

## 论著

### 白芍总苷对系统性红斑狼疮CD<sup>4+</sup> T细胞ITGAL基因表达和启动子甲基化修饰的影响

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#### 摘要:

目的: 探讨白芍总苷(total glucosides of peony, TGP)对系统性红斑狼疮(SLE)患者外周血CD<sup>4+</sup> T细胞甲基化敏感基因ITGAL(CD11a)表达及启动子甲基化修饰的影响。方法: 利用磁珠分选获得外周血CD<sup>4+</sup> T细胞,用不同浓度TGP(0,62.5,312.5和1562.5 mg/L)处理SLE患者CD<sup>4+</sup> T细胞,48 h后收集细胞。MTT法检测处理后CD<sup>4+</sup> T细胞的活力。定量PCR检测ITGAL基因mRNA表达水平。流式细胞术检测CD<sup>4+</sup> T细胞表面CD11a分子表达水平。亚硫酸盐测序法分析ITGAL基因启动子甲基化水平。结果: TGP处理48 h后,各浓度组CD<sup>4+</sup> T细胞活力无明显差异。与对照组相比,高浓度组(1562.5 mg/L)ITGAL基因mRNA表达水平显著降低( $P<0.01$ ),CD<sup>4+</sup> T细胞表面CD11a表达水平亦显著降低( $P<0.01$ )。进一步DNA甲基化水平检测显示高浓度TGP处理组ITGAL基因启动子甲基化水平较对照组显著升高( $P<0.01$ )。结论: TGP可通过升高ITGAL基因启动子甲基化水平降低SLE患者外周血CD<sup>4+</sup> T细胞中CD11a表达水平,初步揭示了TGP抑制SLE自身免疫反应的分子机制。

关键词: 白芍总苷 系统性红斑狼疮 CD<sup>4+</sup> T细胞 ITGAL DNA甲基化

### Effect of total glucosides of peony on expression and DNA methylation status of ITGAL gene in CD<sup>4+</sup> T cells of svstemic lupus erythematosus

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#### Abstract:

Objective: To investigate the effect of total glucosides of peony (TGP) on expression and DNA methylation status of ITGAL gene (CD11a) in CD<sup>4+</sup> T cells from patients with systemic lupus erythematosus (SLE). Methods: CD<sup>4+</sup> T cells were isolated by positive selection using CD4 beads. CD<sup>4+</sup> T cells were treated by TGP at 0, 62.5, 312.5 and 1562.5 mg/L for 48 h. The MTT method was used to assess cell viability; mRNA expression level was measured by realtime-PCR; protein level of CD11a was measured by flow cytometric analysis; DNA methylation status was assayed by bisulfite sequencing. Results: No significant change in cell viability was found in CD<sup>4+</sup> T cells among the different concentration groups ( $P>0.05$ ). Compared with control, the mRNA and protein levels of ITGAL were down-regulated significantly in SLE CD<sup>4+</sup> T cells treated with TGP (1562.5 mg/L) ( $P<0.01$ ). Furthermore, the extent of DNA methylation of ITGAL promoter was increased in TGP (1562.5 mg/L) treated CD<sup>4+</sup> T cells compared with control group ( $P<0.01$ ). Conclusion: TGP can repress CD11a gene expression through enhancing DNA methylation of ITGAL promoter in CD<sup>4+</sup> T cells from patients with SLE. This observation represents a preliminary step in understanding the mechanism of TGP in SLE therapy.

Keywords: total glucosides of peony systemic lupus erythematosus CD<sup>4+</sup> T cells ITGAL DNA methylation

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PubMed

1. Kytteris VC, Juang YT, Tsokos GC. Immune cells and cytokines in systemic lupus erythematosus: an update  
[J]. *Curr Opin Rheumatol*, 2005, 17(5): 518-522.
2. Dean GS, Tyrrell-Price J, Crawley E, et al. Cytokines and systemic lupus erythematosus  
[J]. *Ann Rheum Dis*, 2000, 59(4): 243-251.
3. Bleijis DA, Binnerts ME, van Vliet SJ, et al. Low-affinity LFA-1/ICAM-3 interactions augment LFA-1/ICAM-1-mediated T cell adhesion and signaling by redistribution of LFA-1  
[J]. *J Cell Sci*, 2000, 113 (Pt3): 391-400.
4. Varga G, Nippe N, Balkow S, et al. LFA-1 contributes to signal I of T-cell activation and to the production of T(h)1 cytokines  
[J]. *J Invest Dermatol*, 2010, 130(4): 1005-1012.
5. Lu Q, Kaplan M, Ray D, et al. Demethylation of ITGAL (CD11a) regulatory sequences in systemic lupus erythematosus  
[J]. *Arthritis Rheum*, 2002, 46(5): 1282-1291.
6. Oelke K, Lu Q, Richardson D, et al. Overexpression of CD70 and overstimulation of IgG synthesis by lupus T cells and T cells treated with DNA methylation inhibitors  
[J]. *Arthritis Rheum*, 2004, 50(6): 1850-1860.
7. Kaplan M, Lu Q, Wu A, et al. Demethylation of promoter regulatory elements contributes to perforin overexpression in CD<sup>4+</sup> lupus T cells  
[J]. *J Immunol*, 2004, 172 (6): 3652-3661.
8. Lu Q, Wu A, Tesmer L, et al. Reactivation of the inactive X in T cells from women with lupus  
[J]. *J Immunol*, 2007, 179(9): 6352-6358.
9. Richardson BC, Liebling MR, Hudson JL. CD<sup>4+</sup> cells treated with DNA methylation inhibitors induce autologous B cell differentiation  
[J]. *Clin Immunol Immunopathol*, 1990, 55(3): 368-381.
10. Cao W, Zhang W, Liu J, et al. Paeoniflorin improves survival in LPS-challenged mice through the suppression of TNF-alpha and IL-1beta release and augmentation of IL-10 production  
[J]. *Int Immunopharmacol*, 2011, 11(2): 172-178.
11. Huang H, Chang EJ, Lee Y, et al. A genome-wide microarray analysis reveals anti-inflammatory target genes of paeonol in macrophages  
[J]. *Inflamm Res*, 2008, 57(4): 189-198.
12. Zhang LL, Wei W, Wang NP, et al. Paeoniflorin suppresses inflammatory mediator production and regulates G protein-coupled signaling in fibroblast-like synoviocytes of collagen induced arthritic rats  
[J]. *Inflamm Res*, 2008, 57(8): 388-395.
13. Liu DF, Wei W, Song LH. Protective effect of paeoniflorin on immunological liver injury induced by bacillus calmette-guerin plus lipopolysaccharide: modulation of tumour necrosis factor-alpha and interleukin-6 mRNA  
[J]. *Clin Exp Pharmacol Physiol*, 2006, 33(4): 332-339.
14. 丁朝霞, 杨少锋, 吴启富, 等. 白芍总苷对MRL/lpr小鼠狼疮性肾炎的影响  
[J]. *南方医科大学学报*, 2011, 31(4): 656-660. DING Zhaoxia, YANG Shaofeng, WU Qifu, et al. Therapeutic effect of total glucosides of paeony on lupus nephritis in MRL/lpr mice  
[J]. *Nan Fang Yi Ke Da Xue Xue Bao*, 2011, 31(4): 656-660.
15. 张洪峰, 肖卫国, 侯平. 白芍总苷治疗系统性红斑狼疮的临床研究  
[J]. *中国中西医结合杂志*, 2011, 1(4): 476-479. ZHANG Hongfeng, XIAO Weiguo, HOU Ping. Clinical study of total glucosides of paeony in patients with systemic lupus erythematosus  
[J]. *Chinese Journal of Integrated Traditional and Western Medicine*, 2011, 1(4): 476-479.
16. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus  
[J]. *Arthritis Rheum*, 1997, 40(9): 1725.
17. Richardson BC, Strahler JR, Pivrotto TS, et al. Phenotypic and functional similarities between 5-azacytidine-treated T cells and a T cell subset in patients with active systemic lupus erythematosus  
[J]. *Arthritis Rheum*, 1992, 35(6): 647-662.
18. Kaneko H, Tokano Y, Hashimoto H, et al. The expression of lymphocyte function associated antigen-1, intercellular adhesion molecule-1 on peripheral blood lymphocytes in patients with systemic lupus erythematosus  
[J]. *Nihon Rinsho Meneki Gakkai Kaishi*, 1996, 19(1): 60-68.
19. 周同, 江永娣, 姚建, 等. 系统性红斑狼疮患者淋巴细胞粘附分子表达的观察  
[J]. *中华内科杂志*, 1995, 34(8): 545-547. ZHOU Tong, JIANG Yongdi, YAO Jian, et al. Expression of adhesion molecules on lymphocyte in patients with systemic lupus erythematosus  
[J]. *Chinese Journal of Internal Medicine*, 1995, 34(8): 545-547.
20. Zhao M, Sun Y, Gao F, et al. Epigenetics and SLE: RFX1 downregulation causes CD11a and CD70 overexpression by altering epigenetic modifications in lupus CD<sup>4+</sup> T cells  
[J]. *J Autoimmun*, 2010, 35(1): 58-69.
21. Li Y, Zhao M, Yin H, et al. Gadd45a overexpression contributes to autoimmunity by promoting DNA demethylation in lupus T cells

[J]. Arthritis Rheum, 2010, 62(5): 1438-1447.

22. Zhao S, Wang Y, Liang Y, et al. MicroRNA-126 regulates DNA methylation in CD<sup>4+</sup> T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1

[J]. Arthritis Rheum, 2011, 63(5): 1376-1386.

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1. 吴新华, 左晓霞, 伍招娣, 张卫社, 扶琼. 妊娠合并系统性红斑狼疮的临床分析[J]. 中南大学学报(医学版), 2006, 31(02): 271-273

2. 张赛丹, 吴森, 陈峰, 左晓霞, 张晶. 系统性红斑狼疮患者超声心动图改变与抗心磷脂抗体的关系 [J]. 中南大学学报(医学版), 2006, 31(05): 692-695

3. 冯浩, 张桂英, 谢红付, 陈明亮, 施为, 王玲艳.

## 系统性红斑狼疮合并丙型肝炎病毒感染的临床研究

[J]. 中南大学学报(医学版), 2006, 31(06): 891-893

4. 季迎<sup>1</sup>, 张浩<sup>1</sup>, 袁洪<sup>2</sup>, 阳国平<sup>2</sup>, 张柯<sup>1</sup>, 谢丽华<sup>1</sup>. 趋化素样因子-1在狼疮性肾炎患者肾组织中的表达[J]. 中南大学学报(医学版), 2007, 32(03): 490-493

5. 刘敏姬, 沈守荣. 结直肠癌与DNA甲基化[J]. 中南大学学报(医学版), 2009, 34(12): 1266-1270

6. 朱熊兆, 彭素芳, 马秀玲, 李婷. 母爱剥夺对成年大鼠情绪及多巴胺转运蛋白基因表达的影响[J]. 中南大学学报(医学版), 2010, 35(1): 32-37

7. 彭再梅<sup>1</sup>, 山长婷<sup>2</sup>, 王惠芳<sup>1</sup>. 诱导痰RASSF1A, p16和DAPK基因启动子区

甲基化在肺癌诊断中的价值[J]. 中南大学学报(医学版), 2010, 35(3): 247-253

8. 蒋姣伏<sup>1</sup>, 柳永和<sup>2,\*</sup>, 张传兴<sup>2</sup>. 女性系统性红斑狼疮病人性激素水平[J]. 中南大学学报(医学版), 2005, 30(3): 315-317

9. 唐艳<sup>1,2</sup>, 吴芳<sup>1</sup>, 胡春宏<sup>1</sup>. RUNX3基因启动子甲基化与早期非小细胞肺癌的预后[J]. 中南大学学报(医学版), 2011, 36(7): 650-654

10. 李懿莎, 罗卉, 谢艳莉, 左晓霞. 狼疮性膀胱炎2例并文献复习[J]. 中南大学学报(医学版), 2011, 36(8): 813-816