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论著

五没食子酰基葡萄糖对卵巢癌HO-8910细胞凋亡调控基因表达与胱天蛋白酶凋亡途径的影响

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摘要 目的 探讨五没食子酰基葡萄糖(PGG)诱导卵巢癌HO-8910细胞凋亡的作用及诱导胱天蛋白酶凋亡途径的机制。方法 PGG 10,20,40和80 μmol·L^{-1}处理HO-8910细胞48,72和96 h后,MTT法检测细胞存活率;Hoechst 33258染色观察HO-8910细胞核形态改变,AnnexinⅤ-FITC/PI双染流式细胞术检测细胞凋亡率;Western 印迹法检测细胞内胱天蛋白酶酶原及活性形式;RT-PCR检测凋亡调控基因Bax、Bcl-2、Bcl-XL、凋亡抑制因子1(CIAP-1)、CIAP-2、存活蛋白、神经元凋亡抑制蛋白(NIAP)、X连锁凋亡抑制蛋白(XIAP)和细胞周期蛋白D1 mRNA表达。结果 PGG 10~80 μmol·L^{-1}分别作用48,72和96 h,随浓度的增加,细胞存活率明显降低, *r*分别为0.93,0.95和0.86($P<0.05$)。PGG 40 μmol·L^{-1}使HO-8910细胞的细胞核染色质固缩,出现凋亡形态学改变,早期凋亡率从正常对照组的(0.6±0.1)%分别增加到(3.4±1.1)%,(9.8±3.7)%和(19±4.5)%,对晚期凋亡率影响不明显。PGG 20~80 μmol·L^{-1}使HO-8910细胞内胱天蛋白酶3, 胱天蛋白酶7和胱天蛋白酶9及其底物多聚腺苷二磷酸核糖聚合酶(PARP)的剪切水平增加, PGG 20~80 μmol·L^{-1}均抑制死亡受体FAS的蛋白表达水平并使胱天蛋白酶8总剪切水平降低。PGG 20~80 μmol·L^{-1}抑制HO-8910细胞中细胞周期蛋白D1,Bcl-2,Bcl-XL和NIAP mRNA的表达,上调CIAP-1 mRNA的表达,对基因Bax,CIAP-2和XIAP mRNA表达影响不明显;PGG 20 μmol·L^{-1}抑制存活蛋白基因mRNA的表达,但是增加处理浓度却上调存活蛋白基因mRNA的表达。结论 PGG可能通过抑制凋亡抑制基因Bcl-2和Bcl-XL的表达从而诱导HO-8910细胞内胱天蛋白酶9依赖的内源性凋亡途径,并诱导细胞凋亡。

关键词 五没食子酰基葡萄糖 卵巢癌HO-8910细胞 细胞凋亡 Bcl-2家族 凋亡抑制因子 胱天蛋白酶
分类号 R285.5

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Effect of pentagalloylglucose on expression of apoptosis regulator genes and caspase-dependent apoptosis pathways in HO-8910 cells

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Abstract

OBJECTIVE To explore the effect of pentagalloylglucose(PGG) on the apoptosis of ovarian cancer cells and the mechanism underlying the induced caspase-dependent apoptosis pathways in ovarian cancer HO-8910 cells. METHODS HO-8910 cells were cultured with PGG 10,20,40 and 80 μmol·L^{-1} for 48, 72 or 96 h. The cell survival rate was detected by MTT assay. The morphological alteration of nucleus of HO-8910 cells was observed under a fluorescence microscope after Hoechst 33258 staining and the apoptosis ratio was determined by AnnexinⅤ-FITC/PI double-staining combined with flow cytometry assay. Western blotting was employed to detect the pro-caspases or active caspases(c-caspases). The mRNA expression of apoptosis regulator genes Bcl-2, Bcl-XL, CIAP-1, CIAP-2, survivin, NIAP, XIAP and cycle regulator gene cyclin D1 was visualized by RT-PCR. RESULTS PGG inhibited the growth *in vitro* of HO-8910 cells in a time- and concentration-dependent manner during 48, 72 and 96 h treatment($P<0.05$); the correlation coefficient was 0.93, 0.95 and 0.86, respectively. PGG treatment induced nuclear chromatin pycnosis of HO-8910 cells and the morphological alteration of nuclei in apoptosis. The ratio of apoptosis in HO-8910 cells rose with lengthened treatment and increased doses of PGG. PGG 20-80 μmol·L^{-1} promoted the cleavage of caspases 3, 7 and 9 and the related PARP substrate in HO-8910 cells. However, PGG 20-80 μmol·L^{-1} inhibited the protein expression of the death receptor FAS and the cleavage of caspase 8 at 24 and 36 h, but down-regulated the mRNA expression of cyclin D1, Bcl-2, Bcl-XL and NIAP genes vat 12 h. It had on effect on Bax,CIAP-2 and XIAP mRNA, but up-regulated the mRNA expression of CIAP-1. The effect of PGG on the surviving mRNA was not concentration-dependent. CONCLUSION PGG might induce caspase 9-dependent endogenous caspase pathways by inhibiting the expression of apoptosis inhibitor genes, and trigger HO-8910 cell apoptosis. It's likely that PGG has repressed the caspase 8-dependent apoptosis pathway in HO-8910 cells.

Key words pentagalloylglucose HO-8910 cells apoptosis Bcl-2 family apoptosis-inhibiting factors caspases

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