

黄芪对弓形虫 *wx2b2a* 表位疫苗免疫小鼠后抗急性弓形虫感染的免疫调节作用

谢荣华¹, 舒衡平²

摘要: 目的 探讨黄芪对弓形虫 *wx2b2a* 表位疫苗免疫小鼠后抗急性弓形虫感染的免疫保护作用。方法 将小鼠随机分成 pcDNA3-W2b2a 组、pcDNA3-W2b2a + 黄芪治疗组、pcDNA3 + 黄芪治疗组、黄芪治疗组、pcDNA3 及生理盐水对照组。将弓形虫 pcDNA3-W2b2a 肌注免疫 pcDNA3-W2b2a 组、pcDNA3-W2b2a + 黄芪治疗组小鼠 3 次, 末次免疫后 4 周, 每组小鼠腹腔注射 10^2 个速殖子, 感染后 2 d 起, pcDNA3-W2b2a + 黄芪治疗组、pcDNA3 + 黄芪治疗组及黄芪治疗组小鼠给予黄芪 75 mg/d 灌胃治疗, 连续用药 7 d, 用 ELISA 法测定免疫前、末次免疫后 4 周、感染后 6 d 小鼠血清 IgG 水平及免疫前、末次免疫后 2 周、感染后 4、6、8 d 小鼠 IFN-γ、IL-18 水平, 并观察弓形虫感染后小鼠的生存时间。结果 pcDNA3-W2b2a 免疫小鼠后血清 IgG 抗体水平均高于其它组 ($P < 0.05$), 末次免疫后 4 周, 感染后第 6 d pcDNA3-W2b2a、pcDNA3-W2b2a + 黄芪治疗组小鼠特异性 IgG 抗体水平无显著性差异 ($P > 0.05$); 末次免疫后 2 周、感染后 4 d、6 d、8 d pcDNA3-W2b2a + 黄芪治疗组小鼠血清 IFN-γ 水平分别高于其它组 ($P < 0.05$); 感染后各组小鼠血清 IL-18 水平持续上升, 但感染后 8 d, 黄芪治疗后小鼠血清 IL-18 水平显著低于 pcDNA3 和生理盐水对照组 ($P < 0.05$); 小鼠 RH 株速殖子感染后, pcDNA3-W2b2a + 黄芪治疗组小鼠存活时间明显长于 pcDNA3-W2b2a 组、pcDNA3 + 黄芪治疗组及黄芪治疗组 ($P < 0.05$)。结论 黄芪可增强弓形虫 *wx2b2a* 表位疫苗免疫小鼠后抗急性弓形虫感染的免疫调节作用。

关键词: 弓形虫; 表位疫苗; 黄芪; 免疫调节

中图分类号: R382.5

文献标识码: A

文章编号: 1002-2694(2015)09-0822-04

Immunomodulatory effect of *Astragalus* on immune mice from the epitope vaccines *wx2b2a* of *Toxoplasma gondii* against acute *T. gondii* infection

XIE Rong-hua¹, SHU Heng-ping²

(1. Hunan Polytechnic of Environment and Biology, Hengyang 421001, China;

2. Xiangya School of Medicine, Central South University, Changsha 410078, China)

Abstract: We studied the immunomodulatory effect of *Astragalus* on immune mice from the epitope vaccines *wx2b2a* of *Toxoplasma gondii* (*T. gondii*) against acute *T. gondii* infection. The mice were randomly divided into Group pcDNA3-W2b2a, Group pcDNA3-W2b2a + *Astragalus* treatment, Group pcDNA3 + *Astragalus* treatment, Group *Astragalus* treatment, and Group pcDNA3 and physiological saline. The mice in Group pcDNA3-W2b2a and Group pcDNA3-W2b2a + *Astragalus* treatment were intramuscularly immunized with pcDNA3-W2b2a of *T. gondii* for three times. Four weeks after the last immunization, the mice in each group were intraperitoneally injected with 10^2 tachyzoites. Starting from 2 days after infection, the mice in Group pcDNA3-W2b2a + *Astragalus* treatment, Group pcDNA3 + *Astragalus* treatment, Group *Astragalus* treatment were orally treated with *Astragalus* with 75 mg/d for 7 days. ELISA method was taken to assay the serum levels of IgG before immunization, 4 weeks after the last immunization and 6 day post-infection (dpi), and the levels of IFN-γ and IL-18 before immunization, 2 weeks after the last immunization and 4, 6 and 8 dpi, as well as to observe the survival time of the mice attacked by *T. gondii*. The serum levels of IgG of the mice which were immune with pcDNA3-W2b2a were higher than those in other groups ($P < 0.05$). The levels of IgG antibodies in Group pcDNA3-W2b2a, Group pcDNA3-W2b2a + *Astragalus* treatment were almost the same in four weeks after the last immunization and 6 dpi ($P > 0.05$). The levels of IFN-γ in Group pcDNA3-W2b2a + *Astragalus* treatment were higher than those in other groups ($P < 0.05$) in 2 weeks after the last immunization and 4, 6, 8 dpi. The serum levels of

湖南省林业科技创新专项资金(No. XLK201432), 湖南省科技计划项目(No. 2014FJ3126), 衡阳市社会科学基金(No. 2014D100), 衡阳市科学技术发展计划项目(No. 2014KJ27)联合资助
通讯作者: 舒衡平, Email: hengpingshu@xysm.net

作者单位: 1. 湖南环境生物职业技术学院, 衡阳 421001;
2. 中南大学湘雅医学院, 长沙 410078

IL-18 kept elevating after infection. But they are significantly lower than those in Group pcDNA3 and physiological saline after 8 days with *Astragalus* treatment ($P<0.05$). After infection with RH tachyzoites, the mice in Group pcDNA3-W2b2a + *Astragalus* treatment lived longer than those in Group pcDNA3-W2b2a, Group pcDNA3 + *Astragalus* treatment, and Group *Astragalus* treatment ($P<0.05$). *Astragalus* can strengthen the immunomodulatory effect on immune mice from the epitope vaccines *wx2b2a* of *T. gondii* against acute *T. gondii* infection.

Keywords: *Toxoplasma gondii*; epitope vaccine; *Astragalus*; immunomodulatory

Supported by grants from the Special Foundation of Forestry Science and Technology Innovation of Hunan (No. XLK201432), the Science and Technology Project of Hunan (No. 2014FJ3126), the Social Science Fund of Hengyang (No. 2014D100), the Science and Technology Development Project of Hengyang (No. 2014KJ27)

Corresponding author: Shu Heng-ping, Email: hengpingshu@xysm.net

弓形虫是一种机会性致病原虫,引起人兽共患弓形虫病,免疫功能正常者感染弓形虫绝大多数无症状,或者症状很轻,免疫功能抑制或缺陷者(如器官移植、恶性肿瘤及艾滋病人)感染是导致其死亡的原因之一。目前常采用乙胺嘧啶和磺胺嘧啶联合治疗弓形虫病,但其毒副作用发生率高,且不能根治^[1]。表位疫苗是利用基因重组技术将一个或者多个抗原表位的编码基因连接在一起,在宿主细胞内利用真核启动子来持续高效表达多个多肽类免疫原,以提高疫苗的免疫效果,其安全性好,诱发的免疫应答针对性强。本研究组在前期已构建了弓形虫新基因 *wx2b2a* 表位疫苗质粒,能够诱导小鼠产生一定的抗弓形虫感染保护性免疫^[2],但效果也不甚理想。人体感染弓形虫后体内免疫应答失衡,而中药黄芪具有双向免疫应答的调节作用^[3],本研究探讨黄芪能否增强弓形虫 *wx2b2a* 表位疫苗免疫小鼠后抗急性弓形虫感染的免疫保护作用。

1 材料与方法

1.1 菌株与质粒 弓形虫 RH 株为本室传代保种,pcDNA3、pcDNA3-W2b2a 为本室构建。

1.2 实验动物 6 周龄昆明小鼠,雌雄各半,18~20 g,购自南华大学实验动物中心。

1.3 主要试剂与药物 黄芪颗粒,四川百利药业有限责任公司,国药准字 Z20003380; HRP 标记的羊抗小鼠 IgG 购自北京博大泰克公司;小鼠 IFN-γ ELISA 试剂盒,深圳晶美生物有限公司;小鼠 IL-18 ELISA 检测试剂盒,日本 MBL 公司。

1.4 动物分组及实验方案 昆明小鼠 90 只随机分成 6 组,雌雄各半,分别为 I 组:pcDNA3-W2b2a 质粒组、II 组:pcDNA3-W2b2a 质粒 + 黄芪治疗组、III 组:pcDNA3 + 黄芪治疗组、IV 组:黄芪治疗组、V 组:pcDNA3、VI 组:生理盐水组。将 pcDNA3-W2b2a 质粒 100 μL 分别免疫 I 组和 II 组小鼠,从

鼠左后腿胫后肌下端,以平行于肌肉纵轴的方向进针,共免疫 3 次,每次间隔 2 周;III 组、V 组小鼠注射 pcDNA3,IV 组、VI 组小鼠注射 100 μL 生理盐水。末次免疫后 4 周,每鼠腹腔注射 0.2 mL 含 10² 的弓形虫 RH 株速殖子悬液。小鼠感染后 2 d 起,II 组、III 组及 IV 组小鼠给予黄芪灌胃治疗,给药剂量每只鼠 75 mg/d, 灌药量 0.4 mL/鼠,其它组给予相同量的蒸馏水灌胃。灌胃前 2 h 禁水禁食。连续给药 7 d。

1.5 ELISA 法测定小鼠血清 IgG 分别于免疫前、末次免疫后 4 周及感染后 6 d 小鼠断尾法取血,分离收集小鼠血清。将每次所取血清样品做 1:100 稀释,用间接 ELISA 法检测免疫小鼠 IgG 抗体。

1.6 IFN-γ 及 IL-18 测定 免疫前、末次免疫后第 2 周及感染后 4、6、8 d 小鼠断尾法取血,分离收集小鼠血清,ELISA 方法测定小鼠血清 IFN-γ 及 IL-18 浓度。按试剂盒说明书操作。

1.7 统计学处理 统计数据采用统计软件 SPSS11.5 非参数 Kruskal-Wallis 检验。以 $\bar{x} \pm s$ 表示, $P<0.05$ 为差异有统计学意义。表格采用 Excel 制图。

2 结 果

2.1 小鼠血清特异性 IgG 抗体水平 pcDNA3-W2b2a 免疫小鼠后血清 IgG 抗体水平均高于其它组($P<0.05$);末次免疫后 4 周,感染后 6 d pcDNA3-W2b2a、pcDNA3-W2b2a + 黄芪治疗组小鼠特异性 IgG 抗体水平差异无统计学意义($P>0.05$) (图 1)。

2.2 小鼠血清 IFN-γ 水平 末次免疫后 2 周、感染后 4 d、6 d、8 d pcDNA3-W2b2a + 黄芪治疗组小鼠血清 IFN-γ 水平分别高于其它组($P<0.05$),而 pcDNA3-W2b2a 组、pcDNA3 + 黄芪治疗组、黄芪治疗组小鼠血清 IFN-γ 水平分别高于 pcDNA3 组

和生理盐水对照组;感染后 8 d 各组小鼠血清 IFN- γ 水平较感染后 6 d 有所下降($P<0.05$)(图 2)。

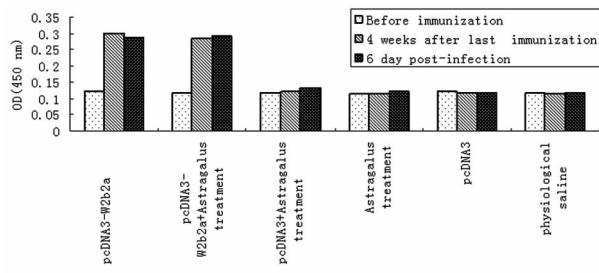


图 1 ELISA 检测小鼠血清特异性 IgG 抗体结果

Fig. 1 Detection of IgG in sera of mice by ELISA

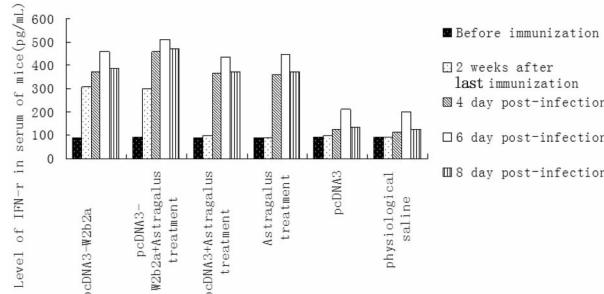


图 2 ELISA 检测小鼠血清 IFN- γ 结果

Fig. 2 Detection of IFN- γ in serum of mice by ELISA

表 1 速殖子攻击后各组小鼠存活时间($\bar{x}\pm s$)

Tab. 1 Survival time of mice in different groups challenged with RH strain tachyzoit

组别 Groups	小鼠数量/只 No. of mice	不同时间小鼠存活的数量/h No. of mice in different time/h							平均生存时间/h Mean survival time /h
		144	168	192	216	240	264	288	
pcDNA3-W2b2a	15	15	13	7	4	3	1	0	214±7 [#]
pcDNA3-W2b2a+黄芪治疗组	15	15	15	12	7	5	3	2	235±11 ^{*#}
pcDNA3-W2b2a+Astragalus treatment	15	15	13	7	3	4	1	0	208±21 [#]
pcDNA3+黄芪治疗组	15	15	13	7	3	4	1	0	208±21 [#]
pcDNA3+Astragalus treatment	15	15	13	7	4	3	1	0	211±25 [#]
黄芪治疗组	15	15	13	7	4	3	1	0	211±25 [#]
Astragalus treatment	15	15	13	7	4	3	1	0	211±25 [#]
pcDNA3	15	15	12	7	0	0	0	0	177±11
生理盐水	15	15	12	7	0	0	0	0	174±9
physiological saline	15	15	12	7	0	0	0	0	174±9

注: * 与 pcDNA3-W2b2a、pcDNA3 + 黄芪治疗组、黄芪治疗组比较, $P<0.05$; # 与 pcDNA3 和生理盐水组比较, $P<0.05$ 。

Note: * As compared with the pcDNA3-W2b2a group, pcDNA3 + Astragalus treatment group, Astragalus treatment group, $P<0.05$; # As compared with the pcDNA3 group, physiological sale group, $P<0.05$.

3 讨论

为增强弓形虫疫苗的免疫效果,用其制成多表位疫苗,能诱导机体产生较高水平的保护性免疫应答。魏庆宽^[4]构建 pcDNA3-ROP2-p30-HSP70 多基因核酸疫苗能诱发小鼠产生细胞免疫和体液免

疫,实验组小鼠存活时间明显延长。范久波^[5]等研究弓形虫新基因 wx 、 $wx2$ 表位疫苗能够诱导小鼠产生抗弓形虫感染保护性免疫。但单用弓形虫疫苗免疫效果还不是十分理想,目前有学者研究中药黄芪具有免疫调节作用及保护作用。黄芪可促进中性

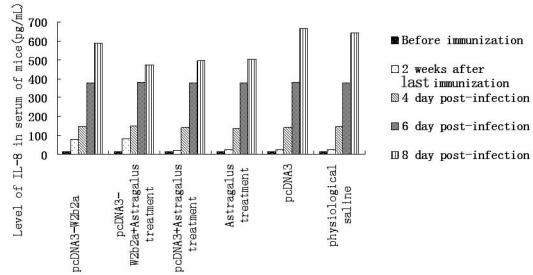


图 3 ELISA 检测小鼠血清 IL-18 结果

Fig. 3 Detection of IL-18 in serum of mice by ELISA

2.4 小鼠感染后的存活时间 末次免疫后 4 周,每鼠腹腔注射 0.2 mL 含 10^2 的弓形虫 RH 株速殖子,实验小鼠均死亡。pcDNA3-W2b2a + 黄芪治疗组小鼠存活时间长于其它组($P<0.05$),pcDNA3-W2b2a、pcDNA3 + 黄芪治疗组及黄芪治疗组小鼠存活时间长于 pcDNA3 和生理盐组($P<0.05$)(表 1)。

粒细胞及巨噬细胞的吞噬功能和杀菌能力, 提高免疫抑制小鼠的 IL-2、TNF- α 、IFN- γ 的水平, 并可促进 T 淋巴细胞增殖^[6]。邱宇安^[7]等研究黄芪含药血清对血管紧张素Ⅱ致内皮细胞凋亡具有保护作用。黄芪注射液能提高重症急性胰腺炎大鼠外周血 GSH-PX、SOD 活性, 降低 ROS 活性和 MDA 浓度^[8], 对重症急性胰腺炎有保护性作用。俞天虹^[9]等研究大剂量黄芪组方的补阳还五汤能显著促进脑缺血后室下区神经干细胞增殖和神经功能恢复。黄芪在寄生虫病防治方面也具有一定的发展潜力, 但其在直接抗寄生虫病效果方面还有待进一步研究, 黄佩珺^[10]等研究结果表明黄芪对低剂量速殖子感染的小鼠有保护作用, 而对高剂量速殖子感染小鼠的保护作用不明显。有研究发现, 通过黄芪提取物 (*Astragalus membranaceus* extracts, AmE) 治疗弓形虫感染小鼠, 或接种疫苗的小鼠能够显著延长存活时间, 降低寄生虫的数量, 并增强 Th1 型细胞免疫反应^[11]。本研究结果显示, pcDNA3-W2b2a 可诱导小鼠产生高水平的 IgG 特异性抗体, 但黄芪对此作用不明显; pcDNA3-W2b2a 可刺激小鼠产生高水平 IFN- γ , 感染后 4、6、8 d 黄芪治疗后小鼠血清 IFN- γ 水平分别高于非治疗组, 且 pcDNA3-W2b2a + 黄芪治疗组小鼠血清 IFN- γ 水平最高, 提示黄芪可以促进 pcDNA3-W2b2a 刺激机体产生 IFN- γ , 增加宿主对速殖子的抗虫能力, 但感染后 8 d 小鼠血清 IFN- γ 水平较感染后 6 d 有所下降, 提示小鼠可能处于代偿性抗炎反应(CARS)引起的免疫抑制阶段, 黄芪则通过诱生 IFN- γ 改善宿主的免疫抑制状态。张晓莉^[12]等研究黄芪水煎剂及黄芪多糖可提高隐孢子虫感染小鼠 CD4、CD4/CD8 及 IL-2、IL-4 和 IFN- γ 水平增强免疫功能促进隐孢子虫感染小鼠恢复。末次免疫后 2 周、感染后 4、6、8 d 各组小鼠血清 IL-18 水平呈持续上升; 感染后 8 d, pcDNA3-W2b2a + 黄芪治疗组小鼠血清 IL-18 显著低于 pcDNA3 和生理盐水对照组, 提示黄芪可能抑制 IL-18 的表达。本实验提示黄芪对弓形虫感染具有双向调节作用, 一方面, 诱导 IFN- γ 早期生成, 上调抗虫免疫应答; 另一方面抑制 IL-18 生成, 下调免疫应答^[13]。Mordue^[14]等发现唯一可决定急性弓形虫感染小鼠生存的因子是 IL-18, 中和 IL-18 的作用可延长小鼠 2 d 的生存时间。小鼠感染试验表明, pcDNA3-W2b2a + 黄芪治疗组小鼠存活时间明显长于 pcDNA3-W2b2a 组和黄芪治疗组。由此可见, 黄芪可增强弓形虫 *wx2b2a* 表位疫苗免疫小鼠后抗急性弓形虫感染的免疫保护作用。

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收稿日期:2015-02-27;修回日期:2015-07-20

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收稿日期:2015-02-15;修回日期:2015-07-20