ETV5 promotes follicular helper T cell differentiation and lupus pathogenesis

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Background Follicular helper T (TFH) cells induce germinal center response to produce high affinity antibodies against a specific pathogen. Excessive formation of TFH cells are closely associated with the onset of antibody-mediated systemic autoimmune diseases, such as systemic lupus erythematosus (SLE). Our previous study has shown that ETV5 promotes murine TFH cell differentiation. However, its role in human TFH cell differentiation and the pathogenesis of SLE has not been investigated.

Methods We analyzed the autoimmune phenotype and cell population in ETV5 deficient lupus mouse models. Autoimmunity was evaluated by checking autoantibody levels, immune cell infiltration into non-lymphoid organs, and kidney IgG deposition. The frequency of TFH, TFR, and GC B cells was measured by flow cytometry. The expression levels of ETV5 in human samples were analyzed by qRT-PCR and western blot.

Results The frequency of TFH cells is decreased in the spleen of T cell-specific ETV5 null mice compared with control mice. In addition, ETV5 deficiency in T cells substantially suppresses autoimmunity in lupus mouse models. TFH cells have higher levels of ETV5 than non-TFH cells in humans as well as in mice. ETV5 overexpression also promotes human TFH cell differentiation. Furthermore, ETV5 levels are significantly higher in CD4 T cells from SLE patients than in those from healthy control, suggesting that ETV5 may be an SLE-promoting factor.

Conclusions In this study, we show that ETV5 is a transcription factor that promotes the pathogenesis of lupus autoimmune disease via enhancing TFH cell differentiation. We are currently investigating the molecular mechanism of how ETV5 promotes TFH cell differentiation.

References

1. Mingfang Li, Li Luo, Chuanchuan Lin, Bing Ni, Lijun Zou, Zhipiang Song, Fei Hao, Na Luo. Dermatology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Dermatology, Southwest Hospital, Army Medical University, Chongqing, China; Immunology, Institute of Immunology, PLA, Army Medical University, Chongqing, China

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Background Systemic lupus erythematosus (SLE) is an autoimmune disease in which defective T cells, immune complex deposition, and other immune system alterations contribute to pathological changes of multiple organs and organ systems. Our aim was to investigate the effects of 1,25-(OH)2 vitamin D3 (VitD3) on the activation of myeloid dendritic cells (mDCs) by autologous DNA immune complex (DNA-IC), and the effects of VitD3 on immune system balance during SLE.

Methods We purified DNA-ICs from SLE patients and isolated peripheral blood mDCs before and after histone deacetylase3 (HDAC3) gene interference by siRNA. mDC was stimulated by DNA-ICs and/or VitD3. The expression of NF-kB subunit RelB detected by WB. TNF-α, IL-10 secretion was detected by ELISA respectively. The immune balance of Treg/Th17 cells was determined after the co-culture of homologous CD4+ T lymphocytes with different stimulators primed mDCs.

Results Our in vitro studies indicated that DNA-ICs were internalized and consumed by mDCs. Further analysis indicated that VitD3 blocked the effects of DNA-ICs on RelB, IL-10, and TNF-α in mDCs. Co-culture of mDCs and CD4+ T cells indicated that VitD3 inhibited multiple processes mediated by DNA-ICs, including the proliferation of mDCs, downregulation of IL-10, and upregulation of TNF-α. Additional co-culture experiments indicated that VitD3 reversed the effects of DNA-ICs in regulating the percentages of CD4+CD127-Foxp3+ T cells and CD4+IL17+ T cells.

Conclusions Our results indicated that autologous DNA-ICs stimulated activation of mDCs during SLE, and that VitD3 inhibited the stimulatory effects of DNA-ICs and maintained the Treg/Th17 immune cell balance. These results suggest that VitD3 may have therapeutic value for treatment of SLE.

References

1. Mingfang Li, Li Luo, Chuanchuan Lin, Bing Ni, Lijun Zou, Zhipiang Song, Fei Hao, Na Luo. Dermatology, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; Dermatology, Southwest Hospital, Army Medical University, Chongqing, China; Immunology, Institute of Immunology, PLA, Army Medical University, Chongqing, China

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Background

Thrombocytopenia is a common manifestation associated with the presence of antiphospholipid antibodies (aPLs). A specific guideline for management of aPLs associated thrombocytopenia is still absent.

Methods

This is a single-center observational prospective study. Patients with aPLs associated thrombocytopenia were recruited. Patients with systemic lupus erythematosus (SLE) related major organ involvement were excluded. Treatment response, adverse effects, bleeding events were monitored.

Results

A total of 61 patients were enrolled with a median treatment duration of 22 months. The overall response rate in this cohort was 80.3% (n = 49), including 49.2% of complete responses (n = 30) (table 1). Compared to commonly used second line therapy for immune thrombocytopenia like eltrombopag and rituximab, the response rate was similar. The median time to achieve a response was 3 months (IQR 1, 3). Within the first 3 months, the mean platelet count of patients with overall response elevated continuously (figure 1). A total of 8 (16.3%) patients with a response experienced a loss of response, 12.2% (n = 6) during treatment, the other in the process of tapering. The median duration of response under treatment was 24.5 months (IQR 9.8, 40.3). 11 (18%) patients had a sustained response after the termination of tacrolimus treatment. Patients diagnosed with SLE had a significantly higher rate of achieving overall response (91.3% vs 73.7%). Side effects were reported in 9.8% (n = 6) of the patients in this cohort and treatment was interrupted due to side effects in 3.3% (n = 2) of patients.

Conclusions

This study suggests that tacrolimus has adequate efficacy and is well tolerated for aPLs associated

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Abstract LO-040 Table 1

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 61)</th>
<th>Nonresponders (n = 12)</th>
<th>Overall responders (n = 49)</th>
<th>Complete response (n = 30)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Total follow-up months, mean (SD)</td>
<td>37.6 (19.3)</td>
<td>27.4 (22.1)</td>
<td>40.1 (17.9)</td>
<td>43.5 (16.9)</td>
<td>0.09*a</td>
</tr>
<tr>
<td>Duration of treatment, months, median (IQR)</td>
<td>22 (11, 42)</td>
<td>10 (5.8, 13)</td>
<td>27 (14, 44)</td>
<td>31 (14.3, 43.8)</td>
<td>0.009*a</td>
</tr>
<tr>
<td>Follow-up after cessation of treatment, months, mean (SD)</td>
<td>30.9 (18.5)</td>
<td>24.3 (18.8)</td>
<td>32.9 (18.7)</td>
<td>31.6 (20.1)</td>
<td>0.5*a</td>
</tr>
<tr>
<td>Time to response, months, median (IQR)</td>
<td></td>
<td>/</td>
<td>3 (1, 3)</td>
<td>2 (1, 3)</td>
<td>0.5*b</td>
</tr>
<tr>
<td>LR during treatment, n (%)</td>
<td></td>
<td>/</td>
<td>6 (12.2)</td>
<td>4 (13.3)</td>
<td>1*b</td>
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<tr>
<td>LR after cessation of treatment, n (%)</td>
<td></td>
<td>/</td>
<td>2 (4.1)</td>
<td>0</td>
<td>0.5*b</td>
</tr>
<tr>
<td>Duration of response under treatment, months, median (IQR)</td>
<td></td>
<td>/</td>
<td>24.5 (9.8, 40.3)</td>
<td>27.5 (9.3, 40.8)</td>
<td>0.4*b</td>
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<tr>
<td>Patients achieved TFR, n (%)</td>
<td></td>
<td>/</td>
<td>11 (22.4)</td>
<td>8 (26.7)</td>
<td>0.5*b</td>
</tr>
<tr>
<td>Duration of TFR, months, mean (SD)</td>
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<td>/</td>
<td>32.7 (19)</td>
<td>33.3 (20.8)</td>
<td>0.9*b</td>
</tr>
<tr>
<td>Concentration of tacrolimus, ng/ml, mean (SD)</td>
<td>5.9 (2.9)</td>
<td>6.6 (3.6)</td>
<td>6.6 (3.6)</td>
<td>5.0 (2.6)</td>
<td>0.6*b</td>
</tr>
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</table>

thrombocytopenia. Patients with mild to moderate SLE might benefit the most from tacrolimus treatment.

**LO-041** SEVERE THROMBOCYTOPENIA IS ASSOCIATED WITH ADVERSE PREGNANCY OUTCOMES IN OBSTETRIC ANTIPHOSPHOLIPID SYNDROME

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Background Thrombocytopenia is a common complication of antiphospholipid syndrome (APS). It is a main concern for hemorrhage risk on the current standard treatment of low dose aspirin (LDA) and low molecular weight heparin (LMWH) in obstetric APS (OAPS). This study assesses the possible relationship between the different levels of thrombocytopenia and adverse pregnancy outcomes (APOs) in OAPS patients.

Methods A retrospective study was conducted at Peking University People’s Hospital, Beijing, China. The demographic, clinical, immunologic, and pregnancy outcomes of the OAPS patients were collected. Univariate and multivariate logistic regression analyses were applied to assess the association between APOs and thrombocytopenia, especially severe thrombocytopenia (<30×10⁹/L).

Results A total of 206 participants were included in the analysis. There were 30 with mild to moderate thrombocytopenia (30–100×10⁹/L) and 19 with severe thrombocytopenia (<30×10⁹/L) among 176 OAPS patients in pregnancy. The rate of the hypocomplementemia in severe thrombocytopenia group (36.84%) was higher than that in the non-severe group (20.00%) and in control group (9.57%) (P = 0.005). Severe thrombocytopenia was associated with a higher APOs of OAPS, such as preterm delivery before 34 weeks (Model I: OR, 16.09; 95%CI, 3.69–70.10, P = 0.0002; Model II: OR, 10.33; 95%CI, 2.02–52.88, P = 0.0051), uteroplacental insufficiency (Model I: OR, 3.35; 95%CI, 1.14–9.85, P = 0.028; Model II: OR, 5.98; 95%CI, 1.62–22.14, P = 0.0074), and gestational hypertension (Model I: OR, 5.26; 95%CI, 1.16–23.82, P = 0.031; Model II: OR, 9.45; 95%CI, 1.43–62.45, P = 0.0198), but not the mild to moderate thrombocytopenia after adjusting for demographic and laboratory factors. After adding medication adjustments, these factors above become insignificant (p > 0.05).

Conclusions The risk of APOs depends on the different levels of thrombocytopenia in OAPS patients. Only severe thrombocytopenia is associated with adverse pregnancy outcomes. The effective OAPS treatments may improve pregnancy outcomes.