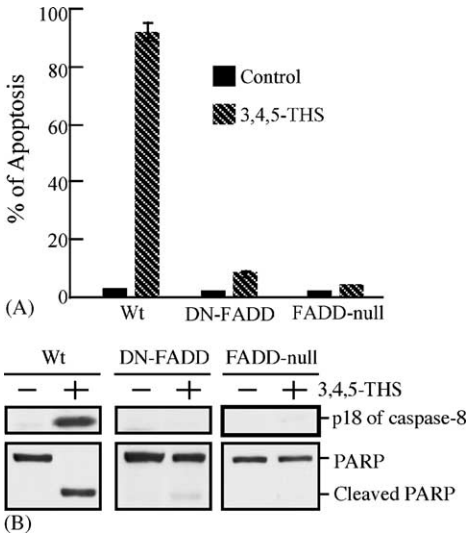

Fig. 3. 3,4,5-THS induces FADD-dependent apoptosis. Wild type (wt), DN-FADD and FADD-null Jurkat cells were left untreated or treated with 50 μM of 3,4,5-THS for 12 h. An aliquot of the cells was fixed, stained with DAPI and apoptotic cells were scored under a fluorescence microscope. The rest of the cells were subjected to Western blot analysis to detect caspase-8 and PARP.

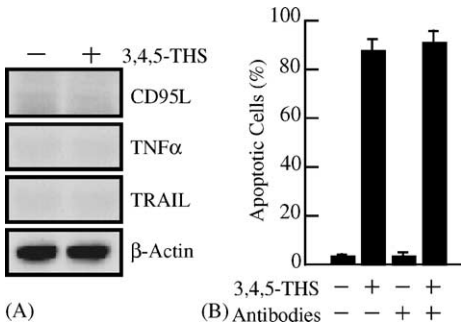

Fig. 4. Apoptosis induction by 3,4,5-THS does not involve CD95L, TNFα and TRAIL. (A) Jurkat cells were left untreated (−) and treated (+) with 50 μM of 3,4,5-THS for 12 h, and then analyzed by Western blot for presence of CD95L, TNFα and TRAIL. (B) Jurkat cells were cultured in medium containing NOK-1 monoclonal CD95L antibody (1 μg/ml), TNFα polyclonal antibody (1 μg/ml) and TRAIL polyclonal antibody (1 μg/ml) in absence or presence of 50 μM of 3,4,5-THS for 12 h, then, the cells were stained with DAPI and viewed under a fluorescence microscope to score apoptotic cells.

pathway [17–19]. Therefore, to investigate the possibility of FADD-dependent caspase-8 activation and apoptosis in Jurkat cells treated with 3,4,5-THS, we compared the apoptotic responses of wild type (wt), DN-FADD and FADD-null Jurkat cells after a 12-h treatment with 50 μM 3,4,5-THS. The results showed that 3,4,5-THS induced apoptosis in wt, but not DN-FADD and FADD-null, Jurkat cells (Fig. 3A). Concurrently, 3,4,5-THS induced caspase-8 activation and PARP cleavage in wt, but not in DN-FADD and FADD-null, Jurkat cells (Fig. 3B). These results demonstrated that 3,4,5-THS-induced apoptosis in Jurkat cells required FADD-dependent activation of caspase-8.

3.3. 3,4,5-THS-induced activation of caspase-8 is independent on CD95L, TNFα and TRAIL

Jurkat cells express CD95 that mediates the apoptotic effect of CD95L [20,21], TNF-receptor that mediates the apoptotic effect of TNF α [22], and death receptors-4 and -5 that mediate the apoptotic effect of TRAIL [23]. Each death receptor, upon stimulation by its respective ligand, activates caspase-8 and consequently apoptosis in a FADD-dependent manner [24,25]. Therefore, we investigated whether treatment of Jurkat cells with 3,4,5-THS would result in expression and/or activation of CD95L, TNFα, or TRAIL. In this investigation, Jurkat cells were left untreated or treated with 50 μM of 3,4,5-THS for 12 h and then analyzed by Western blot to detect CD95L, TNFα and TRAIL. The results showed that CD95L, TNFα and TRAIL were undetectable in both the untreated and 3,4,5-THS-treated cells (Fig. 4A). Alternatively, Jurkat cells were cultured in medium containing a mixture of antibodies that neutralize CD95L, TNFα and TRAIL, and received no treatment or were treated with 50 μM 3,4,5-THS for 12 h. Subsequently, the cells were stained with DAPI and apoptotic cells were scored under a fluorescent microscope [18]. The results showed that the presence of the antibodies had no effect on the ability of 3,4,5-THS to induce apoptosis in the cells (Fig. 4B). Therefore, we concluded that 3,4,5-THS-induced FADD-dependent caspase-8 activation and apoptosis did not require the presence of death ligands CD95L, TNFα, and TRAIL in Jurkat cells.

3.4. 3,4,5-THS, but not resveratrol, induces apoptosis in a human colon cancer cell line

Finally, we investigated whether 3,4,5-THS could induce apoptosis in other cell types that were resistant to the apoptotic effect of resveratrol. For this investigation, we identified human colon carcinoma HCT116 breast carcinoma MCF-7 cell lines that were resistant to the

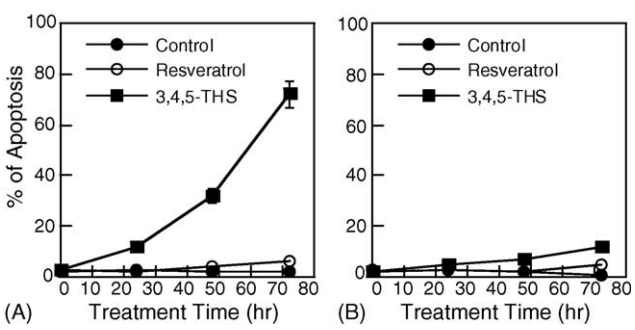

Fig. 5. Apoptotic effect of 3,4,5-THS and resveratrol on HCT116 and MCF-7 cells. HCT116 (A) and MCF-7 (B) cells were left untreated or treated for 24, 48, and 72 h before they were harvested, stained with DAPI, and examined for apoptosis induction under a fluorescence microscope.

apoptotic effect of up to 100 μM resveratrol over a period of 72 h. We found that treatment for 72 h with 100 μM 3,4,5-THS induced significant degree of apoptosis in a time-dependent manner in HCT116, but not MCF-7, cells (Fig. 5). Therefore, the ability of 3,4,5-THS to induce apoptosis by a resveratrol-insensitive mechanism was not limited to the Jurkat cell line.

4. Discussion

In this report, we have described experimental findings to show that Jurkat cells, that are relatively resistant to the apoptotic effect of resveratrol, are arrested at the G1-phase of the cell cycle (Fig. 1B and C). These observations indicated that these Jurkat cells were specifically defective in a mechanism that mediates the apoptotic effect of resveratrol. In this line, it was previously reported that treatment of numerous leukemia cell types including the Jurkat T-cells with resveratrol induced depolarization of mitochondrial membrane and consequently caspase-9 activation and apoptosis [12]. Although there was no clear explanation for the difference between the published [12] and our results (this report), it was nevertheless interesting to us that treatment of these resveratrol-resistant Jurkat cells with the resveratrol analogue, 3,4,5-THS, rapidly induced extensive apoptosis (Fig. 1). It was also interesting that treatment of the HCT116 colon carcinoma cells, which were resistant to the apoptotic effect of resveratrol (Fig. 5), with 3,4,5-THS slowly induced significant apoptosis in a time-dependent fashion (Fig. 5). Currently, we have been testing many human cancer cell lines for resistance and sensitivity to the apoptotic effect of resveratrol and 3,4,5-THS, respectively. We will then investigate whether 3,4,5-THS induces apoptosis by a FADD-dependent mechanism in all cell types or by different mechanisms according to cell types. Recently, we suggested that the presence of 3,4-dihydroxyl groups was important for 3,4,5-THS to exhibit apoptotic activity in Jurkat cells [15]. Although the mechanism by which 3,4,5-THS induces apoptosis in HCT116 cells remains to be determined, we have demonstrated that structural difference between 3,4,5-THS and resveratrol (Fig. 1A) can be correlated with the ability of these compounds to induce activation of the FADD-dependent apoptotic mechanism.

Specifically, our results demonstrated that 3,4,5-THS induced activation of caspase-8 and apoptosis in wild type Jurkat cells (Fig. 2), but not in DN-FADD and FADD-null Jurkat cells (Fig. 3), indicating that activation of caspase-8 and subsequent apoptosis required activation of a FADD-dependent mechanism in the 3,4,5-THS-treated cells. Although it remains to be investigated whether 3,4,5-THS would induce FADD-dependent apoptosis in other cell types, the observed requirement of FADD for caspase-8 activation in the 3,4,5-THS-treated Jurkat cells strongly suggested that formation of a DISC (death-inducing signaling complex) was responsible for the production of active caspase-8 from procaspase-8. In general, the DISC contains a death ligand-activated death receptor, FADD and procaspase-8 [24,25]. Since our data showed that the known death ligands CD95L, TNFα and TRAIL were not involved in apoptosis of the 3,4,5-THS-treated cells (Fig. 4), it was plausible that FADD-dependent caspase-8 activation required either a yet to be identified death ligand or was independent of death ligands. In a conventional DISC, the ligand-activated death receptor utilizes its C-terminal death domain (DD) to interact with the DD at the C-terminal of FADD [24,25], and FADD uses its N-terminal death effector domain (DED) to bind to the DED in procaspase-8 [24,25]. The DN-FADD that was expressed in the DN-FADD Jurkat cells lacks the DED, but retains the DD. Thus, this DN-FADD is unable to interact with procaspase-8, but is still capable of interacting with the DD of a death receptor and therefore behaves in a dominant negative manner. If 3,4,5-THS could induce apoptosis without engaging a death receptor in a DISC-like complex, then there would have been no effect of the DN-FADD on the apoptotic response of Jurkat cells to 3,4,5-THS. The fact that the DN-FADD Jurkat cells were incapable of responding to the apoptotic effect of 3,4,5-THS to produce active caspase-8 (Fig. 3) suggests that a death receptor was most likely required to mediate the observed FADD-dependent apoptotic effect of 3,4,5-THS on Jurkat cells. Also, it is possible that the 3,4,5-THS-treated cells might contain an alternative type of DISC consisting of a death receptor-like factor containing DD, which interacts with the DD in FADD, which then binds to procaspase-8 via the DED to DED interaction. Therefore, we will attempt to identify and characterize the putative novel apoptosis regulator, which interacts with FADD and mediates the apoptotic effect of 3,4,5-THS.

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