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负载HER-2/neu多肽的树突状细胞激发特异性CTL反应 点此下载全文

孟东 时伟锋 孙春雷 时宏珍 史央 朱晨瑶 唐金海

苏州大学 附属第四医院 乳腺外科，江苏 无锡，214035;苏州大学 附属第四医院 乳腺外科，江苏 无锡，214035;苏州大学 附属第四医院 乳腺外科，江苏 无锡，214035;南京市免疫细胞工程技术研究中心，南京得康生物技术有限公司，江苏 南京，210019;南京市免疫细胞工程技术研究中心，南京得康生物技术有限公司，江苏 南京，210019;南京市免疫细胞工程技术研究中心，南京得康生物技术有限公司，江苏 南京，210019;江苏省肿瘤医院 普通外科，江苏 南京，210000

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摘要：

目的:探讨以HER-2/neu为靶抗原、树突状细胞（dendritic cell，DC）为抗原载体激发特异性细胞毒性T淋巴细胞（cytotoxic T lymphocytes，CTL）反应的能力及研制治疗型乳腺癌疫苗的可行性。 方法： 采集17例HLA-A201 +HER-2/neu +乳腺癌患者外周血，分离单个核细胞与外周血淋巴细胞(peripheral blood lymphocyte，PBL)，并诱导为成熟DC（mature dendritic cell，mDC）；人工合成HER-2/neu多肽\[E75(KIFGSLAFL)和GP2(IISAVVGIL) 2条\]负载mDC后体外反复致敏PBL（3次，每周1次），检测其激发HER-2/neu特异性CTL的能力与CTL的杀伤活性。同时于患者腹股沟淋巴结富集区皮内注射负载HER-2/neu多肽的DC，每周1次，共接种4次，检测接种前后患者外周血细胞因子和特异性的CTL 水平变化，并进行DTH试验。 结果： 患者外周PBL经过负载HER-2/neu多肽DC共3轮致敏后，HER-2/neu多肽特异的CTL平均比例比对照组（未负载HER-2/neu多肽DC组）明显增高\[（5.41±1.44）% vs （0.41±0.12）%，P< 0.05\]；致敏后PBL对负载HER-2/neu多肽T2靶细胞的杀伤率明显高于对照组（未负载DC诱导的CTL）\[效靶比为30∶1时，（35.5±4.7）% vs （ 11.2± 1.4）%， P< 0.05\]。接种负载HER-2/neu多肽的DC后，患者体内血清中细胞因子IL-2、IL-12、IFN-γ水平较治疗前显著升高\[（ 409.09± 89.39）vs （148.79±28.32）ng/ml，（56.23±14.08）vs（24.49±56.23）ng/ml，（146.57±25.97）vs （ 67.77± 39 35）ng/ml；均P<0.05\]，TNF-α和IL-10水平较治疗前变化不大（P>0.05）。患者DTH试验阳性率为47%（8/17），DTH阳性患者外周血中特异性CTL比例明显上升。 结论： 负载HER-2/neu多肽的DC体内、外均具有激发特异性CTL反应能力，可诱导Th1型细胞因子的分泌，未发生临床不良反应。

关键词：树突状细胞 乳腺癌 HER-2/neu多肽 细胞毒性T淋巴细胞 免疫治疗

Specific CTL response induced by dendritic cells pulsed with HER-2/neu peptide Download Fulltext

MENG Dong SHI Wei-feng SUN Chun-lei SHI Hong-zhen SHI Yang ZHU Chen-yao TANG Jin-hai

Department of Breast Surgery, Fourth Affiliated Hospital of Soochow University, Wuxi 214035, Jiangsu, China;Department of Breast Surgery, Fourth Affiliated Hospital of Soochow University, Wuxi 214035, Jiangsu, China;Department of Breast Surgery, Fourth Affiliated Hospital of Soochow University, Wuxi 214035, Jiangsu, China;Nanjing Immune Cell Engineering Technology Research Center, Nanjing Decon Bio-Technology Co., LTD, Nanjing 210019, Jiangsu, China;Nanjing Immune Cell Engineering Technology Research Center, Nanjing Decon Bio-Technology Co., LTD, Nanjing 210019, Jiangsu, China;Nanjing Immune Cell Engineering Technology Research Center, Nanjing Decon Bio-Technology Co., LTD, Nanjing 210019, Jiangsu, China;Department of General Surgery, Jiangsu Cancer Hospital, Nanjing 210009, Jiangsu, China

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Abstract:

Objective：To explore the potential of autologous dendritic cells (DCs) pulsed with HER-2/neu peptide in inducing specific cytotoxic T lymphocyte (CTL) response and feasibility of breast cancer vaccines. Methods: Seventeen breast cancer patients with positive HLA-A201 and HER-2/neu were enrolled and their peripheral blood mononuclear cells and lymphocytes were isolated and induced into DCs and pulsed with HER-2/neu peptide. The killing effect of CTLs against T2 cell line pulsed with HLA-A201-binding peptide HER-2/neu was determined. The patients were inoculated subcutaneously near the inguinal region with auto-DCs pulsed with HER-2/neu peptide for 4 times every week. The immunological responses and clinical responses were examined in 1 week after the final vaccination. Results: The average percentage of special CTLs primed by DCs pulsed with HER-2/neu peptide was significantly higher than that in the control group (CTLs primed by DCs unloaded with HER-2/neu peptide) （\[5.41±1.44\]% vs \[0.41±0.12\]%, P<0.05). CTLs induced by DCs exerted a stronger killing effect on T2 cell line pulsed with HER-2/neu peptide than that in control group （\[35.5±4.7\]% vs \[11.2±1.4\]% at the ratio of E \[effect\] to T \[target\] as 30∶1，P<0.05). Vaccination of DCs was well tolerated and no toxicity was observed. The cytokine levels in sera such as IL-2, IL-12 and IFN-γ were increased after vaccinations （\[148.79±28.32\] ng/ml vs \[409.09±89.39\] ng/ml,\[24.49±56.23\] ng/ml vs \[56.23±14.08\] ng/ml, \[67.77±39.35\] ng/ml vs \[146.57±25.97\] ng/ml, respectively, all P<0.05). The cytokine levels in sera such as TNF-α and IL-10 had no significant changes before and after vaccination. The results of DTH test were positive in 8 patients (8/17), and the percentages of antigen-specific IFN-γ + CD8 +T increased in 8 patients (8/17). Conclusion: Auto-DC vaccines pulsed with HER-2/neu peptide can elicit specific immune responses ex vivo and in vivo, and induce secretion of Th1 type cytokines from DCs and have no adverse reaction.

Keywords:dendritic cell breast cancer HER-2/neu peptide cytotoxic T lymphocyte immunotherapy

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