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论著

丙氨酰-谷氨酰胺下调口服他克莫司损伤的肠黏膜组织中iNOS和TNF-α的表达

万云乐[1]；吴丽花[2]；余松峰[2]；金晶[2]；柯庆宏[2]；郑树森[2]

1 中山大学第二附属医院肝胆外科，器官移植中心， 广东 广州 510120； 2 浙江大学医学院附属第一医院外科研究所，多器官联合移植重点实验室， 浙江 杭州 310003

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摘要 目的： 研究丙氨酰-谷氨酰胺(Ala-Gln)对口服FK506损伤的肠黏膜组织中iNOS和TNF-α分子表达的影响。 方法： BALB/c小鼠24只，随机分成对照组、FK506低剂量组、FK506高剂量组及Ala-Gln治疗组，分别给以0.2 mL生理盐水、FK506 0.1 mg/kg、1.0 mg/kg灌胃和FK506 1.0 mg/kg灌胃及丙氨酰-谷氨酰胺0.5 g/kg腹腔注射。隔天给药，6周后采集回肠标本。HE染色和扫描电镜观察肠黏膜组织形态学改变；FITC-dextran(FD4)检测肠黏膜通透性；RT-PCR检测小肠黏膜iNOS和TNF-α mRNA的表达情况；Western blotting检测iNOS和TNF-α蛋白表达水平。结果： FK506高剂量组的肠黏膜对FD4的通透性明显增加，扫描电镜示小肠绒毛破坏明显，而Ala-Gln治疗组小肠绒毛破坏减轻，对FD4的通透性下降；FK506高剂量组小肠黏膜iNOS mRNA和TNF-α mRNA表达增强，而Ala-Gln治疗组表达则明显下调；iNOS和TNF-α蛋白表达水平的变化与此一致。结论： FK506通过上调iNOS和TNF-α的表达对小肠黏膜产生损伤，使小肠壁的通透性增加。Ala-Gln对FK506所致的肠黏膜屏障功能损伤具有保护作用，该作用可能与下调iNOS和TNF-α的表达有关。

关键词 他克莫司； 肠黏膜； 丙氨酰-谷氨酰胺； 一氧化氮合酶； 肿瘤坏死因子

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Alanyl-glutamine down-regulates iNOS and TNF-α expression in injured intestinal mucosa induced by oral FK506

WAN Yun-le[1], WU Li-hua[2△], YU Song-feng[2], JIN Jing[2], KE Qing-hong[2], ZHENG Shu-sen[2△]

1 Centre of Organ Transplantation, Department of Hepatobiliary and Pancreatic Surgery, 2nd Affiliated Hospital, Sun Yat-sen University, Guangzhou 510120, China; 2 Key Lab of Multi-organ Combined Transplantation, Ministry of Public Health, Institute of Surgery, 1st Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China. E-mail: wanyldr@163.com

Abstract

<FONT face=Verdana>AIM: To investigate the effects of alanyl-glutamine (Ala-Gln) on expression of iNOS and TNF-α in injured intestinal mucosa induced by oral tacrolimus(FK506).
METHODS: Twenty-four BALB/c mice were randomized to receive orally 0.2 mL of normal saline solution (groupⅠ), 0.2 mL of FK506 in a dose of 0.1 mg/kg (groupⅡ) or 1.0 mg/kg (groupⅢ), and orally high-dose FK506 (0.2 mL, 1.0 mg/kg) plus intraperitoneal injection of Ala-Gln (0.5 g/kg)(groupⅣ),respectively. Damages of intestinal mucosa were determined by pathological examination. Intestinal mucosal permeability was analysed by FITC-dextran fluorescence assay. Expression of iNOS and TNF-α in intestine was detected by RT-PCR and Western blotting.
RESULTS: Severe damage on the villi and increased intestinal permeability were observed in high-dose FK506 treated mice according to scanning electron microscopy and FITC-dextran flux respectively. The erosion and increased intestinal permeability were significantly alleviated by Ala-Gln treatment. Transcription of iNOS mRNA and TNF-α mRNA, which was up-regulated in high-dose FK506 treated group, was also markedly down-regulated in mice combined with Ala-Gln-treatment. A significantly increased expression of iNOS and TNF-α protein was found in the high-dose FK506 treated mice, while small amounts of these proteins were identified in the Ala-Gln-treated group.
CONCLUSION: FK506 could induce a significant impairment of intestinal mucosa morphologically, which might be associated with up-regulated expression of iNOS and TNF-α in small intestinal

mucosa. Subsequently, the intestinal permeability is increased. Ala-Gln has a strong protective effect on FK506-induced intestinal barrier dysfunction, probably relates to the down-regulation of iNOS and TNF-α expression.</FONT>

Key words Tacrolimus Intestinal mucosa Alanyl-glutamine Nitric-oxide synthase Tumor necrosis factor

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通讯作者 万云乐 wanyldr@163.com