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论文

功劳木中异汉防己碱对P-糖蛋白介导的人乳腺癌细胞多药耐药性的逆转作用

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摘要：

本文探讨了异汉防己碱对P-糖蛋白(P-gp)介导的人乳腺癌细胞多药耐药性的逆转作用。首先以RT-PCR和免疫组化方法分别从RNA和蛋白水平检测MCF-7/DOX细胞P-gp表达情况，以明确MCF-7/DOX细胞的耐药特征；然后采用MTT法检测异汉防己碱的内在细胞毒性及其对阿霉素(DOX)的增敏作用，并以RF(reversal fold)值评价其逆转效果；同时应用流式细胞仪(FCM)对细胞内DOX的蓄积量进行了分析；再以免疫组化方法检测异汉防己碱对MCF-7/DOX细胞P-gp表达水平的影响；最后采用罗丹明蓄积和外排试验检测了异汉防己碱对P-gp功能的影响。整个试验以维拉帕米作为阳性对照。实验结果表明：MCF-7/DOX细胞是具有多药耐药表型且P-gp表达阳性的细胞株；无毒剂量异汉防己碱可明显增强DOX对MCF-7/DOX细胞的细胞毒性(RF=3.89)，明显高于维拉帕米(RF=2.54)的逆转活性($P<0.05$)，但其几乎不影响DOX对MCF-7细胞的抑制作用；异汉防己碱对MCF-7/DOX细胞P-gp表达水平无明显影响，但其可有效抑制P-gp的药物外排功能。因此，异汉防己碱可有效逆转P-gp介导的人乳腺癌细胞的多药耐药性，它可能成为有效多药耐药逆转剂的候选药物。

关键词： 异汉防己碱 P-糖蛋白 多药耐药性 MCF-7/DOX细胞

Reversal effect of isotetrandrine, an isoquinoline alkaloid extracted from Reversal effect of isotetrandrine, an isoquinoline alkaloid extracted from *Caulis Mahoniae*, on P-glycoprotein-mediated doxorubicin-resistance in human breast cancer (MCF-7/D

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Abstract:

This study investigated the reversal effect of isotetrandrine, an isoquinoline alkaloid extracted from *Caulis mahoniae*, on P-glycoprotein-mediated multidrug resistance in human breast cancer doxorubicin-resistant (MCF-7/DOX) cells. RT-PCR assay and immunity histochemistry assay were used to determine the expression level of *mdr1* gene and P-gp in MCF-7/DOX cells to elucidate resistant character of MCF-7/DOX cells. The activity of isotetrandine to enhance doxorubicin cytotoxicity was tested using MTT (3-(4,5-dimethylthiazol)-2,5-diphenyltetrazolium bromide) assay and was evaluated by the reversal fold (RF) values. Intracellular accumulation of doxorubicin was assessed by the determination of doxorubicin-associated fluorescence intensity. Effect of isotetrandrine on the expression level of P-gp in MCF-7/DOX cells was then determined by immunity histochemistry assay. The ability of isotetrandrine to inhibit P-gp function was evaluated by detecting the accumulation and efflux of rhodamine123 (Rh123) with flow cytometry (FCM). Verapamil was employed as a comparative agent in whole experiment. The results indicated that MCF-7/DOX cells had phenotype of MDR and that the positive expression of P-gp was their resistant character. 10 $\mu g \cdot mL^{-1}$ isotetrandrine could distinctly enhance cytotoxicity of DOX in MCF-7/DOX cells and reversal fold (RF) was significantly higher than that of verapamil ($P<0.05$), but it hardly affected cytotoxicity of DOX in MCF-7 cells and the expression level of P-gp in MCF-7/DOX cells. The ability of isotetrandrine to inhibit P-gp function was reversible, because incubation of MCF-7/DOX cells with isotetrandrine caused a marked increase in uptake and a notable decrease in efflux of Rh123 and a marked increase of intracellular DOX concentrations. In conclusion, isotetrandrine exhibited potent effect on the reversal of P-gp-mediated MDR *in vitro*, suggesting that it might become a candidate of effective MDR reversing agent in cancer chemotherapy.

Keywords: P-glycoprotein multidrug resistance MCF-7/DOX cell isotetrandrine

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