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MDA-7/IL-24基因与化疗药物联合应用对食管癌细胞产生协同抑制作用

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摘要：

探讨人黑素瘤分化相关基因7（melanoma differentiation-associated gene-7，MDA-7）/白介素-24(IL-24)基因对食管癌细胞的抑制作用及其与化疗药物的协同抗瘤作用。方法：RT-PCR法检测人食管癌细胞株TE-11和YES-5中MDA-7/IL-24受体IL-20R1、IL-20R2和IL-22R1的表达水平。用携带MDA-7/IL-24基因的重组人复制缺陷腺病毒Ad-MDA-7感染TE-11和YES-5细胞， Ad-LacZ为对照腺病毒，人成纤维细胞株OUMS-24为对照细胞。MTT法检测感染细胞抑制率，Western blotting法检测感染前后细胞中的MDA-7水平。化疗药物5-氟尿嘧啶（5-FU）、顺铂（CDDP）、丝裂霉素（MMC）和足叶乙甙（VP-16）分别与Ad-MDA-7联合作用于食管癌细胞株，MTT法检测单独或联合应用对食管癌细胞的抑制作用，流式细胞术检测Ad-MDA-7与化疗药单独或联合应用后食管癌细胞周期的变化，Western blotting检测Ad-MDA-7与化疗药联合作用后细胞凋亡和增殖的相关分子的变化。结果：TE-11和YES-5细胞均表达3种IL-24受体。Ad-MDA-7感染后，两种食管癌细胞中均有MDA-7蛋白表达，同时细胞均被剂量依赖性地抑制生长，Ad-MDA-7达3×104VP/细胞时TE-11细胞抑制率超过80%、YES-5细胞超过50%；同剂量Ad-LacZ对细胞无抑制作用，成纤维细胞OUMS-24被Ad-MDA-7感染后没有发生明显细胞抑制。Ad-MDA-7分别与5-FU、CDDP、MMC和VP-16联合应用后，与单独应用相比产生了更强的抗肿瘤协同效应。Ad-MDA-7与5-FU联合应用诱导细胞更多停滞在S和G2/M期，subG1期细胞比例明显增加。与单用5-FU相比，联合应用时Ad-MDA-7诱导了更多的细胞凋亡相关蛋白cleaved caspase-8、 -9、 -3的表达，增加了Akt的磷酸化，但降低了IκB-α的表达水平。结论：MDA-7/IL-24与化疗药联合应用于食管癌细胞，产生了更强的抗肿瘤协同效应，为临床化疗和基因治疗的联合应用提供新选择。

关键词：食管癌 腺病毒 MDA-7 IL-24 基因治疗 化学治疗

Enhanced cytotoxicity of chemotherapeutic agents in combination with adenoviruses expressing MDA-7/IL-24 to esophageal carcinoma cells in vitro

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Abstract:

To evaluate the synergic antitumor effects of chemotherapeutic agents and melanoma differentiation-associated gene-7-expressing adenoviruses (Ad-MDA-7) in esophageal carcinoma cells in vitro. Methods: Human esophageal carcinoma TE-11 and YES-5 cells and human fibroblasts (control) underwent Ad-MDA-7 infection and chemotherapy, either each alone or in combination. Changes in mRNA levels of the IL-24 receptor complexes before and after treatment were assessed by RT-PCR. Cell viability was determined by MTT assays. Cell cycle progression was analyzed by flow cytometry. Results: Transcripts for IL-24 receptor complex components, IL-20R2, IL-20R1 and IL-22R1, were detected in both TE-11 and YES-5 cells but only IL-20R2 mRNA was detected in fibroblasts. TE-11 and YES-5 cells were susceptible were to Ad-MDA-7-mediated cytotoxicity in a dose-dependent manner; at 3×104 VP/cell, cytotoxicity was >80% and >50%, respectively, in TE-11 and YES 5 cells. In contrast, fibroblasts were resistant to Ad-mad-7. The cytotoxicity of 5-fluorouracil, cisplatin, mitomycin C or etoposide, each in combination with Ad-MDA-7 infection was significantly higher than that of these therapeutic agents and Ad-MDA-7, each alone. Increases in G2/M-phase and S-phase arrests were observed in cells, respectively, infected with Ad-MDA-7 and treated with 5-FU . The combination of Ad-mad-7 and 5-FU augmented sub-G1 populations. Compared with 5-FU alone, the combination regimen resulted in increases in caspase-8, -9, -3 expression and Akt phosphorylation and a decrease in IκB-α level. Conclusion: These data collectively suggest that adenovirus delivery of melanoma differentiation-associated gene-7 may enhance the sensitivity of esophageal carcinoma cells to chemotherapeutic agents through Akt activation.

Keywords:esophageal carcinoma adenovirus MDA-7 IL-24 gene therapy chemotherapy

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