Skin Repair and Immunoregulatory Effects of Myeloid Suppressor Cells from human cord blood on Atopic Dermatitis

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Abstract

Background: In our previous study, we achieved large-scale expansion of bone marrow-derived suppressor cells (MDSCs) derived from CD34+ cells cultured in human umbilical cord blood (hUCB) and demonstrated the immunomodulatory properties of these cells. This study aimed to assess the therapeutic efficacy of hUCB-MDSCs in the treatment of atopic dermatitis (AD).

Methods: Dermatophagoides farinae (Df)-induced NC/Nga mice (clinical score of 7) were treated with hUCB-MDSCs or control drug. The mechanisms underlying the therapeutic effects of hUCB-MDSCs were evaluated using dermatitis scores, immunological parameters, skin histology, and skin barrier function analysis.

Results: hUCB-MDSCs demonstrated immuno-suppressive effects on both human and mouse CD4+ T cells. hUCB-MDSC administration significantly reduced the clinical severity scores and was associated with histopathological changes, such as reduced inflammatory cellular infiltration, epidermal hyperplasia, and fibrosis. hUCB-MDSC administration decreased the serum levels of IgE, IL-4, IL-5, IL-13, IL-17, thymus- and activation-regulated chemokine (TARC), and thymic stromal lymphopoietin (TSLP). Additionally, hUCB-MDSCs altered the expression of skin barrier function-related proteins such as filaggrin, involucrin, loricrin, and cytokeratin 10 and suppressed Df restimulated T-cell activation through cell–cell interactions. Furthermore, hUCB-MDSCs promote skin recovery and maintain their therapeutic effect even after recurrence. Conclusions: hUCB-MDSC administration improved Df-induced AD-like skin lesions and led to the restoration of skin barrier function. Furthermore, hUCB-MDSC treatment inhibited inflammatory responses and suppressed T-cell immune function. Therefore, the results of this study support the potential for hUCB-MDSCs as a novel treatment for AD.

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Figure 4. Effects of human umbilical cord blood-myeloid-derived suppressor cell therapy on the level of IgE and inflammatory mediators in the serum of Dermatophagoides farina-induced NC/Nga mice.
Supplementary Figure 1. Biological process analysis of human umbilical cord blood (hUCB)-myeloid-derived suppressor cells (MDSCs).
Supplementary Figure 2. Specific migration of human umbilical cord blood (hUCB)-myeloid-derived suppressor cells (MDSCs) into the injured skin.
Supplementary Figure 3. Maintenance of the therapeutic effect of human umbilical cord blood (hUCB)-myeloid-derived suppressor cells (MDSCs) and rapid reduction in the efficacy of dexamethasone (Dexa) upon restimulation of an atopic dermatitis (AD) model with Dermatophagoides farinae (Df).

Clinical skin scores

Days

0 7 14 21 28 35 42 49 56 63 70

Df alone
Df+Dexa
Df+hUCB-MDSCs
Figure 1. Immunobiological characterization of human umbilical cord blood (hUCB) myeloid-derived suppressor cells (MDSCs) in vitro using human and mouse T cells.

A

- Isotype control
  - CD3: 0% 0%
  - CD3+CD11b+: 0.65% 0%
  - CD3+CD11b+CD14+: 0%

- CD3+CD19+
  - CD3: 0.52%
  - CD3+CD19+: 0.62%
  - CD3+CD19+CD56+: 0.23%
  - CD3+CD19+CD56+CD14+: 0.15%

B

- iNOS
- IDO
- ARG1

C

- No stimulation
- Stimulation + hUCB MDSC

### Suppression (%)
- CD4: 0.8 95.23 33.47
- CD8: 2.4 97.25 59.33
Figure 2. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy against Dermatophagoides farinae (Df)-induced atopic dermatitis-like skin lesions in NC/Nga mice.

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Figure 3. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on skin barrier repair and skin fibrosis in Dermatophagoides farinae (Df)-induced atopic dermatitis-like skin lesions in NC/Nga mice.

A

![Images of skin sections showing normal, Df alone, Df+Dexa, Df+hUCB-MDSC (1 x 10⁴), Df+hUCB-MDSC (1 x 10⁵), Df+hUCB-MDSC (1 x 10⁶) treatments.]

**skin fibrosis**

![Bar graph showing dermal thickness (μm) with statistical significance indicated by asterisks and ns (not significant).]
Figure 5. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on the regulation of differentiation to CD4+ T cell subsets.

A

![Images of splenic masses](image)

- Normal
- Df alone
- Df+Dexa
- Df+hUCB-MDSCs (1 x 10^4)
- Df+hUCB-MDSCs (1 x 10^5)
- Df+hUCB-MDSCs (1 x 10^6)

![Graph](image)

- Splenic mass (mg)
- Normal, Df alone, Df+Dexa, Df+hUCB-MDSCs (1 x 10^4), Df+hUCB-MDSCs (1 x 10^5), Df+hUCB-MDSCs (1 x 10^6)

**Note:** The graph shows statistically significant differences between the groups, indicated by asterisks: ** for p < 0.01, **** for p < 0.0001, and ns for non-significant differences.
Figure 6. Mechanism of atopic dermatitis-immune cell regulation between human umbilical cord blood (hUCB)-myeloid-derived suppressor cells (MDSCs) and T cells in the atopic dermatitis (AD) mouse model.

**A**

<table>
<thead>
<tr>
<th>Condition</th>
<th>CD4</th>
<th>CD8</th>
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<tbody>
<tr>
<td>None</td>
<td>1.31</td>
<td>1.72</td>
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<tr>
<td>Re-stimulated LN</td>
<td>37.08</td>
<td>48.57</td>
</tr>
<tr>
<td>+MDSC</td>
<td>28.94</td>
<td>31.84</td>
</tr>
<tr>
<td>+MDSC (Transwell)</td>
<td>45.27</td>
<td>47.45</td>
</tr>
<tr>
<td>+MDSC (NOHA)</td>
<td>31.01</td>
<td>31.89</td>
</tr>
<tr>
<td>+MDSC (1400W)</td>
<td>20.42</td>
<td>28.91</td>
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Cell proliferation (%)

Normal LN | AD LN

<table>
<thead>
<tr>
<th>Transwell</th>
<th>No-NOHA</th>
<th>1400W</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
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</table>

Significance levels:

- **ns** (not significant)
- * (p < 0.05)
- **p < 0.01**
- ***p < 0.001***
- ****p < 0.0001***
Supplementary Figure 4. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on axillary lymph nodes (LNs).

A