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5-氮杂-2′-脱氧胞苷抑制肾癌细胞增殖的机制研究

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Title: 5-aza-2′-deoxycytidine inhibits proliferation in renal carcinoma cells *via* suppressing methyltransferases and enhancing P21

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关键词: 5-氮杂-2′-脱氧胞苷; 肾细胞癌; 细胞增殖; 细胞信号抑制因子3; P21

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摘要: 目的 探讨5-氮杂-2′-脱氧胞苷（5-Aza-CdR）抑制肾癌细胞增殖的分子机制。方法 采用不同浓度的5-Aza-CdR作用于769-P和ACHN 2种肾癌细胞，处理72 h后CCK-8法检测其对细胞增殖的影响；5-Aza-CdR处理769-P细胞48 h后，流式细胞仪测定细胞周期分布，RT-PCR测定甲基化转移酶DNMT1、DNMT3a、DNMT3b以及细胞信号抑制因子3(suppressor of cytokine signaling 3，SOCS3)的表达，Western blot测定SOCS3、P21在蛋白质水平的表达；siRNA干扰SOCS3表达以后，加5-Aza-CdR处理769-P细胞48 h，Western blot检测细胞内SOCS3、P21的表达。 结果 5-Aza-CdR可以剂量性依赖地抑制肾癌细胞系769-P和ACHN的增殖（$P<0.05$），且使769-P细胞阻滞在G_2/M期。RT-PCR检测发现，5-Aza-CdR可以下调DNMT1和DNMT3a的表达和上调SOCS3的表达（$P<0.05$）。Western blot检测发现5-Aza-CdR可以促进SOCS3蛋白质的表达，并且伴随着P21蛋白的升高。在干扰SOCS3的表达后，用5-Aza-CdR处理769-P细胞48 h，P21的表达明显降低。 结论 5-Aza-CdR通过抑制甲基化转移酶，增强SOCS3介导P21的表达，从而抑制肾癌细胞769-P增殖。

Abstract: Objective To investigate the underlying molecular mechanism of 5-aza-2′-deoxycytidine (5-Aza-CdR) in inhibition of renal carcinoma cell proliferation. Methods Cell proliferation was assessed by CCK-8 assay after the renal carcinoma cell lines 769-P and ACHN were treated with 5-Aza-CdR at different

concentrations for 72 h. Flow cytometry was used to detect cell cycle in 769-P cells after treatment of 5-Aza-CdR at different concentrations for 48 h. RT-PCR was used to detect the expression of methyltransferases DNMT1/3a/3b and suppressor of cytokine signaling 3 (SOCS3). The expression of P21 and SOCS3 at protein level was detected by Western blot analysis, and detected again in the 769-P cells with SOCS3 knockdown by small interfering RNA (siRNA) after 48 hours' treatment of 5-Aza-CdR at different concentrations. Results CCK-8 assay revealed that 5-Aza-CdR remarkably inhibited the proliferation in the 2 cell lines in a dose-dependent manner (P<0.05). 5-Aza-CdR treatment also resulted in the 769-P cells arrested at G_2/M phase. RT-PCR showed 5-Aza-CdR down-regulated DNMT1 and DNMT3a but up-regulated SOCS3 (P<0.05). Western blotting found that 5-Aza-CdR enhanced the expression of SOCS3 and P21. After knocking down the expression of SOCS3 of 769-P cells, we treated 769-P cells with 5-Aza-CdR for 48 h and found that the up-regulation of P21 was weakened compared with control group. Conclusion 5-Aza-CdR suppresses DNA methyltransferases, and enhances the expression of P21 mediated by SOCS3, and then inhibits the proliferation in renal carcinoma 769-P cells.

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