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论著

不同化疗药物对结肠癌细胞获得性TRAIL基因耐药的逆转作用

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摘要 目的：探讨不同化疗药物对结肠癌DLD1细胞获得性TRAIL基因耐药的逆转作用及其可能的机制。 方法：将不同化疗药物联合重组腺病毒载体（Ad）介导的TRAIL基因处理对Ad/gTRAIL耐药的结肠癌DLD1-TRAIL/R细胞，通过MTT法检测治疗后肿瘤细胞的存活率，以评价化疗药物对TRAIL基因耐药的逆转作用；然后进一步在体内评价该逆转策略的有效性；接着通过Western免疫印迹等方法探讨逆转耐药的可能机制。结果：在体外检测了5-氟脲嘧啶、丝裂霉素、阿霉素、氟脲苷、依立替康以及顺铂6种化疗药物对DLD1-TRAIL/R细胞TRAIL基因耐药的逆转作用，结果发现只有5-氟脲嘧啶和丝裂霉素能够使DLD1-TRAIL/R细胞对Ad/gTRAIL重新敏感。进一步的结果表明联合5-氟脲嘧啶和Ad/gTRAIL能在体内有效地抑制DLD1-TRAIL/R细胞来源的肿瘤生长，且该抑制作用明显强于其它对照组。结论：联合使用Ad/gTRAIL和5-氟脲嘧啶或丝裂霉素能在体内外有效地逆转DLD1-TRAIL/R细胞对TRAIL基因的获得性耐药，其中丝裂霉素的逆转作用可能与其诱导的Bax过度表达有关。

关键词 基因,TRAIL； 结肠肿瘤 药物疗法

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扩展功能

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Effects of different chemotherapeutic agents on reversing the acquired resistance to TRAIL gene in DLD1 colon cancer cells

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Abstract

<P><FONT face=Verdana>AIM:To evaluate effects of different chemotherapeutic agents on reversing the acquired resistance to TRAIL gene and clarify the involved mechanisms in DLD1-TRAIL/R colon cancer cells. METHODS:Human colon cancer cell line DLD1-TRAIL/R cells that were resistant to TRAIL-expressing adenovector (Ad/gTRAIL) were treated with Ad/gTRAIL combined with different chemotherapeutic agents. Then, the cell viability was measured by MTT method, and apoptotic signaling conditions, including activation of caspase-3 and caspase-8, expression of Bax and Bcl-XL, were measured by Western blotting analysis. RESULTS:In vitro data showed that several chemotherapeutic agents, including 5-fluorouracil (5-FU) and mitomycin c (MMC), overcome the acquired resistance to TRAIL gene in DLD1-TRAIL/R colon cancer cells. The combination of Ad/gTRAIL and 5-FU effectively suppressed tumor growth in vivo in subcutaneous tumors established from DLD1-TRAIL/R cells. Further data showed that treatment with the combination of Ad/gTRAIL and 5-FU or MMC led to enhance the activation of caspase-3. Moreover, MMC but not 5-FU induced overexpression of Bax gene that was sufficient to overcome the resistance to TRAIL gene in DLD1-TRAIL/R cells. CONCLUSION:Chemotherapeutic agents, such as 5-FU and MMC, overcome the acquired resistance to TRAIL gene in DLD1-TRAIL/R cells. The candidate mechanisms for MMC but not 5-FU to overcome this resistance might involve the induction of over-expressed Bax protein in DLD1-TRAIL/R cells. </FONT></P>

Key words Genes TRAIL Colonic neoplasms Drug therapy

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