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顺铂和紫杉醇对CIK 细胞杀伤食管癌细胞活性的影响及其分子机制研究*

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Effect of cisplatin and paclitaxel on the cytotoxicity of cytokine-induced killer cells on esophagus carcinoma and its molecular mechanisms

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摘要

目的：研究紫杉醇、顺铂对人食管癌EC9706细胞NKG 2D 配体表达及CIK 细胞杀伤活性的影响，探讨相关分子机制。方法：MTT 法测定紫杉醇、顺铂对EC9706细胞的24h 半数抑制浓度（IC 50）。 流式细胞仪检测1/ 2 IC 50浓度紫杉醇、顺铂作用前、后EC9706细胞NKG 2D 配体的表达。乳酸脱氢酶释放法检测效靶比2 0 ：1、3 0 ：1 时，CIK 细胞对1/ 2 IC 50浓度紫杉醇、顺铂作用前、后EC9706细胞的杀伤活性。荧光定量PCR 法检测1/ 2 IC 50浓度紫杉醇、顺铂作用EC9706细胞24h 前、后DNA 损伤修复基因（ATM 、ATR 、CHK 1、CHK 2、P 53）表达的变化。结果：紫杉醇、顺铂的24h 半数抑制浓度分别为10、5 μ g/mL 。1/ 2 IC 50浓度紫杉醇作用24h后，EC9706细胞MICB、ULBP2、ULBP3 表达均明显增强（P < 0.05），MICA、ULBP1 表达无显著性变化（P > 0.05）；1/ 2 IC 50浓度顺铂作用24h 后，EC9706细胞 MICA、MICB、ULBP2、ULBP3 表达均明显增强（P < 0.05），ULBP1 表达无显著性变化（P > 0.05）。效靶比 20 ：1、30 ：1 时，CIK 细胞对 1/ 2 IC 50浓度紫杉醇、顺铂作用后的 EC9706细胞的杀伤活性均明显增强（P < 0.05）。1/ 2 IC 50浓度紫杉醇作用 24h后，DNA 损伤修复基因表达均无显著性变化（P > 0.05）；1/ 2 IC 50浓度顺铂作用24h 后，ATM 、ATR 、CHK 1、CHK 2 基因表达均明显增加（P < 0.05），P 53基因表达无显著性变化（P > 0.05）。 结论：顺铂、紫杉醇均可增强CIK 细胞的杀伤活性，其分子机制可能与激活DNA 损伤修复基因，进而增加NKG 2D 配体表达有关。

关键词 ： 食管癌，紫杉醇，顺铂，细胞因子诱导的杀伤细胞，NKG 2D 配体，DNA 损伤修复基因

Abstract :

Objective:To explore the effect of paclitaxel (PTX) and cisplatin (DDP) on the expression of NKG2D ligands of hu-man esophagus carcinoma cell EC 9706and on the cytotoxicity of cytokine-induced killer (CIK) cells, as well as to discuss its molecu-lar mechanisms. Methods:The half maximal inhibitory concentration (IC50) values of PTX and DDP against EC 9706cells for 24h were measured by MTT assay. The expression levels of NKG 2D ligands (MICA, MICB, ULBP1, ULBP2, and ULBP 3) on the EC 9706 cell surface before and after 24h culture with 1/2 IC50 of PTX or DDP were assayed by flow cytometry. Cytotoxicity of CIK cells against EC9706cells before and after 24h culture with 1/2 IC50 PTX or DDP was analyzed by lactate dehydrogenase release assay at an effector to target cell ratio (E:T) of20:1 and 30:1, respectively. The expression levels of DNA damage repair genes (ATM, ATR, CHK1, CHK2, and p 53) of EC9706cells before and after 24h incubation with1/2 IC50 PTX or DDP were detected by quantitative fluorescent PCR.Results:The IC 50 values of PTX and DDP were 10and 5 μ g/mL, respectively. MICB, ULBP 2, and ULBP 3 on EC 9706cells were upregulated after 24h culture with 1/2 IC50 PTX (P<0.05), and the expression levels of MICA, MICB, ULBP2, and ULBP 3 were higher after 24h culture with 1/2 IC50 DDP (P<0.05). Cytotoxicity of CIK cells against EC 9706cells cultured with 1/2 IC50 of PTX or DDP at E:T of 20:1 and 30:1 was significantly enhanced compared with those untreated (P<0.05). The expression levels of DNA damage repair genes did not significantly increase after 24h treatment with 1/2 IC50 PTX (P>0.05), whereas ATM, ATR, CHK 1, and CHK 2 were over -expressed after24h treatment with 1/2 IC50 DDP (P<0.05). Conclusion:PTX or DDP can enhance the susceptibility of EC9706cells to CIK cell-mediated lysis by upregulating the expression of NKG2D ligands through activating DNA damage repair genes.

Key words : esophagus carcinoma paclitaxel cisplatin cytokine-induced killer cells NKG2D ligands DNA damage repair genes

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