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## 单端孢菌素逆转肺癌耐药A549/DDP细胞耐药性及其机制研究

Effects and Mechanisms of Trichothecenes in Reversing the Drug Resistance of A549/DDP

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中文摘要:

目的 探讨单端孢菌素对肺癌耐顺铂细胞系A549/DDP顺铂耐药性的逆转作用及机制。方法 应用MTS法检测单端孢菌素对A549/DDP细胞顺铂敏感性的影响, 流式细胞术检测肿瘤细胞表面P-糖蛋白(P-Glycoprotein, P-gp)表达以及胞内罗丹明-123(Rhodamine-123, Rh-123)含量的变化, 生化法检测细胞内SOD和GSH的水平, Western blot法和Real time PCR检测肿瘤细胞多药耐药蛋白MDR1、MRP1和Survivin表达的变化, Western blot法检测Akt磷酸化的变化, 液相芯片法检测TGF- $\beta$ , IL-6和IL-8的变化, 应用双荧光报告基因技术检测细胞NF- $\kappa$ B和AP-1转录活性。结果 单端孢菌素可增加细胞对顺铂的敏感性, 经5  $\mu\text{g} \cdot \text{mL}^{-1}$ 和10  $\mu\text{g} \cdot \text{mL}^{-1}$ 单端孢菌素作用72 h后, 耐药逆转倍数(RF)为1.84和3.95倍。经5  $\mu\text{g} \cdot \text{mL}^{-1}$ 和10  $\mu\text{g} \cdot \text{mL}^{-1}$ 单端孢菌素作用24 h后, 肿瘤细胞P-gp表达分别下降了62.6%和19.8%, 细胞中Rh-123含量分别提高了183.3%和308.3%, 细胞内SOD水平下降65.2%和50.1%, GSH水平下降71.6%和46.3%, MDR1的mRNA水平下降了72.7%和52.3%, MRP1的mRNA水平下降了64.0%和22.5%, Survivin的mRNA水平下降了45.8%和14.7%, Akt磷酸化水平下降, TGF- $\beta$ 分泌水平下降了80.2%和51.5%, IL-6分泌水平下降了73.4%和37.2%, IL-8分泌水平下降了71.2%和43.2%, NF- $\kappa$ B转录活性下降42.3%和22.7%, AP-1的转录活性下降了57.4%和32.5%。结论 单端孢菌素逆转A549/DDP对顺铂的耐药性, 这一作用与抑制药物外排, 负调控肿瘤耐药相关蛋白的表达有关。

英文摘要:

OBJECTIVE To investigate the effects and mechanisms of trichothecenes on reversing the cisplatin resistance of lung cancer drug-resistant cell line A549/DDP.

METHODS MTS assay was employed to determine the effect of trichothecenes on A549/DDP sensitivity. The distribution of P-Glycoprotein (P-gp) and intracellular concentration of rhodamine-123 (Rh-123) were determined by flow cytometry. Intracellular level of SOD and GSH was determined by biochemistry assay. The expression of multi-drugs resistant proteins MDR1, MRP1 and Survivin were determined by Western blot and Real time PCR. The phosphorylation of Akt was analyzed by Western blot. Secretion of TGF- $\beta$ , IL-6 and IL-8 were assayed by liquidchip. The transcriptional activities of NF- $\kappa$ B and AP-1 were detected by dual-luciferase reporter gene systems. RESULTS Trichothecenes was able to increase the cisplatin sensitivity of A549/DDP. After treatment with 5 and 10  $\mu\text{g}\cdot\text{mL}^{-1}$  trichothecenes for 72 h, the reverse folds (RF) to adriamycin were 1.84 and 3.95 respectively. After treatment with 5 and 10  $\mu\text{g}\cdot\text{mL}^{-1}$  trichothecenes for 24 h, the expression of P-gp was decreased 62.6% and 19.8%, the intracellular level of Rh-123 was elevated 183.3% and 308.3%, the intracellular level of SOD was decreased 65.2% and 50.1%, GSH was decreased 71.6% and 46.3%. The protein expressions of MDR1, MRP1 and Survivin were downregulated significantly, the mRNA expressions of MDR1 was decreased 72.7% and 52.3%, MRP1 decreased 64.0% and 22.5%, Survivin was decreased 45.8% and 14.7%. In addition, the phosphorylation of Akt decreased. The secretion of TGF- $\beta$  was decreased 80.2% and 51.5%, IL-6 was decreased 73.4% and 37.2%, IL-8 was decreased 71.2% and 43.2%. Finally, transcriptional activity of NF- $\kappa$ B was decreased 42.3% and 22.7% and AP-1 was decreased 57.4% and 32.5%, significantly. CONCLUSION Trichothecenes is able to reverse the cisplatin resistance of A549/DDP. Trichothecenes processes this kind of effect by inhibiting the drug efflux, downregulating the expression of drug-resistant related proteins.

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