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IL-12诱导肝癌微环境中NK细胞活化发挥抗肿瘤作用 点此下载全文

周智锋 江金华 李洁羽 陈强 叶韵斌

福建省肿瘤转化医学重点实验室，福建 福州 3500014； 福建医科大学 福建省肿瘤医院 肿瘤免疫学研究室，福建 福州 3500014;岩市第二医院 肿瘤内科，福建 龙岩 364000;福建省肿瘤转化医学重点实验室，福建 福州 3500014； 福建医科大学 福建省肿瘤医院 肿瘤免疫学研究室，福建 福州 3500014;福建省肿瘤转化医学重点实验室，福建 福州 3500014；福建医科大学 附属协和医院 肿瘤内科，福建 福州 3500014;福建省肿瘤转化医学重点实验室，福建 福州 3500014；福建医科大学 福建省肿瘤医院 肿瘤免疫学研究室，福建 福州 3500014

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摘要：

目的： 探讨IL-12通过诱导肝癌微环境中NK细胞活化诱导抗肿瘤的效果。 方法： NOD/SCID小鼠皮下注射肝癌HepG2细胞，成瘤后腹腔注射人外周血淋巴细胞（peripheral blood lymphocyte， PBL），建立HCC-huPBL荷瘤小鼠模型。将荷瘤小鼠随机分为IL-12组和PBS对照组，瘤内注射IL-12后，观测荷瘤小鼠瘤体积、体重、一般状况的变化，IL-12瘤内注射后第30天ELISA法检测荷瘤小鼠肝癌组织微环境中IL-12、INF-γ含量以及小鼠外周血中天门冬氨酸氨基转移酶（aspartate aminotransferase，AST）及谷丙转氨酶（alanine aminotransferase，ALT）的含量，免疫组化法检测IL-12治疗后肝癌微环境中NK细胞活化性受体NKG2D、NKp44、NKp30、NKp46，以及抑制性受体KIR2DL3/CD158b、NKG2A/CD159a的表达。 结果： 第12、18、24、30天 IL-12组荷瘤小鼠瘤体积均小于PBS组\[（594.47±205.51） vs （832.10±187.49） mm3，（963.61±427.95） vs （1 350.87±468.23）mm3，（1 285.02±368.56） vs （1 975.49±655.54）mm3，（1 903.64±471.34） vs （2 568.77±784.68）mm3，均P<0 05\]。 IL-12组小鼠肝癌组织中IL-12与INF-γ的表达水平均明显高于PBS组\[（2.96±1.02） vs （1.35±0.75） pg/ml，（12.26±4.11） vs （7.81±3.46） pg/ml，均P<0.05\]。IL-12组与PBS组相比，血清ALT水平第7天显著升高\[（73.85±10 71） vs （41.73±13 13）U/L；P<0.05\]，第14天达到高峰。IL-12组治疗后肝癌组织中NK细胞活化性受体NKG2D、NKp44、NKp30的表达较PBS组高（P<0.05），NKp46的表达未见明显升高；而NK细胞抑制性受体CD158b和CD159a表达较PBS组低（P<0.05）。 结论： 肝癌模型小鼠瘤体内IL-12注射可上调瘤组织内NK细胞活化性受体、IL-12、IFN-γ的表达，下调抑制性受体的表达，从而抑制小鼠模型中肿瘤的生长。

关键词：NK细胞 活化性受体 抑制性受体 IL-12 IFN-γ 移植性肝癌

IL-12 plays anti-tumor effect by inducing NK cell activation in hepatic carcinoma microenvironment Download Fulltext

Zhou Zhifeng Jiang Jinhua Li Jieyu Chen Qiang Ye Yunbin

Key Laboratory of Tumor Translational Medicine in Fujian Province, Fuzhou 350014, Fujian, China;Laboratory of Tumor Immunology, Fujian Provincial Tumor Hospital, Fujian Medical University, Fuzhou 350014, Fujian, China;Department of Medical Oncology, Second Hospital of Longyan City, Longyan 364000, Fujian, China;Key Laboratory of Tumor Translational Medicine in Fujian Province, Fuzhou 350014, Fujian, China;Laboratory of Tumor Immunology, Fujian Provincial Tumor Hospital, Fujian Medical University, Fuzhou 350014, Fujian, China;Key Laboratory of Tumor Translational Medicine in Fujian Province, Fuzhou 350014, Fujian, China;Department of Medical Oncology, Union Hospital Affiliated to Fujian Medical University, Fuzhou 350014, Fujian, China;Key Laboratory of Tumor Translational Medicine in Fujian Province, Fuzhou 350014, Fujian, China;Laboratory of Tumor Immunology, Fujian Provincial Tumor Hospital, Fujian Medical University, Fuzhou 350014, Fujian, China

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Abstract:

Objective:To explore the enhanced anti-tumor effect of IL-12 through inducing NK cell activition in hepatic carcinoma microenviroment. Methods: The hepatic cacinoma HepG2 cells were subcutaneously injected into NOD/SCID mice, and human peripheral blood lymphocytes (PBL) were introperitoneally injected after tumor formation to establish HCC-huPBL tumor-bearing mouse model. The tumor-bearing mice were randomized into IL-12 group and PBS control group. Mice were intratumoral injected with IL-12, and the changes of tumor volume and body weight as well as general conditions of tumor-bearing mice were observed. ELISA assay was performed to examine the expression levels of IL-12 and INF-γ in the microenvironment of hepatic carcinoma tissues in tumor-bearing mice, and the aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in peripheral blood of mice 30 days after IL-12 intratumoral injection. Immunohistochemistry assay was used to analyze the expressions of NK-activating receptors: NKG2D, NKp44, NKp30, NKp46, and inhibitory NK receptors: KIR2DL3/CD158b and NKG2A/CD159a in hepatic carcinoma microenvironment after IL-12 treatment. Results: On day 12, 18, 24 and 30, the tumor volumes were smaller in the IL-12 group than those in the PBS group (\[594.47±205.51\] vs \[832.10±187.49\] mm3, \[963.61±427.95\] vs \[1 350 87±468.23\] mm3, \[1 285.02±368.56\] vs \[1 975.49±655.54\] mm3, \[1 903.64±471.34\] vs \[2 568.77±784.68\] mm3, P<0.05). The expression levels of IL-12 and IFN-γ in the IL-12 group were significantly higher than those in the PBS group (\[2.96±1.02\] vs \[1.35±0.75\] pg/ml, \[12.26±4.11\] vs \[7.81±3.46\] pg/ml, P<0 05). The serum ALT level significantly increased in the IL-12 group compared to the PBS group on day 7 (\[73 85±10.71\] vs \[41.73±13.13\] U/L, P<0.05), and reached a peak at day 14. The expressions of NK-activating receptors NKG2D, NKp44 and NKp30 were statistically higher in the IL-12 group than those in the PBS group (P<0 05), the expression level of NKp46 showed no significant up-regulation, while the expression levels of NK inhibitory receptors CD158b and CD159a were decreased compared to the PBS group (P<0.05). Conclusion: IL-12 intratumoral injection can up-regulate the expressions of NK-activating receptors, IL-12 and IFN-γ, and down-regulate the NK inhibitory receptors in the hepatic carcinoma mouse model, therefore effectively inhibiting the tumor growth in mouse model.

Keywords:NK cell activatory receptor inhibitory receptor IL-12 IFN-γ transplanted hepatic carcinoma

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