

论著

减毒鼠伤寒沙门氏菌作为肿瘤基因治疗载体的低毒性和靶向性研究

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摘要

目的 研究基因工程减毒的沙门氏菌VNP20009的低毒性和对于肿瘤细胞的靶向性。方法 将野生型沙门氏菌(对照组)和VNP20009(研究组)分别通过尾静脉注射感染正常小鼠, 观察其生存期差别; 将绿色荧光蛋白(GFP)标记VNP20009, 红色荧光蛋白(Red Fluorescent Protein, RFP)和GFP分别标记小鼠前胃癌细胞(MFC)的胞质和胞核, 尾静脉注射感染离体肿瘤细胞和荷瘤小鼠, 以双色荧光成像的定性方法和组织匀浆细菌培养的定量方法显示细菌在离体肿瘤细胞、在体肿瘤和正常组织中的生长情况。结果 接受野生型沙门氏菌注射的对照组小鼠在注射后4d全部死亡, 而接受VNP20009注射的研究组小鼠在注射后10d依然全部存活; VNP20009能在离体肿瘤细胞中持续增殖并引起核碎裂; 在体实验中, 感染后第6天, 正常组织中的细菌明显减少, 到第15天时几乎消失, 但在肿瘤组织中依然持续增殖。细菌在肿瘤/正常组织(肝脏)中的比例在感染后第4天约为224: 1, 第6天为1020: 1。结论 基因工程减毒的沙门氏菌VNP20009有着良好的低毒性以及肿瘤靶向性, 具有作为肿瘤基因治疗载体的潜力。

关键词 [沙门氏菌](#); [肿瘤](#); [细菌载体](#); [肿瘤靶向性](#)

分类号

Study of hypotoxicity and tumor-targeting ability of attenuated Salmonella as a vector for cancer gene therapy

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Abstract

Objective Study the hypotoxicity and tumor-targeting ability of genetically modified attenuated *S. typhimurium* VNP20009. Methods Non-tumor-bearing mice were infected intravenously with VNP20009 (case) or wild-type (control). Survival rate was observed; GFP-labeled VNP20009 and MFC murine gastric cancer cell lines labeled with RFP in the cytoplasm and GFP in the nucleus were established. The dual-color MFC cell lines in vitro and tumor-bearing (RFP-labeled MFC gastric cancer cell lines) mice were infected with GFP-labeled VNP20009. Growths of bacteria in vitro were observed under fluorescence microscopy. Growth of bacteria in vivo were observed under fluorescence microscopy to determine the extent of infection and cfu of normal tissues and tumors were determined by harvesting these tissues and homogenizing and planting supernatants on nutrient media. Results All mice infected with wild-type *S. typhimurium* expired by 4 days. In contrast, all mice infected with VNP20009 survived. The GFP-expressing VNP20009 grew in the cytoplasm of GFP-RFP-labeled MFC cells and caused nuclear destruction. In in vivo experiments, the number of bacteria had markedly regressed in the normal tissue. By day 15, GFP-labeled bacteria could no longer be seen. In contrast, the bacteria grew continuously in the MFC tumor. The tumor/liver bacteria ratios were 224:1 by day 4 and 1020:1 by day 6 after infection. Conclusions The genetically modified attenuated *S. typhimurium* VNP20009 has the very ability of tumor-targeting and hypotoxicity, which has great potential as a vector for cancer gene therapy.

Key words [Salmonella](#) [tumor](#) [bacteria vector](#) [tumor-targeting](#)

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