The effects of vitamin E succinate on the expression of c-jun gene and protein in human gastric cancer SGC-7901 cells

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Abstract

AIM: To investigate the effects of vitamin E succinate (VES) on the expression of c-jun gene and protein in human gastric cancer SGC-7901 cells.

METHODS: After SGC-7901 cells were treated with VES at different doses (5, 10, 20 mg·L⁻¹) at different time, reverse transcription-PCR technique was used to detect the level of c-jun mRNA; Western Blot was applied to measure the expression of c-jun protein.

RESULTS: After the cells were treated with VES at 20 mg·L⁻¹ for 3 h, the expression rapidly reached its maximum that was 3.5 times of UT control (P<0.01). The level of c-jun mRNA was also increased following treatment of VES for 6 h. However, the expression after treatment of VES at 5 mg·L⁻¹ for 24 h was 1.6 times compared with UT control (P<0.01). Western blot analysis showed that the level of c-jun protein was obviously elevated in VES-treated SGC-7901 cells at 20 mg·L⁻¹ for 3 h. The expression of c-jun protein was gradually increased after treatment of VES at 20 mg·L⁻¹ for 3, 6, 12 and 24 h, respectively, with an evident time-effect relationship.

CONCLUSION: The levels of c-jun mRNA and protein in VES-treated SGC-7901 cells were increased in a dose- and time-dependent manner; the expression of c-jun was prolonged by VES, indicating that c-jun is involved in VES-induced apoptosis in SGC-7901 cells.

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INTRODUCTION

RRR-α-tocopheryl succinate (vitamin E succinate, VES), a derivative of natural vitamin E, has been shown to be a potent growth inhibitor of various cancer cell types in vitro and in vivo[17,27]. Growth inhibition by VES is attributed to cell cycle blockage[9,11,13,18], induced cellular differentiation[11,12], increased expression of biologically active transforming growth factor-β (TGF-β) and their type II cell surface receptors[11,13,14] and the induction of apoptosis[15-18]. VES is noteworthy not only for its antiproliferative effects on tumor cells, but also for its non-toxic effect on normal cell types.

Gastric cancer is one of the most common tumors in China[19-28]. Up to date, the exact mechanisms of tumorigenesis is still unclear, but our previous studies showed that VES can block cell cycle, arrest DNA synthesis and induce apoptosis in human gastric cancer SGC-7901 cells, therefore inhibiting the cell growth[29-32]. In addition, our in vivo research in our laboratory demonstrated that VES inhibited benzo(a)pyrene (B(a)P)-induced forestomach carcinogenesis in female mice[33]. The exact mechanisms of apoptosis are not clearly known, but we found that VES can secrete and activate biologically active TGF-β and then TGF-β increases the kinase activity of c-jun N-terminal kinase (JNK) followed by phosphorylation of c-jun, and finally activated c-jun triggers apoptosis in human gastric cancer SGC-7901 cells[34]. In this study, the expression of c-jun mRNA was detected using reverse-transcription polymerase chain reaction (RT-PCR) technique and the level of c-jun protein was measured using western blot in order to further investigate the mechanisms of VES-triggered apoptosis.

MATERIALS AND METHODS

Materials

VES was purchased from Sigma Co. Ltd. RPMI 1640 media and TRIzol total RNA isolation kit were obtained from Gibco BRL, TITANIUM™ one-step RT-PCR kit from Clontech. Inc. c-jun (H79) rabbit polyclonal antibody was from Santa Cruz Biotechnologies.

Methods

Cell culture Human gastric cancer cell lines SGC-7901 were maintained in RPMI 1640 medium supplemented with 100mL·L⁻¹ fetal calf serum (FCS), 100 kU·L⁻¹ penicillin, 100 mg·L⁻¹ streptomycin and 2 mmol·L⁻¹ L-glutamine under 50 mL·L⁻¹ CO₂ in a humidified incubator at 37 °C. SGC-7901 cells were incubated for different time periods in the presence of VES at 5, 10 and 20 mg·L⁻¹ (VES was dissolved in absolute ethanol and diluted in RPMI 1640 complete condition media corresponding to a final concentration of VES and 1 mL·L⁻¹ ethanol), succinic acid, vitamin E and ethanol equivalents as vehicle (VEH) control and condition media only as untreated (UT) control.

RT-PCR After SGC-7901 cells were treated with VES for 3, 6 and 24 h, respectively, total cellular RNA was isolated by using TRIzol Reagent according to the manufacturer’s instructions. The concentration and purity of total RNA were determined by DU640 nucleic acid and protein analyzer (Beckman, USA). One-step RT-PCR was carried out following the manufacturer’s instructions. RT-PCR mixture was heated 1h at 50 °C for reverse transcription and 5 min at 95 °C for pre-denaturation, then into 34 PCR cycles of 30 s at 94 °C for...
denaturation, 30 s at 60 °C for annealing, 30 s at 72 °C for extension in PTC-100 programmable thermal controller (MJ Research, USA). The corresponding fragment of c-jun gene was amplified with specific primers synthesized[35]. β-actin gene was designed as an internal standard with purpose to remove false negative outcome (Table 1).

**Table 1** Nucleotide sequence and size of the expected PCR products for oligonucleotide primers used for RT-PCR

| Genes     | Sequence                             | Size (bp) |
|-----------|--------------------------------------|-----------|
| c-jun     | Upstream: 5’-GGA AAC GAC CTT CTA TGA CGA GCC C-3’ | 335       |
|           | Downstream: 5’-GAA CCC CTC CTG CTC ATC TGT CAG G-3’ |           |
| β-actin   | Upstream: 5’-GTG GGC CGC TCT AGG CAC CAA-3’       | 540       |
|           | Downstream: 5’-CTC TTT GAT GTC ACG CAC GAT TTC-3’ |           |

The amplified products were separated in 20 g·L⁻¹ agarose gel stained with ethidium bromide. After electrophoresis, the gel was observed and photographed under ultraviolet reflector. The density and area of each band were analyzed using ChemiImager® 4000 Digital System (Alpha Innotech Corporation, USA).

**Western blot** SGC-7901 cells treated with VES were harvested, washed in PBS and lysed in lysis buffer containing 150 mmol·L⁻¹ NaCl, 1 mL·L⁻¹ NP-40, 5 mg·L⁻¹ sodium deoxycholate, 1 g·L⁻¹ SDS, 50 mmol·L⁻¹ Tris (pH 7.4), 1 mmol·L⁻¹ DTT, 0.5 mmol·L⁻¹ NaVO₃, 10 mmol·L⁻¹ phenylmethylsulfonyl fluoride (PMSF), 10 mg·L⁻¹ trypsin, 10 mg·L⁻¹ apotinin and 5 mg·L⁻¹ leupeptin. Following the centrifugation of 12 000×g for 30 min at 4 °C, the amount of protein in the supernatant was determined using Biorad DC protein assay. Equal amount of protein was separated on 10 % SDS-PAGE and transferred to nitrocellulose filter (Gibco BRL, USA) overnight. Blocked with 50 g·L⁻¹ defatty milk, the filter was incubated with c-jun (H79) rabbit polyclonal antibody and horseradish peroxidase-conjugated IgG, finally developed with DAB.

**Statistical analysis**

The data were expressed as t±s. Statistical analysis was performed using student’ s t-test. P<0.05 was considered significant.

**RESULTS**

**Effect of VES on the expression of c-jun mRNA in SGC-7901 cells**

1 µg of total cellular RNA from groups of control, succinate, vitamin E, VES at 5, 10 and 20 mg·L⁻¹ was added to amplify c-jun and β-actin genes by RT-PCR. Baseline expression of c-jun mRNA was observed in SGC-7901 cells (Figure 1). After the cells were treated with VES at 20 mg·L⁻¹ for 3 h, the expression rapidly reached its maximum that was 3.5 times of UT control (P<0.01). The level of c-jun mRNA was also increased following treatment of VES for 6 h. However, the expression after treatment of VES at 5 mg·L⁻¹ for 24 h was 1.6-fold increase compared with UT control (P<0.01), while there was no significant difference between 10 and 20 mg·L⁻¹ VES groups and UT control group (Table 2).

**Effect of VES on the expression of c-Jun protein in SGC-7901 cells**

Western blot analysis showed that the level of c-Jun protein was obviously elevated in VES-treated SGC-7901 cells at 20 mg·L⁻¹ for 3 h in a significant dose-dependent manner (Figure 2A, 2B). Meanwhile, compared with the cells in UT control group, the VES-treated cells at 20 mg·L⁻¹ exhibited 1.8-, 2.0-, 2.3- and 2.8-fold increases in the expression of c-jun protein for 3, 6, 12 and 24h, respectively, with an evident time-effect relationship (Figure 3A,3B).

![Figure 1](www.wjgnet.com)  
**Figure 1** Effect of VES on the expression of c-jun mRNA in SGC-7901 cells for different time points by RT-PCR. A: treatment of VES for 3 h; B: treatment of VES for 6 h; C: treatment of VES for 24 h. 1: UT control; 2: succinate; 3: vitamin E; 4: VES at 5 mg·L⁻¹; 5: VES at 10 mg·L⁻¹; 6: VES at 20 mg·L⁻¹; M: molecular weight marker.

**Table 2** The relative expression of c-jun mRNA in SGC-7901 cells (n=6, x±s)

| Groups      | 3h   | 6h   | 24h  |
|-------------|------|------|------|
| UT control  | 0.469±0.092 | 0.432±0.095 | 0.368±0.104 |
| succinate   | 0.426±0.082 | 0.408±0.078 | 0.361±0.083 |
| vitamin E   | 0.514±0.101 | 0.430±0.081 | 0.367±0.075 |
| 5mg·L⁻¹VES  | 0.550±0.115 | 0.621±0.089 | 0.584±0.097 |
| 10mg·L⁻¹VES | 0.471±0.086 | 0.584±0.101 | 0.421±0.077 |
| 20mg·L⁻¹VES | 1.663±0.109 | 0.905±0.099 | 0.411±0.094 |

*P<0.05, **P<0.01, vs UT control.
certain cell types, induction of c-jun activity can also be modulated directly at the protein level. In addition to this transcriptional mode of regulation, shock, H

Transcription of c-jun mRNA rises after exposure of cells to a number of treatment including ultraviolet, irradiation, heat shock, \( \text{H}_2\text{O}_2 \), TNF-\( \alpha \) and other apoptosis-associated factors. In addition to this transcriptional mode of regulation, c-jun activity can also be modulated directly at the protein level. In certain cell types, induction of c-jun is observed during apoptosis. There is some evidence that prolonged expression of c-jun in selected vulnerable cells suggests neuronal cell death.

Apoptosis is an innate program of cell suicide that is required for removal of unnecessary or damaged cells from bodily structures. Apoptosis is complex and regulated by a variety of factors. Previous studies showed that the induction of apoptosis in tumor cells is one of the important mechanisms of VES-induced cell growth inhibition. In the present study, the expression of c-jun mRNA and protein was measured in human gastric cancer SGC-7901 cells treated with VES at different doses for different time points. We found that the expression of c-jun mRNA was evidently promoted after 3 h of VES treatment at 20 mg·L\(^{-1}\) and reduced to the normal level after 24 h of treatment; whereas in the case of VES treatment at 5 mg·L\(^{-1}\), that was also increased after 3 h and remained a high level after 24 h. The data above showed that the c-jun activation was enhanced and prolonged by VES, therefore indicating that c-jun is involved in VES-triggered apoptosis in SGC-7901 cells. The results from western blot analysis showed that the level of c-jun protein was elevated following SGC-7901 cells were treated with VES at different doses for 3 h and with VES at 20 mg·L\(^{-1}\) for different time in a dose- and time-dependent manner.

The diversity of signals and signaling pathways that are directed toward c-jun is also reflected in the biological responses, in which the transcription factors have been implicated. It is reported that the mainly biological functions of c-jun are blockage of cell cycle and induction of apoptosis. The study presented here demonstrated that VES can obviously increase the expression of c-jun mRNA and protein in human gastric cancer SGC-7901 cells, implicating that c-jun is involved in VES-induced apoptosis.

**REFERENCES**

1. **Fariss MW**, Merson MH, O Harata TM. The selective antiproliferation effects of \( \alpha \)-tocopherol hemisuccinate and cholesteryl hemisuccinate on murine leukemia cells result from the action of the intact compounds. Cancer Res 1994; 54:3346-3357

2. **Ottino P**, Duncan JR. Effect of \( \alpha \)-tocopherol succinate on free radical and lipid peroxidation levels in BLM melanoma cells. Free Radical Biol Med 1997; 22:1145-1151

3. **Israel K**, Sanders BG, Kline K. \( \alpha \)-Tocopherol Succinate inhibits the proliferation of human prostatic tumor cells with defective cell cycle / differentiation pathway. Nutr Cancer 1995; 24:161-169

4. **Turley JM**, Ruscetti FW, Kim SJ, Fu T, Gao FV, Kirchenall-Roberts MC. Vitamin E succinate inhibits proliferation of BT-20 human breast cancer cells; increased binding of cyclin A negatively regulates E2F transcription activity. Cancer Res 1995; 55:2668-2675

5. **Neuzil J**, Weber T, Gellert N, Weber C. Selective cancer cell killing by \( \alpha \)-tocopherol succinate. Br J Cancer 2000; 82:87-89

6. **Pussinen PJ**, Lindner H, Glatter O, Recher H, Kostner GM, Wintersperger A, Malle E, Sattler W. Lipoprotein-associated \( \alpha \)-tocopheryl-succinate inhibits cell growth and induces apoptosis in human MCF-7 and HBL-100 breast cancer cells. Biochim Biophys Acta 2000; 1485:129-144

7. **Malafa MP**, Netzelt LT. Vitamin E succinate promotes breast cancer tumor dormancy. J Surg Res 2000; 93:163-170

8. **Kline K**, Sanders BG. \( \alpha \)-alpha-tocopheryl succinate inhibition of lectin-induced T cell proliferation. Nutr Cancer 1993; 19:241-252

9. **Yu W**, Sanders BG, Kline K. Modulation of murine EL-4 thymic lymphoma cell proliferation and cytokine production by Vitamin E succinate. Nutr Cancer 1996; 25:137-149

10. **Kline K**, Yu W, Sanders BG, Vitamin E. Mechanisms of Action as Tumor Cell Growth Inhibitors. Cancer and Nutrition. K.N. Prasad and W.C. Cole(Eds). IOS Press 1998.
Zhao Y et al. VES regulates c-jun expression

785

37-53

11 Klime K, Yu W, Zhao B, Turley JM, Sanders BG. Vitamin E Succinate: Mechanisms of action as tumor cell growth inhibitor. In: Nutrients in Cancer Prevention and Treatment. Prasad KN, Santamaria L and Williams RM (eds), Totowa, NY: Humana 1995:39-56.

12 Kim SJ, Bang OS, Lee YS, Kang SS. Production of inducible nitric oxide is required for monocytic differentiation of U937 cells induced by vitamin E-succinate. J Cell Sci 1998;111:435-441.

13 Simmons-Mc Encha M, Qian M, Yu W, Sanders BG, Kline K. RRR-α-Tocopheryl succinate induces DNA synthesis and enhances the production and secretion of biologically active transforming growth factor-β by avian retrovirus-transformed lymphoid cells. N utr Cancer 1995; 24:171-185.

14 Ariazi EA, Satorini Y, Ellis MJ. Activation of the transforming growth factor beta signaling pathway and induction of cytostasis and apoptosis in mammary carcinomas treated with the anticancer agent perillyl alcohol. Cancer Res 1999;59:1917-1928.

15 Turley JM, Fu T, Russetti FW, Mikovits JA, Bertolotto DC, Birchenal-Roberts M C. Vitamin E succinate induces Fas-meditated apoptosis in estrogen receptor-negative human breast cancer cells. Cancer Res 1997;57:881-890.

16 Yu W, Israell K, Liao QY, Aldaz CM, Sanders BG, Kline K. Vitamin E succinate (VES) induces Fas sensitivity in human breast cancer cells: role for M r 43,000 Fas in VES-triggered apoptosis. Cancer Res 1999;59:953-961.

17 Yu W, Liao QY, Hantash FM, Sanders BG, Kline K. Activation of extracellular signal-regulated kinase and c-Jun-NH2-terminal kinase but not p38 mitogen-activated protein kinases is required for RRR-α-tocopheryl succinate induced apoptosis of human breast cancer cells. Cancer Res 2001;61:6569-6576.

18 Neuzil J, Weber T, Schroder A, Lu M, Ostermann G, Gellett N, Mayne GC, Olenicka B, Negre-Salvayre A, Sticha M, Coffey RJ, Weber C. Induction of cancer cell apoptosis by α-tocopheryl succinate: molecular pathways and structural requirements. FASEB 2001;15:403-415.

19 Hua J. Effect of H2O2 cell proliferation and apoptosis on stomach cancer. Shijie Huaren Xiaohua Zazhi 1999;674-648.

20 Zhu ZH, Xia ZS, He SG. The effects of ATRA and SFu on talameres activity and cell growth of gastric cancer cells in vitro. Shijie Huaren Xiaohua Zazhi 2000;8:669-673.

21 Xiu JZ, Zhu ZG, Liu BY, Yan M, Yin HR. Significance of immunohistochemically detected micrometastases to lymph nodes in gastric carcinomas. Shijie Huaren Xiaohua Zazhi 2000;8:1113-1116.

22 Tu SP, Zhong J, Tan JH, Jiang XH, Qiao MM, Wu YX, Jiang SH. Induction of apoptosis by arsenic trioxide and hydroxy camptothcin in gastric cancer cells in vitro. World J Gastroenterol 2000;6:532-539.

23 Cai L, Yu SZ, Zhang ZF. Helicobacter pylori infection and risk of gastriccancer in Changle County, Fujian Province, China. World J Gastroenterol 2000;6:374-376.

24 Yao XX, Yin L, Zhang JY, Bai WY, Li YM, Sun ZC. H.TERT expression and cellular immunity in gastric cancer and precancerosis. Shijie Huaren Xiaohua Zazhi 2001;9:506-512.

25 Xu AG, Li SG, Liu JH, Gan AH. Function of apoptosis and expression of the proteins Bcl-2, p53 and c-jun in the development of gastric cancer. World J Gastroenterol 2000;7:403-406.

26 Liu DH, Zhang XY, Fan DM, Huang YX, Zhang JS, Huang WQ, Zhang YQ, Huang QS, Ma WY, Chai YB, Jin M. Expression of vascular endothelial growth factor and its role in oncogenesis of human gastric carcinoma. World J Gastroenterol 2001;7:500-505.

27 Wang X, Lan M, Shi YQ, Lu J, Zhong YX, Wu HP, Zai HH, Ding J, Wu KC, Pan BR, Jin JP, Fan DM. Differential display of vincristine-resistance-related genes in gastric cancer SGC7901 cell. World J Gastroenterol 2002;8:54-59.

28 Cao WX, Ou JM, Fei XF, Zhu ZG, Yin HR, Yan M, Lin YZ, Methionine-dependence and combination chemotherapy on human gastric cancer cells in vitro. World J Gastroenterol 2002;8:230-232.

29 Wu K, Ren Y, Guo J. The effects of vitamin E succinate on the cyclic regulation protein of human gastric cancer cells. Wensheng Dulixue Zazhi 1998;12:203-207.

30 Liu BH, Wu K, Zhao DY. Inhibition of human gastric carcinoma cell growth by vitamin E succinate. Wensheng Yanjiu 2002;29:172-174.

31 Wu K, Guo J, Shan YJ, Liu BH. The effects of vitamin E succinate on apoptosis in human gastric cancer. Wensheng Dulixue Zazhi 1999;13:84-90.

32 Liu BH, Wu K. Study on the growth inhibition of Vitamin E Succinate in human gastric carcinoma cell. A libian Jibian Tubian 2000;12:79-81.

33 Wu K, Shan YJ, Zhao Y, Yu JW, Liu BH. Inhibitory effects of RRR-α-tocopheryl succinate on bezo(a)pyrene (B(a)P)-induced forestomach carcinogenesis in female mice. World J Gastroenterol 2001;7:60-65.

34 Wu K, Liu BH, Zhao DY, Zhao Y. The effect of vitamin E succinate on the expression of TFG-β1, c-jun and c-jun in human gastric cancer SGC-7901 cells. World J Gastroenterol 2001;7:83-87.

35 Tetens F, Kliem A, Tscheutschliuren G, Vanarrete Santos A, Fischer B. Expression of proto-oncogenes in bovine endometrial epithelial cells. Acta Veterinar A 2000;349:355.

36 Feng DY, Zheng H, Tan Y, Cheng RX. Effect of phosphorylation of MAPK and Stat3 and expression of c-fos and c-jun proteins on hepatocarcinogenesis and their clinical significance. World J Gastroenterol 2001;7:33-36.

37 Leppa S, Safrich R, Ansgore W, Bohmann D. Differential regulation of c-jun by ERK and JNK during PC12 cell differentiation. EMBO J 1998;17:4404-4413.

38 Zhu YH, Hu DR, Nie OH, Liu GD, Tan ZX. Study on activation and c-fos, c-jun expression of in vitro cultured human hepatic stellate cells. Shijie Huaren Xiaohua Zazhi 2000;8:299-302.

39 Guo YS, Hellmich MR, Wen XD, Townsend CM. Activator protein-1 transcription factor mediates bombesin-stimulated cyclooxygenase-2 expression in intestinal epithelial cells. J Biol Chem 2001;276:22941-22947.

40 Herdegen T, Wachtzig V, c-jun proteins in the adult brain: facts and fiction around abouts of neuroprotection and neurodegeneration. Oncogene 2001;20:2424-2437.

41 Yuen MF, Wu PC, Lai YCH, Lau JYN, Lai CL. Expression of c-myc, c-fos, and c-jun in hepatocellular carcinoma. Cancer 2001;91:106-112.

42 Schroeter H, Spencer J R, Rice Evans C, Williams R J. Flavonoids protect neurons from oxidized low-density-lipoprotein-induced apoptosis involving c-jun N-terminal kinase (JNK), c-jun and caspase 3. Biochem J 2001;358:547-557.

43 Jiang LX, Fu XB, Sun TZ, Yang YH, Gu XM. Relationship between oncogene c-jun activation and fibroblast growth factor receptor expression of ischemia reperfusion intestine in rats. Shijie Huaren Xiaohua Zazhi 1997;4:498-500.

44 Fan M, Goodwin ME, Birrner M, Chambers TC. The c-jun NH2-terminal protein kinase/ AP-1 pathway is required for efficient apoptosis induced by vinblastine. Cancer Res 2001;61:4450-4458.

45 Kondo T, Matsuda T, Kitano T, Takahashi A, Tashima M, Ishikura H, Umehera H, Domae N, Uchiyama T, Okazaki T. Role of c-jun expression increased by heat shock-and ceramide-activated caspase 3 in HL-60 cell apoptosis. J Biol Chem 2000;275:7668-7676.

46 Potapova O, Basu S, Mercola D, Holbrook NJ. Protective role for c-jun in the cellular response to DNA damage. J Biol Chem 2001;276:28546-28553.

47 Behrens A, Sabapathy K, Graef I, Cleary M, Crabbtree GR, Wagner EF. Jun N-terminal kinase 2 modulates thymocyte apoptosis and T cell activation through c-jun and nuclear factor of activated T cell (NF-AT). Proc Natl Acad Sci USA 2001;98:1769-1774.
48 Ashkenazi A, Dixit VM. Apoptosis control by death and decoy receptors. Curr Opin Cell Biol 1999;11:255-260
49 Behrens A, Sibilia M, Wagner EF. Amino-terminal phosphorylation of c-jun regulates stress-induced apoptosis and cellular proliferation. Nat Genet 1999;6:211-216
50 Sun BH, Zhao XP, Wang BJ, Yang DL, Hao LJ, FADD and TRADD expression and apoptosis in primary human hepatocellular carcinoma. World J Gastroenterol 2000;6:223-227
51 Wu K, Guo J, Shan YJ. Inhibitory effects of VES on the growth of human squamous gastric carcinoma cells. In: Johnson IT and Fenwick GR (eds), Dietary anticarcinogens and antimutagens. Chemical and biological aspects. RS C, UK: Athenaeum Press 2000:304-307
52 Zhao Y, Wu K. Cell death molecule Fas/CD95 and apoptosis. Alibian Jibian Tubian 2001;13:55-58
53 Wei XC, Wang XJ, Chen K, Zhang L, Liang Y, Lin XL. Killing effect of TNF-related apoptosis inducing ligand regulated by tetracycline on gastric cancer cell line NCI-N87. World J Gastroenterol 2001;7:559-562
54 Smaele ED, Zazzeroni F, Papa S, Nguyen DU, Jin R, Jones J, Cong R, Franzoso G. Induction of gadd45β by NF-κB downregulates pro-apoptotic JNK signaling. Nature 2001;414:308-313
55 Wu YL, Sun B, Zhang XJ, Wang SN, He HY, Qiao MM, Zhong J, Xu JY. Growth inhibition and apoptosis induction of Sulindac on human gastric cancer cells. World J Gastroenterol 2001;7:796-800
56 Li HL, Chen DD, Li XH, Zhang HW, Lu YQ, Ye CL, Ren XD. Changes of NF-kB, p53, Bcl-2 and caspase in apoptosis induced by JTE-522 in human gastric adenocarcinoma cell line AGS cells: role of reactive oxygen species. World J Gastroenterol 2002;8:431-435
57 Tao HQ, Zou SC. Effect of preoperative regional artery chemotherapy on proliferation and apoptosis of gastric carcinoma cells. World J Gastroenterol 2002;8:451-454
58 Tian G, Yu JP, Luo HS, Yu BP, Yue H, Li JY, Mei Q. Effect of Nimesulide on proliferation and apoptosis of human hepatoma SMCC-7721 cells. World J Gastroenterol 2002;8:483-487
59 Yu W, Simmons MM, You H. RRR-α-Tocopheryl Succinate induction of prolonged activation of c-jun amino-terminal kinase and c-jun during induction of apoptosis in human MDA-MB-435 breast cancer cells. Mol Carcinog 1998;22:247-267
60 Yu W, Sanders BG, Kline K. RRR-α-tocopheryl succinate inhibits EL4 thymic lymphoma cell growth by inducing apoptosis and DNA synthesis arrest. Nutr Cancer 1997;27:92-101
61 Kogure K, Morita M, Nakashima S, Hama S, Tokumura A, Fukuzawa K. Superoxide is responsible for apoptosis in rat vascular smooth muscle cells induced by α-tocopheryl hemisuccinate. Biochim Biophys Acta 2001;1528:25-30
62 Leppa S, Bohmann D. Diverse functions of JNK signaling and c-jun in stress response and apoptosis. Oncogene 1999;18:6158-6162
63 Jiang LX, Fu XB, Sun TZ, Yang YH, Gu XM. Relationship between oncogene c-jun activation and fibroblast growth factor receptor expression of ischemia reperfusion intestine in rats. Shi jie H uaren Xi aohua Zazhi 1999;7:498-500
64 Teng CS. Differential expression of c-jun proteins during Mullerian duct growth and apoptosis: caspase-related tissue death blocked by diethylstilbestrol. Cell Tissue Res 2000;302:377-385

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