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hSulf-1过表达提高乳腺癌MCF-7细胞对PARP抑制剂AZD2281的敏感性

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摘要：

探讨人硫酸酯酶-1（human sulfatase 1，hSulf-1）基因过表达是否提高乳腺癌MCF-7细胞对PARP抑制剂AZD2281的敏感性。方法：采用不同浓度AZD2281处理细胞，并筛选AZD2281处理的最佳浓度。将携hSulf-1基因的重组腺病毒Ad5-hSulf1感染MCF-7细胞，以Ad-hSulf1和AZD2281单独或联合处理MCF-7细胞，以Ad5-EGFP处理为对照。采用流式细胞术检测细胞周期，克隆形成实验检测细胞克隆形成率，Western blotting检测细胞周期蛋白依赖性激酶4（cyclin dependent kinase 4，CDK4）及磷酸化蛋白激酶B（phosphorylated protein kinase B，p-AKT）的表达，Transwell法、MTT法分别检测细胞的迁移及增殖。结果：AZD2281浓度为7 μmol/L时对MCF-7细胞的抑制作用趋于峰值，用于后续实验。Ad5-hSulf1+AZD2281联合处理与AZD2281单独处理相比，MCF-7细胞的G2/M期细胞比例明显增多[（22.15±0.17）% vs（17.44±0.57）%，P<0 01]，细胞克隆形成率[（21.43±1.52）% vs（49.43±1.44）%，P<0.01]及细胞周期蛋白CDK4的表达[（0.67±0.02）vs（0.72±0.02），P<0.05]、AKT的磷酸化水平[（0.17±0.003）vs（0.42±0.02），P<0.01]均明显降低，同时细胞的增殖率和迁移能力也有明显下降[（57.69±4.83）% vs（79.35±5.44）%；（10.33±1.53）个vs（50.67±2.31）个，均P<0.01]。结论：hSulf-1过表达可明显提高乳腺癌细胞MCF-7对AZD2281的化疗敏感性，阻滞细胞周期于G2/M期，并更明显地抑制乳腺癌细胞的增殖和迁移能力，这一效应可能是通过调节细胞周期蛋白CDK4及AKT通路产生的。

关键词：硫酸酯酶-1基因 乳腺癌 MCF-7细胞 周期蛋白 增殖 迁移 化疗敏感性

hSulf-1overexpression enhance the sensitivity of breast cancer MCF-7 cells to the PARP inhibitor AZD2281

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Abstract:

To investigate the possibility of enhance the sensitivity of breast cancer MCF-7 cells to the PARP inhibitor AZD2281 by up-regulate the expression of hSulf-1. Methods: MCF-7 cells were infected with Ad5-hSulf1 or Ad5-EGFP. Transfectants were treated with different concentrations of AZD2281 and the most optimal concentration was determined. In further experiments, both Ad5-hSulf-1-overexpressing MCF-7 cells and Ad5-EGFP-expressing control MCF-7 cells were treated with AZD2281 at the optimal concentration determined. After treatment for 24 h, cell cycle progression was assessed by flow cytometry (FCM), formation ability of MCF-7 cells by colony formation assay, protein levels of cyclin dependent kinase 4 (CDK4) and phosphorylated protein kinase B (p-AKT) Western blotting, cell migration by Transwell assay, and proliferative ability by MTT assay. Results: AZD2281 showed the peak inhibitory activity at a concentration of 7 μmol/L. When this concentration was used,Ad5-EGFP-expressing MCF-7 cells showed significant increased in the proportion of G2/M phase cells ([22.15±0.17]% vs [17.44±0.57]%, P<0.01), the colony formation ability ([21.43±1.52]% vs [49.43±1.44]%, P<0.01), levels of cell cycle protein CDK4 (0.67±0.02 vs 0.72±0 02, P<0.01) and p-AKT (0.17±0.003 vs 0.42±0.02, P<0.01), and the rateof migration ([57.69±4 83]% vs [79.35±5.44]%, P<0.01) and proliferation (10.33±1.53 vs 50.67±2.31, P<0.01), as compared with MCF-7 cells expression Ad5-hSulf-1. Conclusion: The overexpression of hSulf-1 may significantly increase the chemosensitivity of MCF-7 cells to AZD2281, induce ell cycle arrest at G2/M-phase and inhibit cell proliferation and migration capacities, possibly through regulation of CDK4 expression and AKT phosphorylation.

Keywords:human sulfatase-1 (hSulf-1) gene breast cancer MCF-7 cell cycle protein proliferation migration chemosensitivity

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