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雷帕霉素联合顺铂抑制人宫颈癌HeLa细胞裸鼠移植瘤的生长及其机制

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摘要：

目的： 探讨雷帕霉素（rapamycin，RAPA）与顺铂（cisplatin，DDP）单独及联合应用对人宫颈癌HeLa细胞裸鼠皮下移植瘤生长的抑制作用及其可能的机制。方法： 裸鼠皮下接种HeLa细胞，建立人宫颈癌裸鼠皮下移植瘤模型，随机分为对照组、RAPA组、DDP组、RAPA+DDP组。治疗过程中检测肿瘤的质量、体积，RT-PCR、免疫组化及Western blotting检测低氧诱导因子-1α（hypoxia-inducible factor-1alpha，HIF-1α）及血管内皮生长因子（vascular endothelial growth factor，VEGF）mRNA及蛋白的表达。 结果： RAPA+DDP组与RAPA组相比，移植瘤的质量\[（0.42±0.04） vs （0.53±0.03）g，P<0 05\]、体积\[（568 70±36.12） vs （797.81±111.98）mm3，P<0.01\]都明显减小。RAPA+DDP组与DDP组相比，移植瘤的质量\[（0.42±0.04） vs （0.52±0.04）g，P<0.05\]、体积\[（568.70±36.12） vs （766.16±132.27）mm3，P<0.01\]也明显减小。RT-PCR及Western blotting结果显示：RAPA+DDP组与RAPA组、DDP组相比，移植瘤中 HIF-1α mRNA水平下调\[(31.22±0 71） vs （50.58±1.25）、（48.63±1.56），P<0.05\]；HIF-1α蛋白水平也下调\[(38.07±0.09） vs （55.69±3.60）、（59.50±1 54），P<0.05\]。另外，RAPA+DDP组移植瘤中VEGF mRNA水平与RAPA组、DDP组相比明显降低\[(46.64±0.60） vs （62.20±0 62）、（61.64±1.21），P<0.05\]；RAPA+DDP组VEGF蛋白水平也下降\[(119.28±2 69） vs （150.31±4.77）、（153.84±3 39），P<0.05\]。免疫组化结果显示：RAPA+DDP组与RAPA组、DDP组相比，移植瘤中HIF-1α的AOD值降低\[(0.37±0 03） vs （0.57±0 06）、（0.55±0.06），P<0.05\]；RAPA+DDP组移植瘤中VEGF的AOD值也降低\[(0.48±0.03） vs （0.62±0.04）、（0.61±0.07），P<0.05\]。 结论： RAPA与DDP联合应用可抑制宫颈癌HeLa细胞裸鼠皮下移植瘤的生长，其机制可能与下调HIF-1α、VEGF的表达有关。

关键词：宫颈癌 雷帕霉素 顺铂 HeLa细胞 低氧诱导因子-1α 血管内皮生长因子

Inhibitory effect of rapamycin combined with cisplatin on growth of human cervical carcinoma HeLa cell subcutaneous xenografts in nude mice and the mechanisms

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Abstract:

Objective: To evaluate the effect of rapamycin (RAPA) and cisplatin (DDP) used alone or in combination on the growth of human cervical carcinoma HeLa cell subcutaneous xenografts in nude mice and the possible mechanisms. Methods: Nude mice were subcutaneously inoculated with HeLa cells to establish a subcutaneous transplantation tumor model of cervical cancer. Mice were randomly divided into a control group, RAPA group, DDP group, and RAPA+DDP group. The tumor weight and volume were observed during therapeutic process. The mRNA and protein expressions of hypoxia-inducible factor-1alpha (HIF-1α) and vascular endothelial growth factor (VEGF) were detected by RT-PCR, immunohistochemistry and Western blotting. Results: Compared with the RAPA group, the tumor weight (\[0.42±0.04\] vs \[0.53±0.03\]g, P<0.05) and the tumor volume (\[568.70±36.12\] vs \[797.81±111.98\] mm3, P<0.01) were significantly reduced in the RAPA+DDP group. Moreover, in comparison with the DDP group, the tumor weight (\[0.42±0.04\] vs \[0.52±0.04\]g, P<0.05) and the tumor volume (\[568.70±36.12\] vs \[766.16±132.27\]mm3, P<0.01) were significantly reduced in the RAPA+DDP group. RT-PCR and Western blotting results showed that the expression of HIF-1α mRNA in transplanted tumors was down-regulated in the RAPA+DDP group compared with the RAPA and DDP groups (\[31.215±0.706\] vs \[50.58±1.25\], \[48.63±1.56\], P<0.05), and the expression of HIF-1α protein was also down-regulated (\[38.07±0.09\] vs \[55.69±3.60\], \[59.50±1.54\], P<0.05). Moreover, the expression of VEGF mRNA in transplanted tumors was significantly decreased in the RAPA+DDP group compared with the RAPA and the DDP groups (\[46.64±0.60\] vs \[62.20±0.62\], \[61.64±1.21\], P<0.05), and decreased VEGF protein expression can be shown in the RAPA+DDP group (\[119.28±2.69\] vs \[150.31±4.77\], \[153.84±3.39\], P<0.05). Immunohistochemistry showed that the AOD value of HIF-1α in transplanted tumors was decreased in the RAPA+DDP group compared with the RAPA and the DDP groups (\[0.37±0.03\] vs \[0.57±0.06\], \[0.55±0 06\], P<0.05), and decreased AOD value of VEGF can also be shown in the RAPA+DDP group (\[0.48±0.03\] vs \[0.62±0.04\], \[0.61±0.07\], P<0.05). Conclusion: RAPA combined with DDP shows an inhibitory effect on growth of human cervical carcinoma HeLa cell subcutaneous xenografts. The possible underlying mechanism is related to the down-regulation of HIF-1α and VEGF expressions.

Keywords:cervical carcinoma rapamycin（RAPA） cisplatin (DDP) HeLa cell HIF-1α VEGF

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