



粉尘螨壳聚糖纳米疫苗舌下含服对哮喘小鼠的治疗作用

喻海琼^{1, 2*}, 刘志刚², 国华², 周一平¹
¹ 深圳市福田区人民医院, 深圳 518033; ² 深圳大学医学院过敏反应与免疫学研究所, 深圳 518060

Therapeutic Effect on Murine Asthma with Sublingual Use of *Dermatophagoides farinae*/Chitosan Nanoparticle Vaccine

YU Hai-Qiong-1, 2*, LIU Zhi-Gang-2, GUO Hua-2, ZHOU Yi-Beng-1

¹ Shenzhen Futian People's Hospital, Shenzhen 518033, China; ² Allergy and Immunology Institute, School of Medicine, Shenzhen University, Shenzhen 518060, China

摘要

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摘要 目的 制备粉尘螨 (*Dermatophagoides farinae*) 壳聚糖纳米疫苗, 并观察其免疫治疗哮喘小鼠的效果。方法 采用离子凝胶法制备粉尘螨壳聚糖纳米疫苗。30只BALB/c小鼠随机均分为5组, 阴性对照组(A组)用生理盐水处理, 其余组用50 μg粉尘螨粗提液+2 mg氢氧化铝腹腔注射致敏, 第28天开始分别用PBS(B组, 模型组)、空白壳聚糖(C组)、粉尘螨变应原(Der f)组(D组, 1 mg/次)和粉尘螨壳聚糖纳米疫苗(DCN)(E组, 负荷1 mg Der f的DCN/次)舌下含服免疫18次, 每次间隔1 d, 末次免疫后1周用50 μg粉尘螨变应原滴鼻激发, 每天1次, 连续7次。末次激发后24 h检测小鼠的气道高反应性; 末次激发后48 h处死小鼠, 取血, 行肺泡灌洗, 无菌摘取肺组织和脾脏; 计数小鼠肺泡灌洗液(BALF)中细胞总数和嗜酸粒细胞数, 观察BALF和脾细胞上清中IL-4、IL-10和IFN-γ细胞因子水平, 血清中IgE、IgA和IgG2a抗体水平; 运用HE染色观察肺部炎症细胞的浸润程度, 运用MTT法检测脾细胞的淋巴细胞增殖反应, 计算刺激指数(SI)。结果 与B组相比, D、E组气道高反应性和肺部病理改变减轻。D组(36.50×10⁴/ml, 3.72×10⁴/ml)和E组(34.25×10⁴/ml, 2.25×10⁴/ml)的BALF中细胞总数、嗜酸粒细胞数显著少于B组(61.67×10⁴/ml, 14.17×10⁴/ml)(P<0.05)。与B组(IgE: 0.39, IgA: 0.79)相比, D组和E组血清中抗原特异性IgE抗体水平(D: 0.22, E: 0.22)显著降低, 而IgA抗体水平(D: 0.88, E: 1.03)显著升高。D组和E组的BALF中IL-4水平(D: 28.49 pg/ml, E: 20.93 pg/ml)和脾细胞分泌的IL-4(D: 27.82 pg/ml, E: 20.80 pg/ml)水平均显著低于B组(56.33 pg/ml, 45.84 pg/ml)(P<0.05)。而BALF中的IFN-γ(D: 18.80 pg/ml, E: 37.32 pg/ml)、IL-10(D: 118.90 pg/ml, E: 129.15 pg/ml)水平显著高于B组(13.60 pg/ml, 29.61 pg/ml)(P<0.05); 脾细胞分泌的IFN-γ(D: 20.68 pg/ml, E: 42.42 pg/ml)、IL-10(D: 36.31 pg/ml, E: 161.37 pg/ml)水平亦显著高于B组(13.50 pg/ml, 22.52 pg/ml)(P<0.05)。与B组(SI: 0.23)相比, D组(SI: 0.14)和E组(SI: 0.13)的淋巴细胞增殖反应明显抑制。而C组(SI: 0.22)对致敏小鼠无明显疗效。结论 粉尘螨壳聚糖纳米疫苗对致敏小鼠具有免疫治疗作用。

关键词: 粉尘螨 壳聚糖 纳米颗粒 舌下含服疫苗 免疫治疗

Abstract: Objective To prepare *Dermatophagoides farinae* (Der f) /chitosan nanoparticle vaccine (DCN), and to investigate the effect of sublingual administration with DCN in asthma mice model. Methods DCN were prepared by ionotropic gelation. 30 BALB/c mice were randomly divided into 5 groups: normal control group (A), PBS control group (B), Chitosan group (C), Der f group (D), DCN group (E). Group A were treated with normal saline (100 μl) all the time. Mice in other groups were sensitized intraperitoneally with 50 μg dust mite extracts plus 2 mg Al (OH) 3, and on day 28 given a sublingual vaccination of PBS (group B), or empty CS nanoparticles (group C), or Der f (group D, 1 mg Der f) or DCN (group E, loaded with 1 mg Der f). All the mice received 18 doses at 1-day intervals. One week after the last immunization, mice in group B, C, D, and E were intranasally challenged with 50 μg Der f extract daily for seven days. Twenty-four hours after the last challenge, airway hyper-responsiveness (AHR) was assessed by using whole-body plethymography. Two days post challenge, mice were sacrificed and bronchoalveolar lavage fluid (BALF) was collected. Number of the total cells and eosinophils was determined. Level of cytokines in the supernatant of splenocyte culture was assayed by ELISA. Level of Der f specific IgE, IgG2a and IgA in the sera was determined by ELISA. Airway inflammation was analyzed by HE staining. Spleen lymphocyte proliferation responses were analyzed by MTT colorimetry. Results Compared with group B, AHR and the lung inflammation in groups D and E were greatly reduced. Numbers of total cells and eosinophils in BALF of groups D (36.50×10⁴/ml, 3.72×10⁴/ml) and E (34.25×10⁴/ml, 2.25×10⁴/ml) were significantly lower than that of group B (61.67×10⁴/ml, 14.17×10⁴/ml) (P<0.05). The level of specific IgE was significantly lower in groups D (0.22) and E (0.22), and that of IgA in groups D (0.88) and E (1.03) was significantly higher than that in group B (0.79). The level of IL-4 in BALF (D: 28.49 pg/ml, E: 20.93 pg/ml) and cultured splenocytes (D: 27.82 pg/ml, E: 20.80 pg/ml) of groups D and E was significantly lower than that of group B (56.33 pg/ml, 45.84 pg/ml) (P<0.05). While IFN-γ (D: 18.80 pg/ml, E: 37.32 pg/ml) and IL-10 (D: 118.90 pg/ml, E: 129.15 pg/ml) in BALF in groups D and E were significantly higher than that of group B (13.60 pg/ml, 29.61 pg/ml) (P<0.05), and same with IFN-γ (D: 20.68 pg/ml, E: 42.42 pg/ml) and IL-10 (D: 36.31

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pg/ml, E: 161.37 pg/ml) in spleen cultured supernatants of groups D and E ($P<0.05$). The allergen-specific splenocyte proliferation was inhibited in groups D (SI: 0.14) and E (SI: 0.13), and there was no significant difference between group C (SI: 0.22) and group B (SI: 0.23). Conclusion *Dermatophagoides farinae* (Derf) /chitosan nanoparticle vaccine has therapeutic effect on murine asthma.

Keywords: *Dermatophagoides farinae* Chitosan Nanoparticle Sublingual vaccine Immunotherapy

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