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雷帕霉素聚乳酸-聚乙醇酸共聚物纳米粒子对人脐动脉平滑肌细胞细胞周期时相、p27蛋白表达及细胞增殖的影响

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Effects of Rapamycin-loaded Poly(lactic-co-glycolic) Acid Nanoparticles on Distribution of Cell Cycle, Expression of p27 Protein, and Proliferation of Human Umbilical Arterial Vascular Smooth Muscle Cell in vitro

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摘要 摘要：目的 评估本实验室自制包载雷帕霉素（RPM）的聚乳酸-聚乙醇酸共聚物（PLGA）纳米粒子（NPs）对离体培养的人脐动脉平滑肌细胞（HUASMC)细胞周期时相、p27蛋白表达和细胞增殖的影响。方法 按不同浓度RPM-PLGA NPs设定药物作用组，并设立RPM组、PLGA组和M231培养基及平滑肌细胞生长添加剂（M231-SMGs）组作为对照。采用细胞免疫组织化学染色比较不同处理组HUASMC p27蛋白表达阳性率和表达水平的差异，流式细胞技术评价各处理组对HUASMC细胞周期时相的影响，噻唑蓝（MTT）比色法观察不同浓度RPM和RPM-PLGA NPs对HUASMC存活率的影响。结果 10μg/L及以上浓度的RPM和50μg/L及以上浓度的RPM-PLGA NPs可明显抑制HUASMC生长，并呈浓度依赖性。细胞计数绘制生长一时间曲线显示，100μg/L RPM和500μg/L RPM-PLGA NPs作用于HUASMC 24h后细胞计数值明显低于M231-SMGs对照组；单纯PLGA NPs对细胞生长无明显影响；与PLGA组和M231-SMGs培养基对照组相比，RPM组和RPM-PLGA NPs组G0/G1期细胞比例明显增多，S期及G2/M期细胞比例明显减少（P均<0.01），但两组间细胞周期时相比例差异无统计学意义（P>0.05）。细胞免疫组织化学染色结果显示，100μg/L RPM 和500μg/L RPM-PLGA NPs组的HUASMC p27蛋白表达阳性率和表达水平与对照组相比差异无统计学意义（P>0.05），但均较PLGA组和M231-SMGs培养基组明显增加（P <0.01）。结论 RPM-PLGA NPs抑制体外培养的HUASMC 生长效果与RPM相似，并可显著抑制体外培养HUASMC p27蛋白表达，阻抑其细胞周期进程于G1/S 期而抑制其细胞增殖。

关键词： 雷帕霉素 聚乳酸-聚乙醇酸共聚物 纳米粒子 人脐动脉平滑肌细胞 细胞周期 细胞增殖 p27蛋白

Abstract： ABSTRACT:Objective To evaluate the effects of rapamycin(RPM)-loaded poly(lactic-co- glycolic) acid (PLGA) nanoparticles (NPs) on the proliferation, distribution of cell cycle, and expression of p27 protein in human umbilical arterial vascular smooth muscle cell (HUASMC) in vitro. Methods The primarily culture model of HUASMC was successfully established by explant-attached method in vitro. The cells were administrated with different doses of RPM, and RPM-PLGA NPs were observed as treat groups compared with PLGA NPs and M231-SMGs medium cultured group. The effect of RPM-PLGA NPs on proliferation of HUASMC was assessed using 3-(4,5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide（MTT） colorimetry method. The influences of RPM-PLGA NPs on the cell cycle and cellular growth kinetics of HUASMCs were tested by flow cytometry. The effect of RPM-PLGA NPs on the expression of p27 protein of HUASMCs was assessed through an immunohistochemical method. Results Compared with the control group, the proliferation of HUASMCs was inhibited by 50μg/L and higher concentration of RPM-PLGA NPs in a dose-dependent manner (P<0.05). The numbers of cells entering cell cycle of S/G2/M phases were significantly lower in RPM-PLGA NPs and RPM treated groups. Histologically, the expression of p27 were up-regulated in 500μg/L RPM-PLGA NPs and 100μg/L RPM treated group (all P<0.01) when compared with the control group. Conclusions RPM-PLGA NPs has a similar effects as RPM in inhibiting the growth of in vitro cultured HUASMC. It can remarkably suppress the expression of in vitro cultured HUASMC p27 protein, arrest its cell cycle at G1/S phase, and inhibit its proliferation.

Keywords： rapamycin poly(lactic-co-clycolic) acid nanoparticles duman umbilical arterial vascular smootd

muscle cell cell cycle proliferation

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