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 immunosuppressive 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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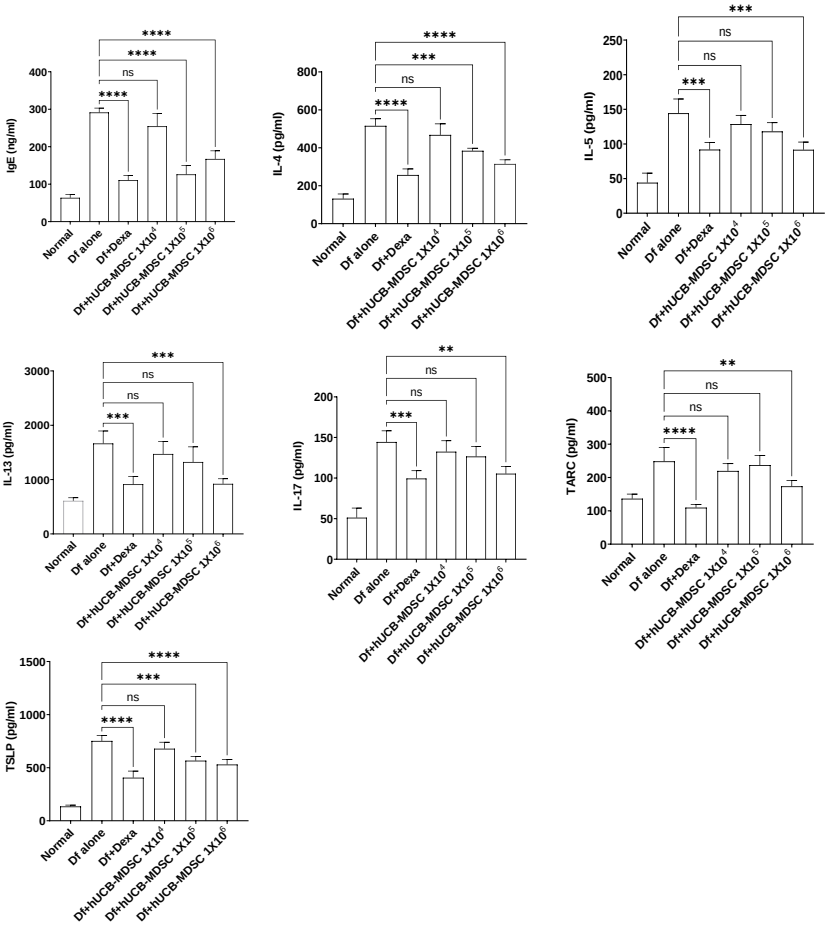
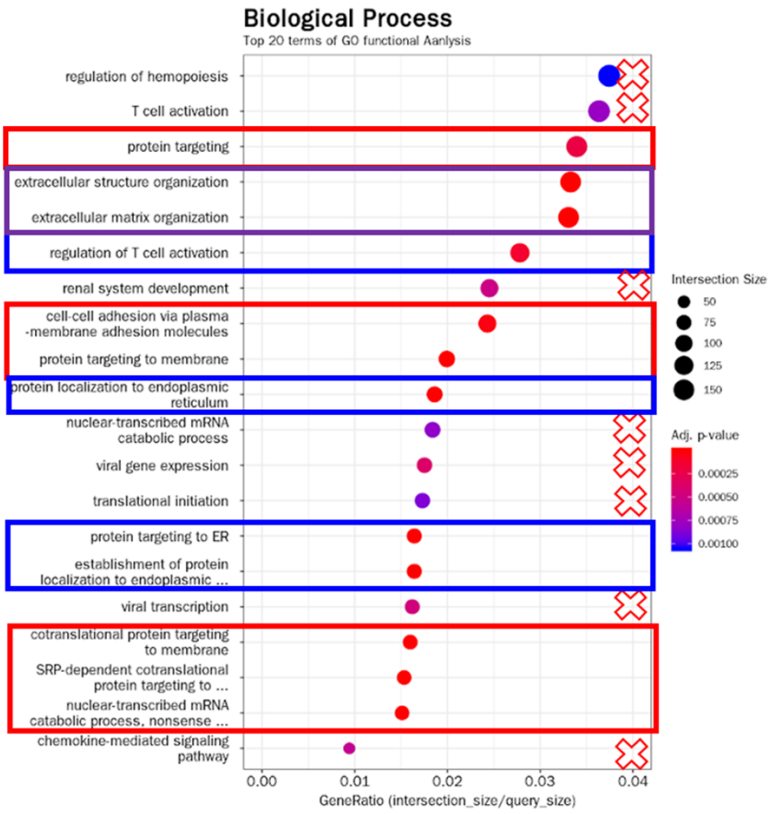
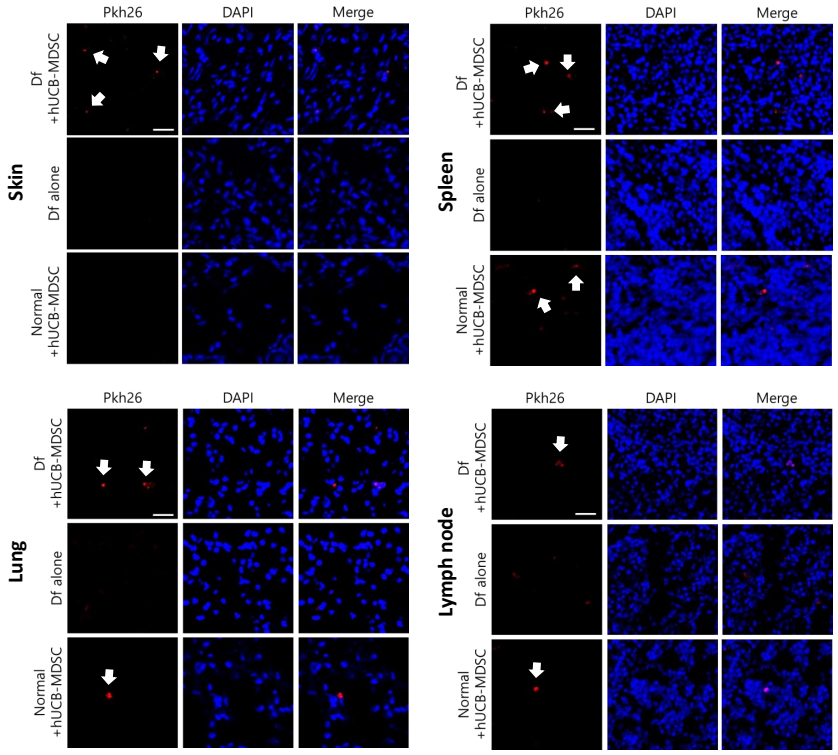
Figure 4. Effects of human umbilical cord blood-myeloid-derived suppressor cell therapy on the level of IgE and inflammatory mediators in the serum of Dermatophagoides farina-induced NC/Nga mice



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).

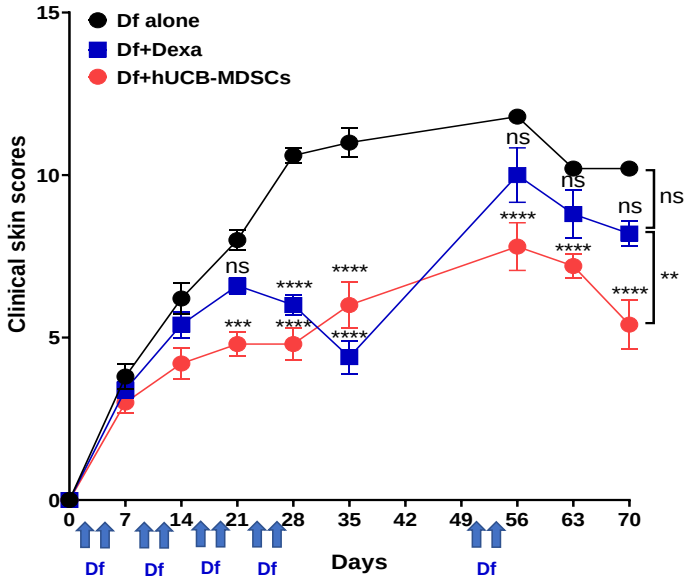
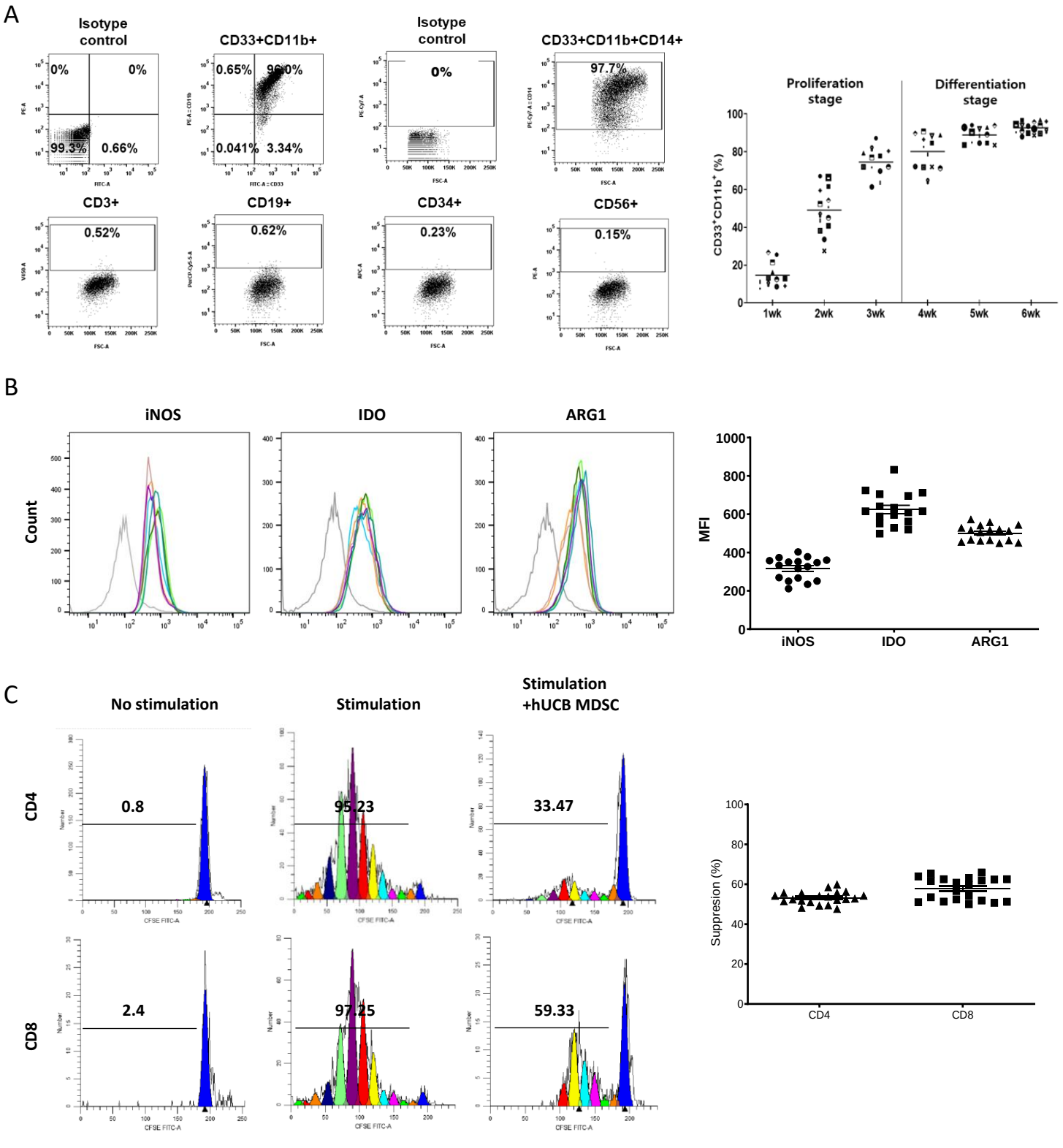


Figure 1. Immunobiological characterization of human umbilical cord blood (hUCB) myeloid-derived suppressor cells (MDSCs) in vitro using human and mouse T cells.



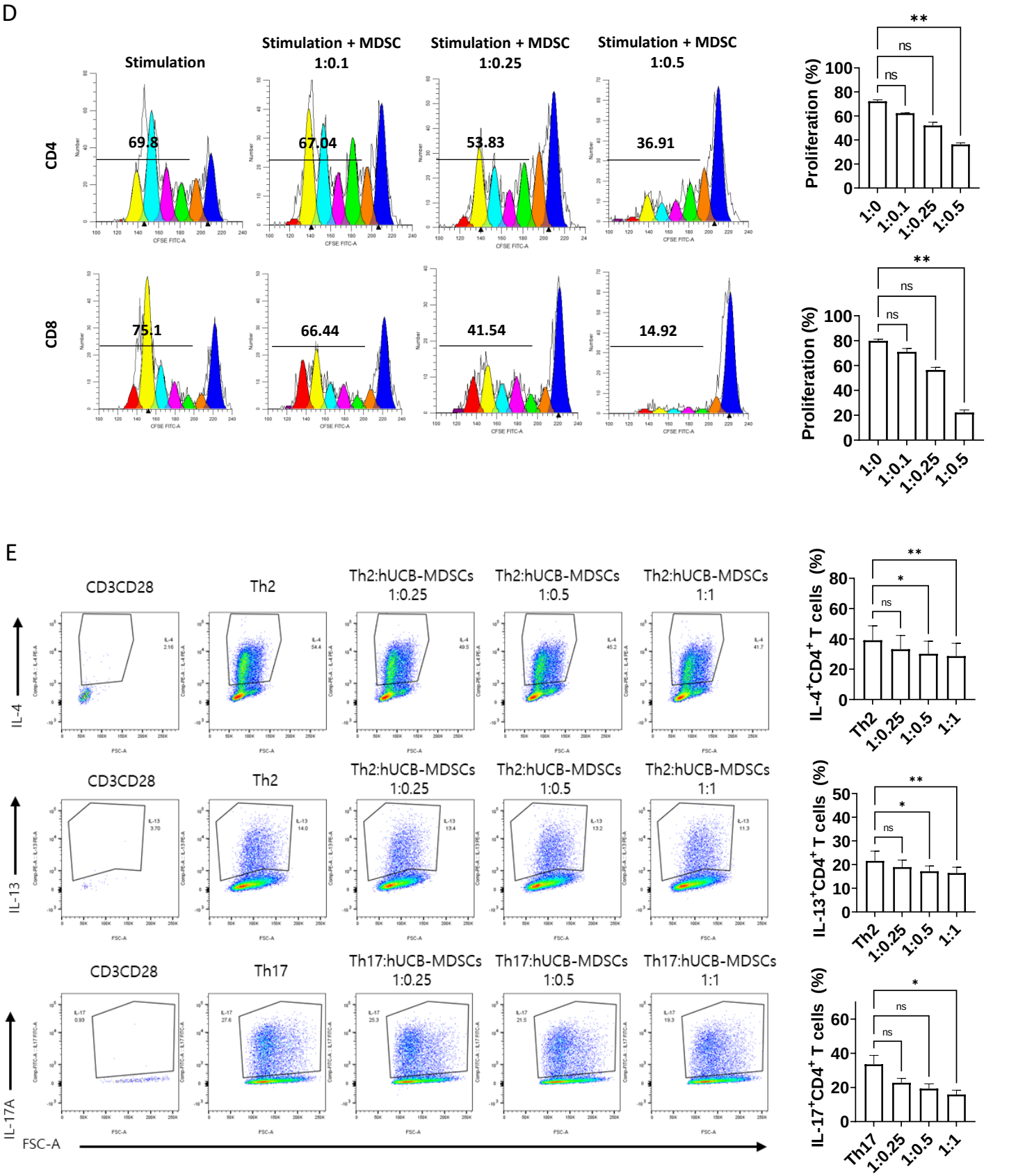
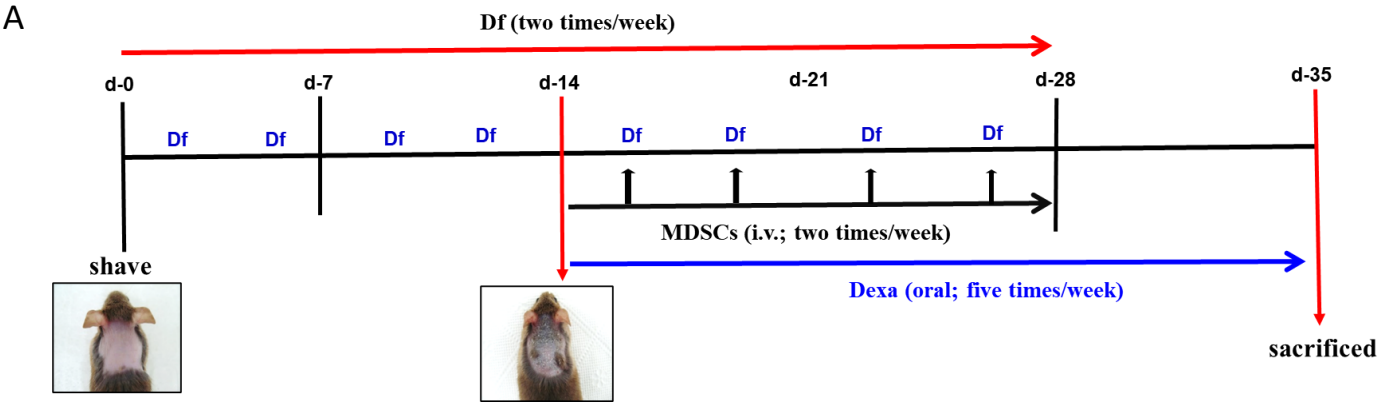
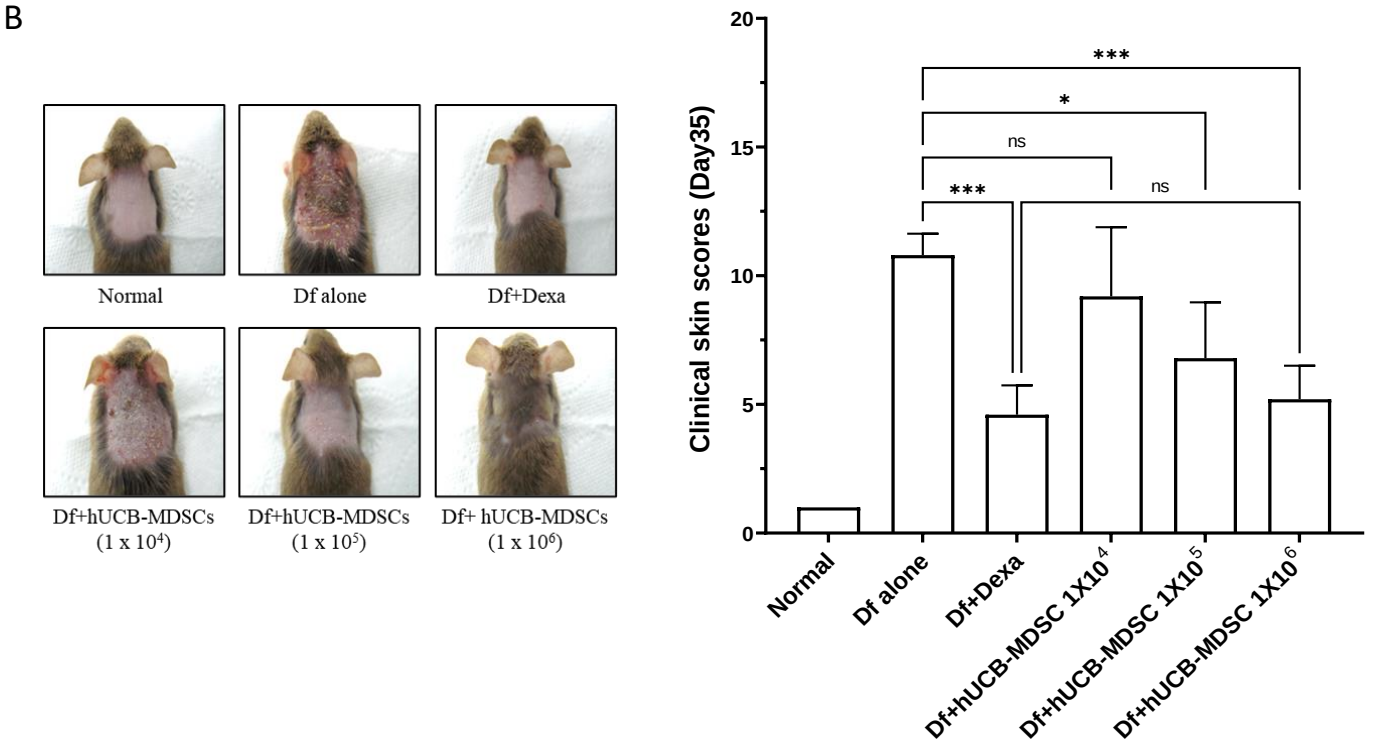
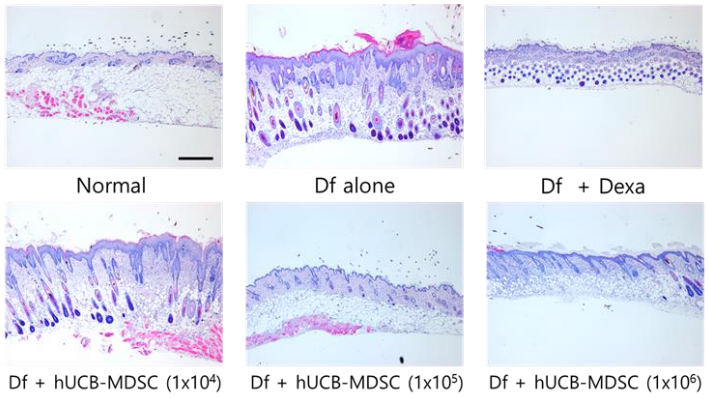

D
Stimulation
Stimulation + MDSC 1:0.1
Stimulation + MDSC 1:0.25
Stimulation + MDSC 1:0.5
CD4
69.8
67.04
53.83
36.91
CD8
75.1
66.44
41.54
14.92
CFSE FITC-A
Number
Proliferation (%)
ns
**
1:0
1:0.1
1:0.25
1:0.5
E
CD3CD28
Th2
Th2:hUCB-MDSCs 1:0.25
Th2:hUCB-MDSCs 1:0.5
Th2:hUCB-MDSCs 1:1
IL-4
IL-13
Th17
Th17:hUCB-MDSCs 1:0.25
Th17:hUCB-MDSCs 1:0.5
Th17:hUCB-MDSCs 1:1
IL-17A
FSC-A
IL-4+CD4+ T cells (%)
IL-13+CD4+ T cells (%)
IL-17+CD4+ T cells (%)
Th2
Th17
*

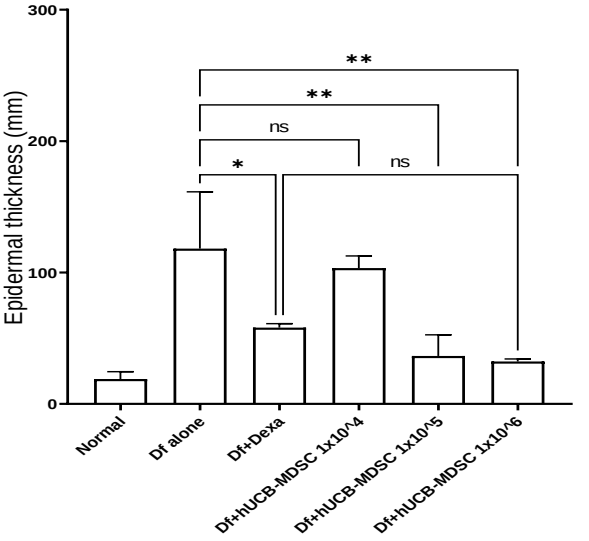
Figure 2. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy against Dermatophagoides farinae (Df)-induced atopic dermatitis-like skin lesions in NC/Nga mice.



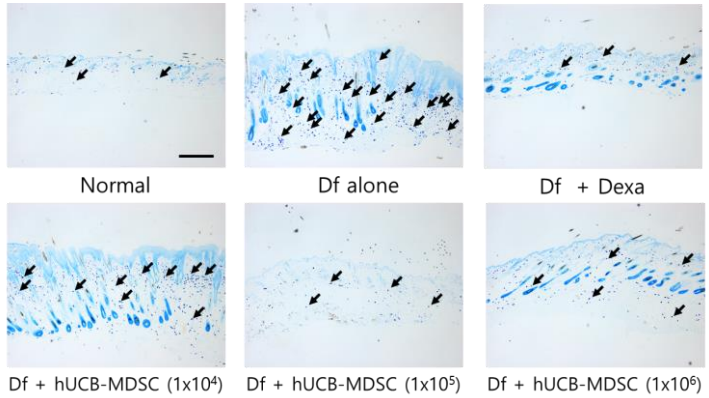


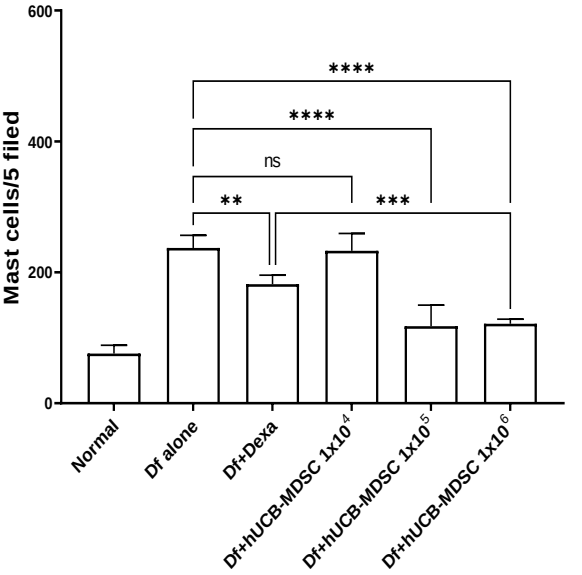
C


Normal
Df alone
Df + Dexa
Df + hUCB-MDSC (1x10⁴)
Df + hUCB-MDSC (1x10⁵)
Df + hUCB-MDSC (1x10⁶)

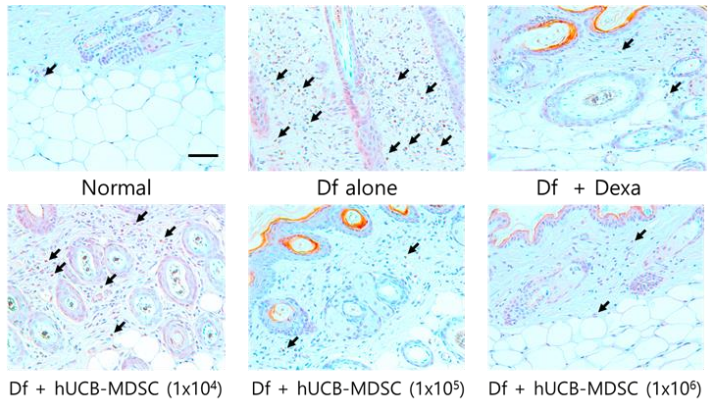

Epidermal thickness (mm)
300
200
100
0
**
**
ns
*
ns
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6

D


Normal
Df alone
Df + Dexa
Df + hUCB-MDSC (1x10⁴)
Df + hUCB-MDSC (1x10⁵)
Df + hUCB-MDSC (1x10⁶)


Mast cells/5 filed
600
400
200
0
****
****
ns
**
***
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10⁴
Df+hUCB-MDSC 1x10⁵
Df+hUCB-MDSC 1x10⁶

E


Normal
Df alone
Df + Dexa
Df + hUCB-MDSC (1x10⁴)
Df + hUCB-MDSC (1x10⁵)
Df + hUCB-MDSC (1x10⁶)

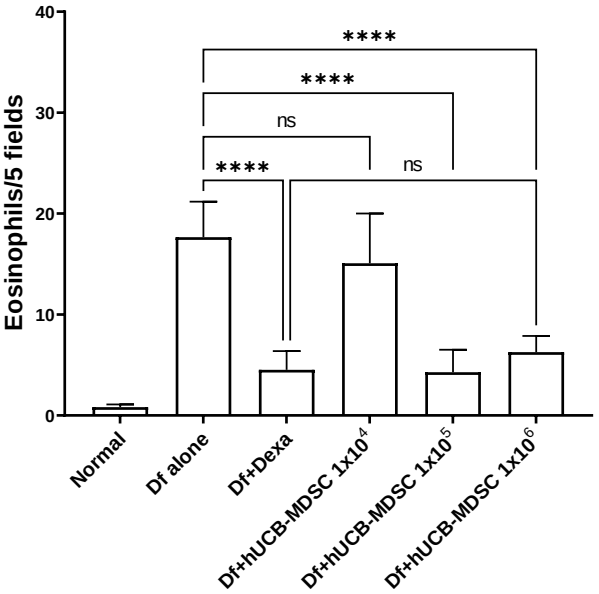
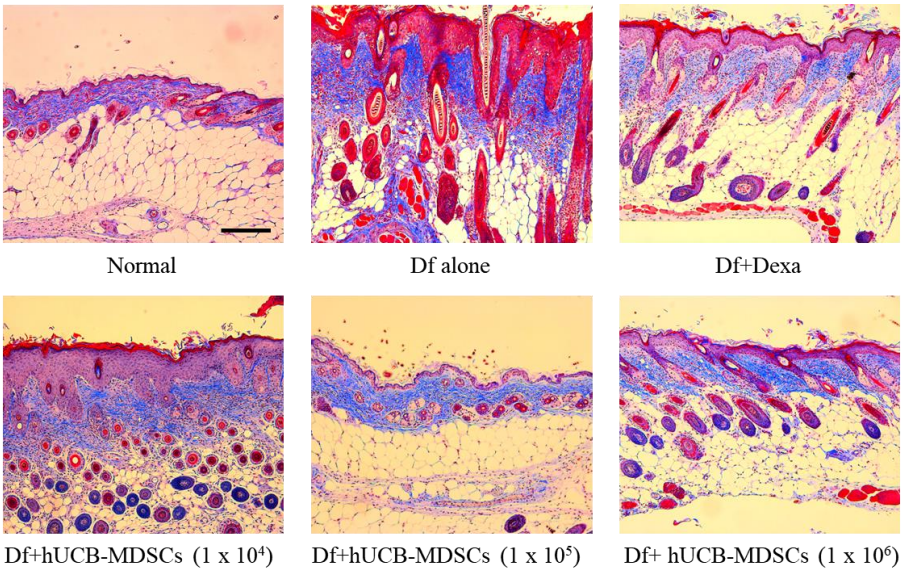
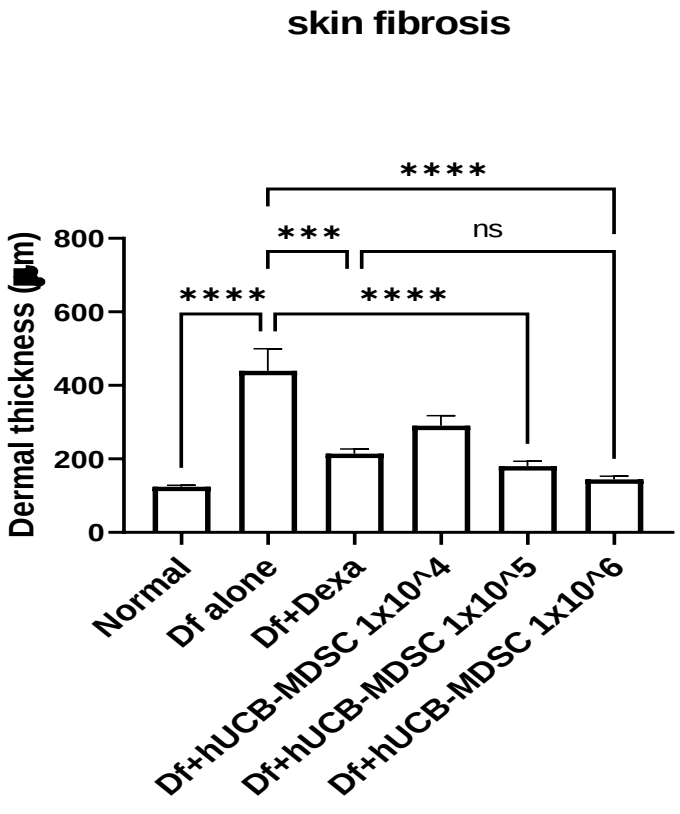

Eosinophils/5 fields
40
30
20
10
0
****
****
ns
****
ns
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10⁴
Df+hUCB-MDSC 1x10⁵
Df+hUCB-MDSC 1x10⁶

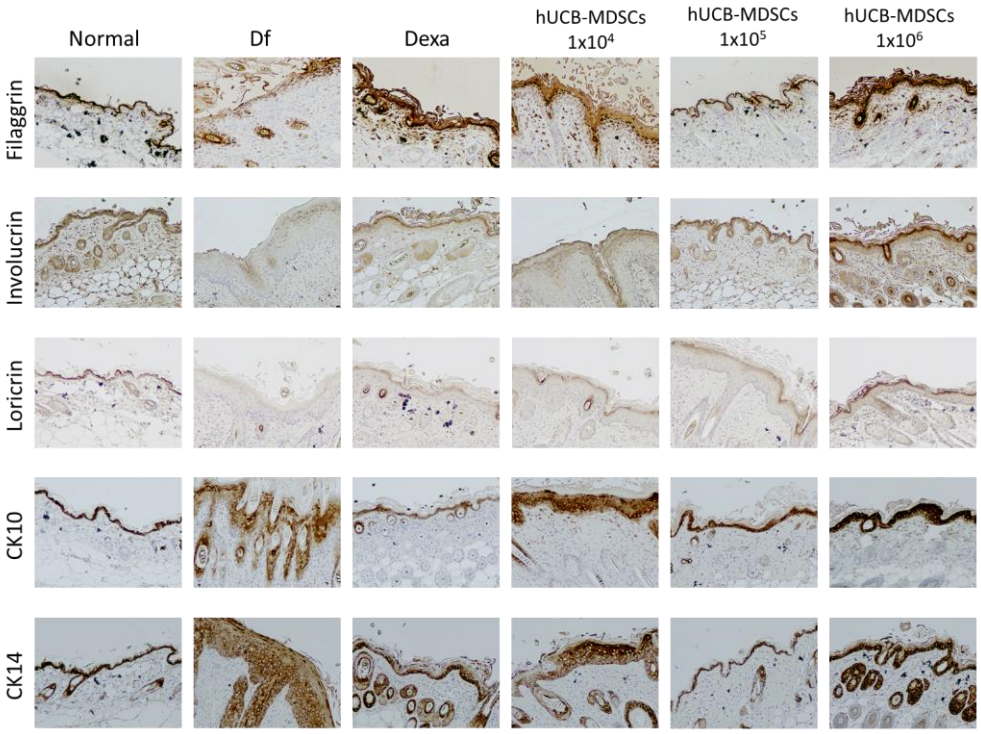
Figure 3. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on skin barrier repair and skin fibrosis in Dermatophagoides farinae (Df)-induced atopic dermatitis-like skin lesions in NC/Nga mice.

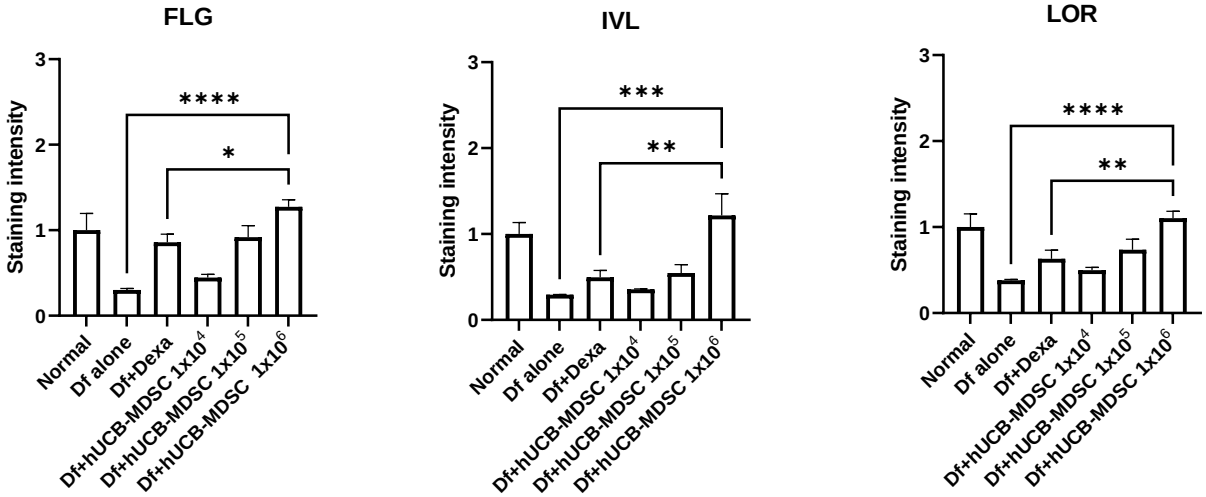
A





B


Normal
Df
Dexa
hUCB-MDSCs 1x10⁴
hUCB-MDSCs 1x10⁵
hUCB-MDSCs 1x10⁶
Filaggrin
Involucrin
Loricrin
CK10
CK14


FLG
IVL
LOR
Staining intensity
****
*
***
**
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10⁴
Df+hUCB-MDSC 1x10⁵
Df+hUCB-MDSC 1x10⁶

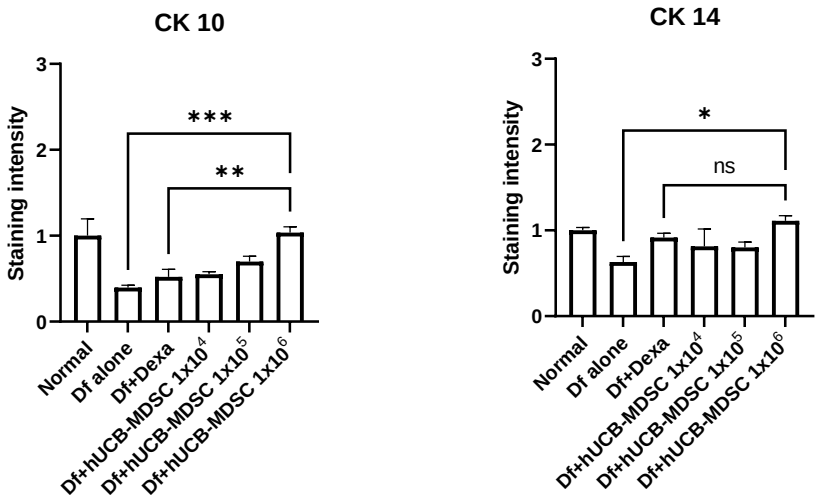
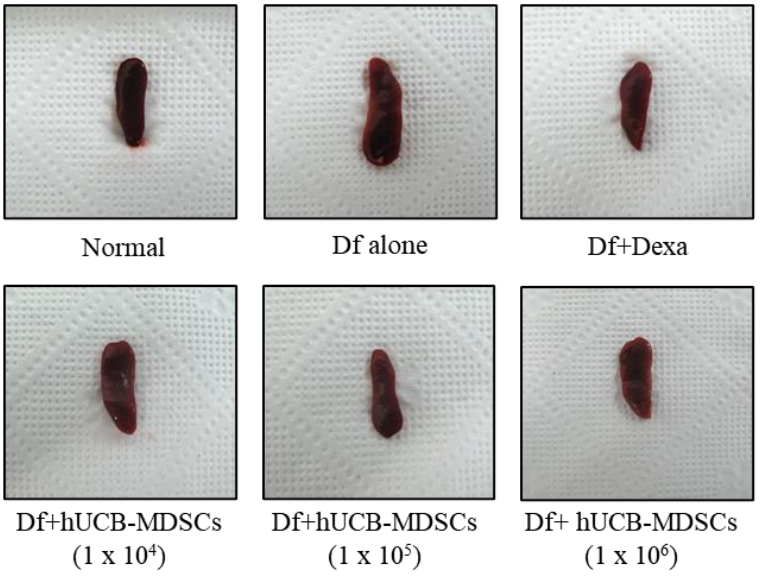
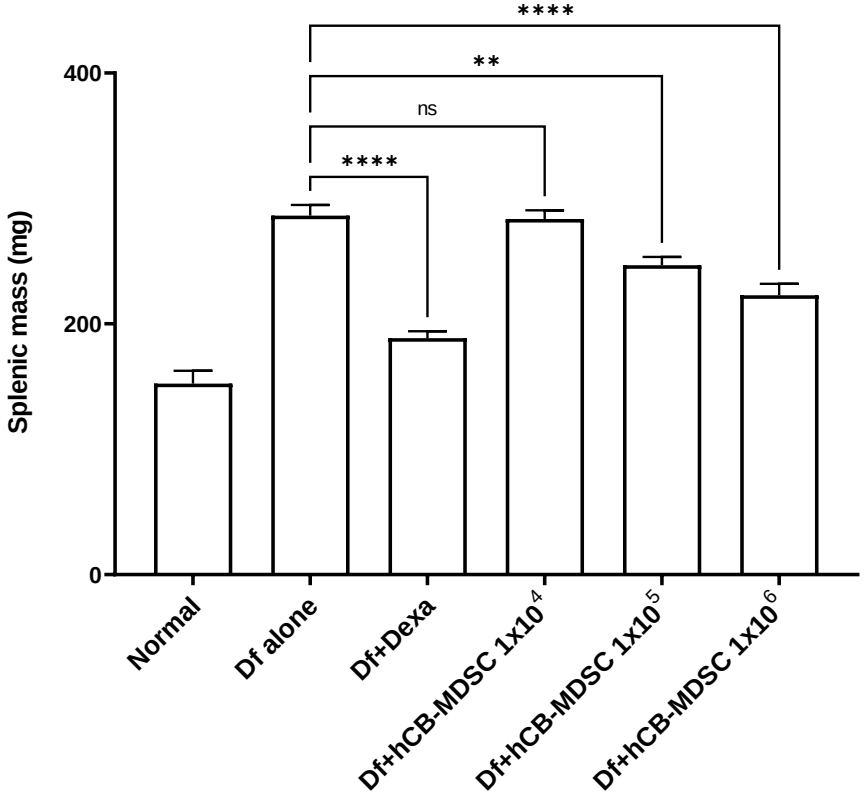

CK 10
CK 14
Staining intensity
***
**
*
ns
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10⁴
Df+hUCB-MDSC 1x10⁵
Df+hUCB-MDSC 1x10⁶

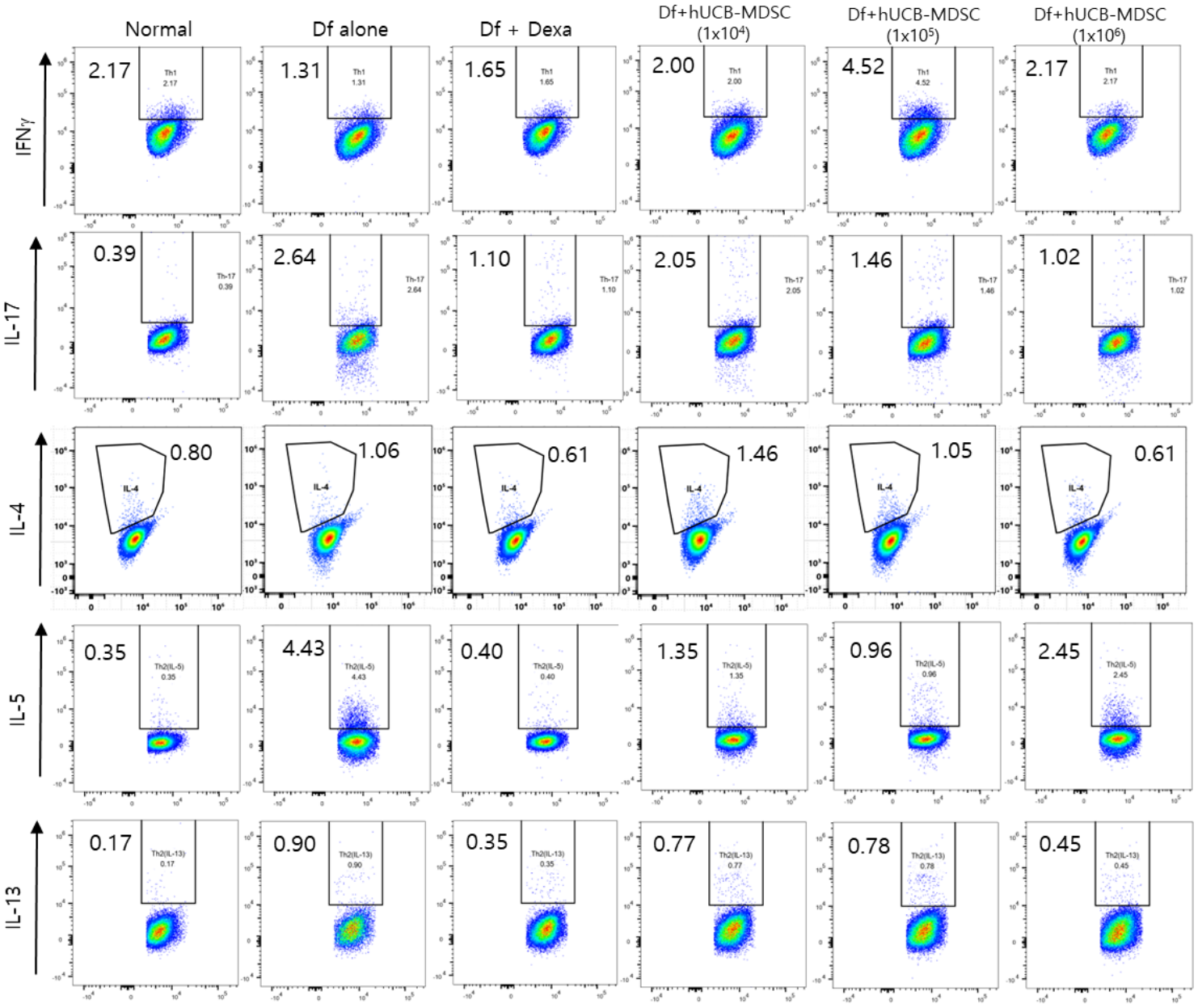
Figure 5. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on the regulation of differentiation to CD4+ T cell subsets.

A

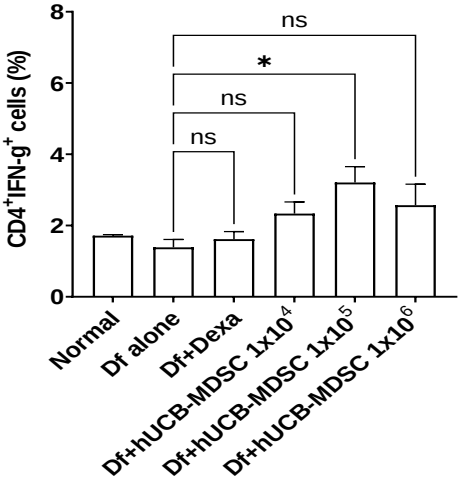


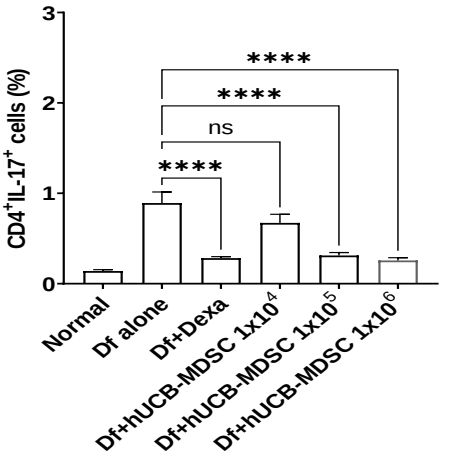


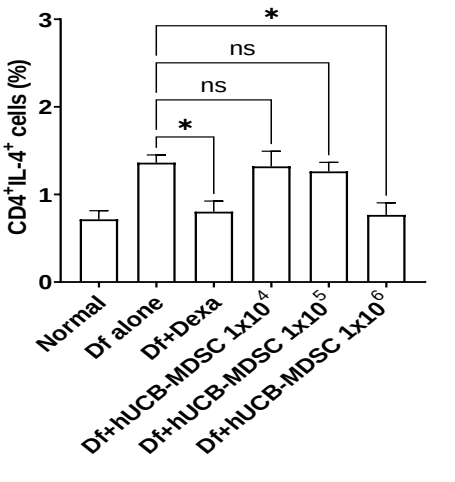
B

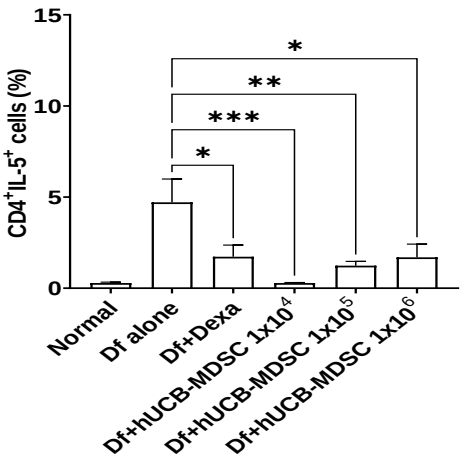

Normal
Df alone
Df + Dexa
Df+hUCB-MDSC (1x10⁴)
Df+hUCB-MDSC (1x10⁵)
Df+hUCB-MDSC (1x10⁶)
IFNγ
2.17
1.31
1.65
2.00
4.52
2.17
IL-17
0.39
2.64
1.10
2.05
1.46
1.02
IL-4
0.80
1.06
0.61
1.46
1.05
0.61
IL-5
0.35
4.43
0.40
1.35
0.96
2.45
IL-13
0.17
0.90
0.35
0.77
0.78
0.45

B (continued)


CD4+IFN-g+ cells (%)
ns
*
ns
ns
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-17+ cells (%)
****
****
ns
****
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-4+ cells (%)
*
ns
ns
*
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-5+ cells (%)
*
**
***
*
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6

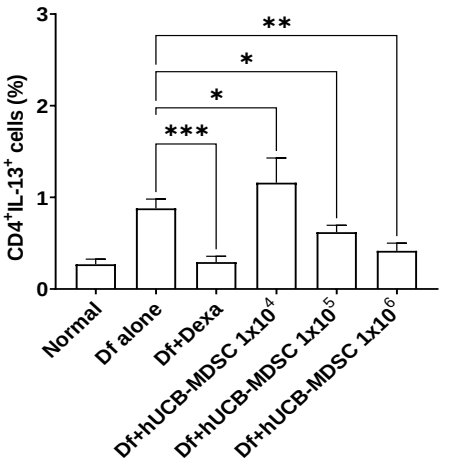
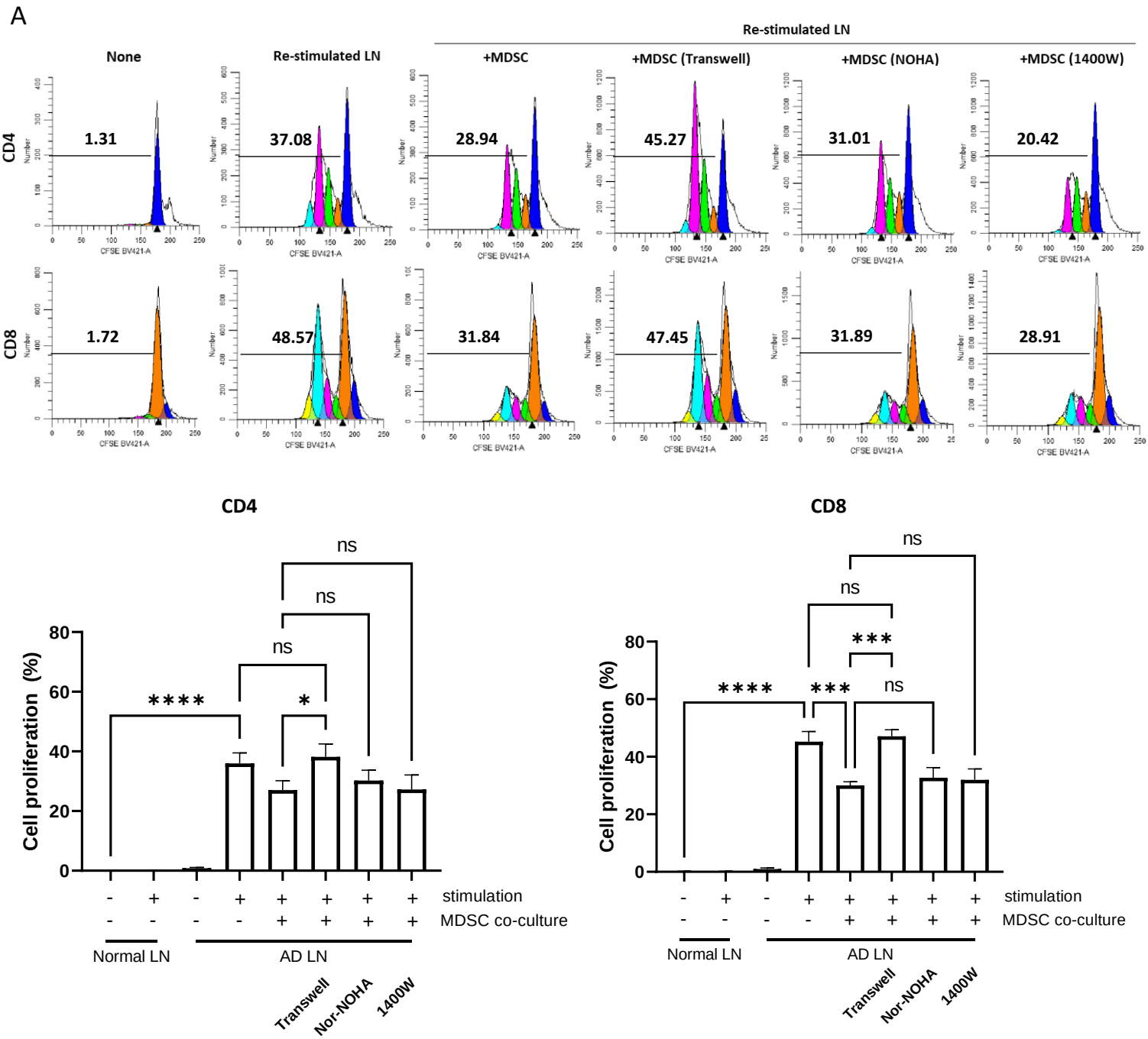
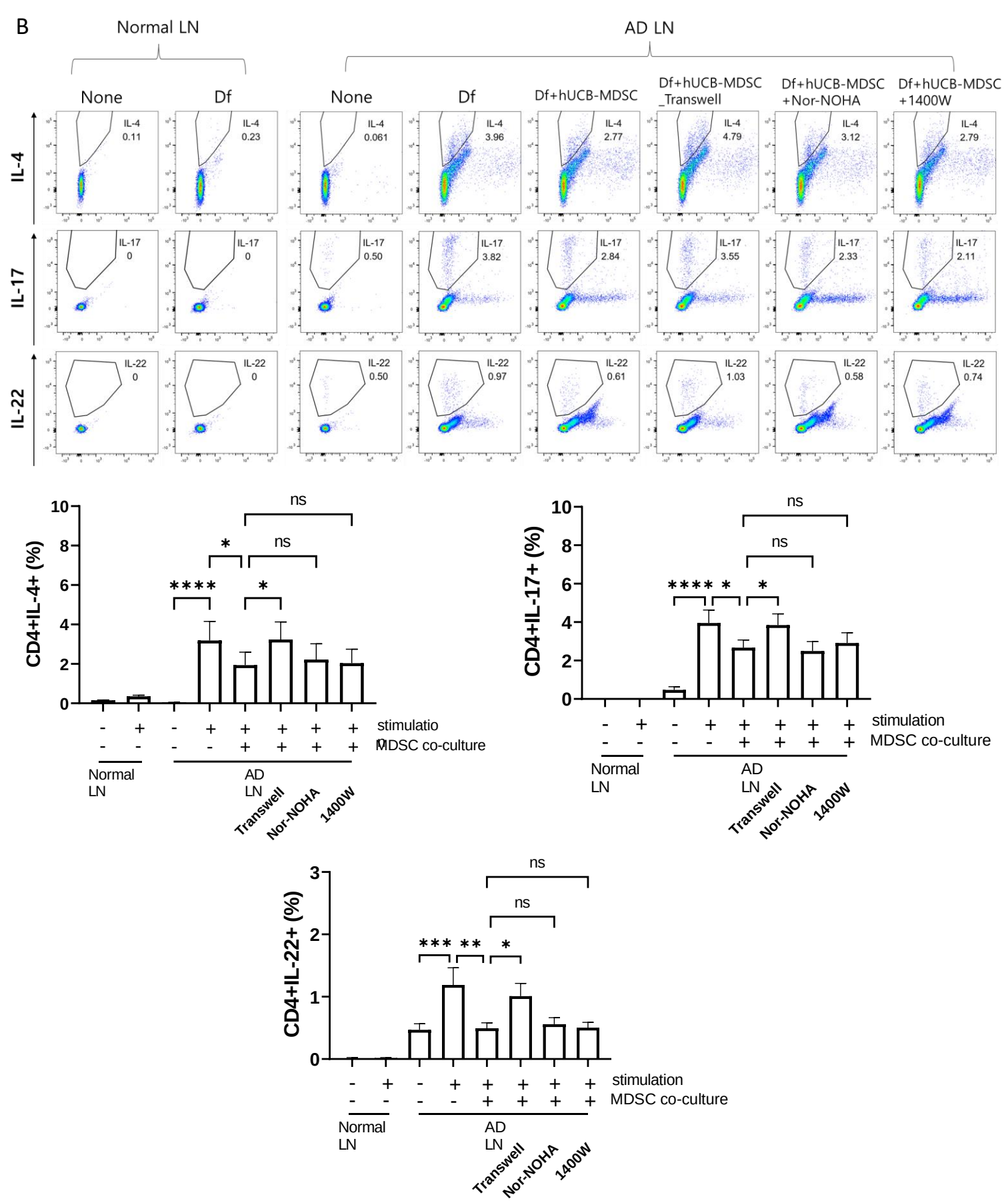

CD4+IL-13+ cells (%)
**
*
*
***
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6

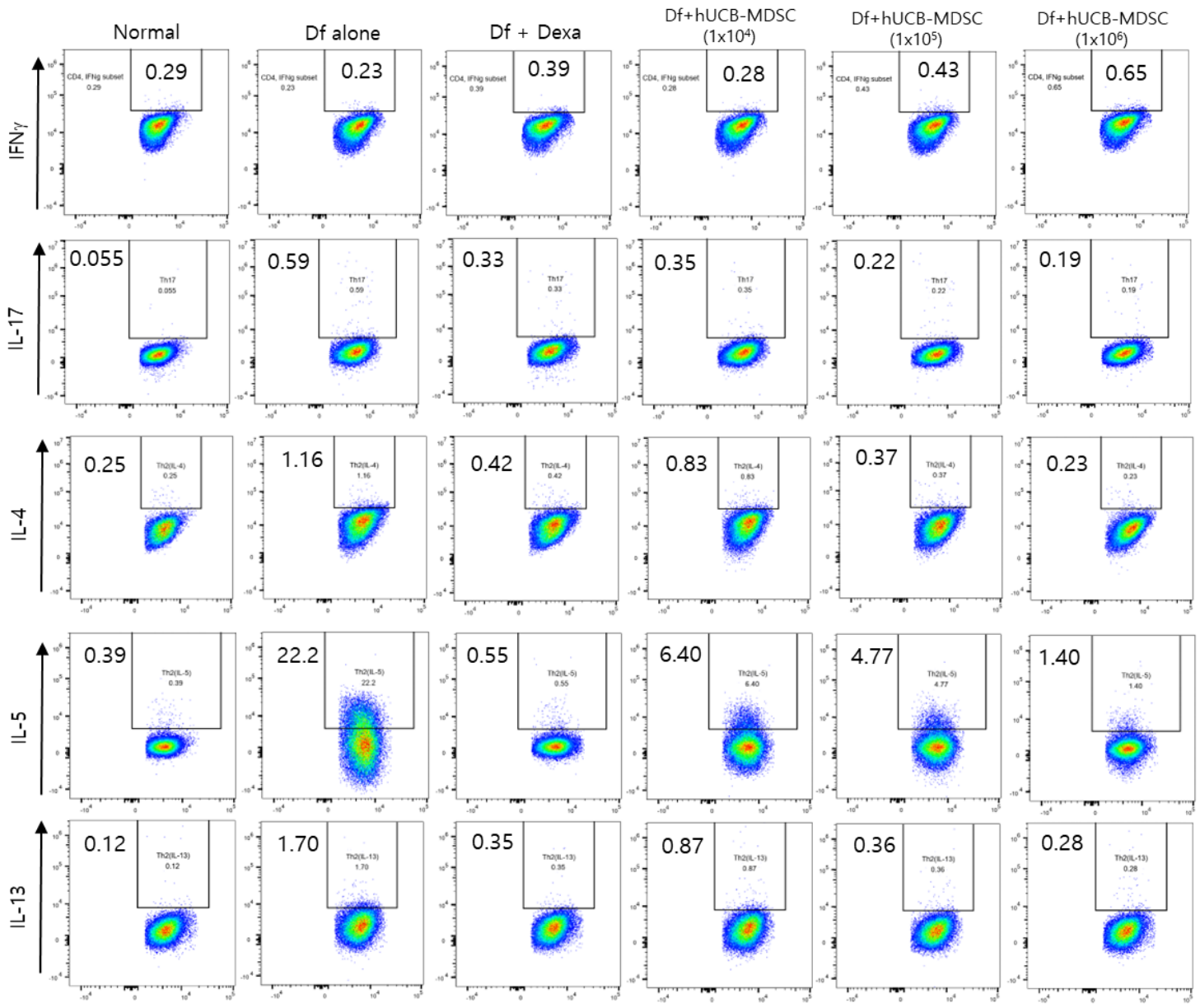
Figure 6. Mechanism of atopic dermatitis-immune cell regulation between human umbilical cord blood (hUCB)-myeloid-derived suppressor cells (MDSCs) and T cells in the atopic dermatitis (AD) mouse model.



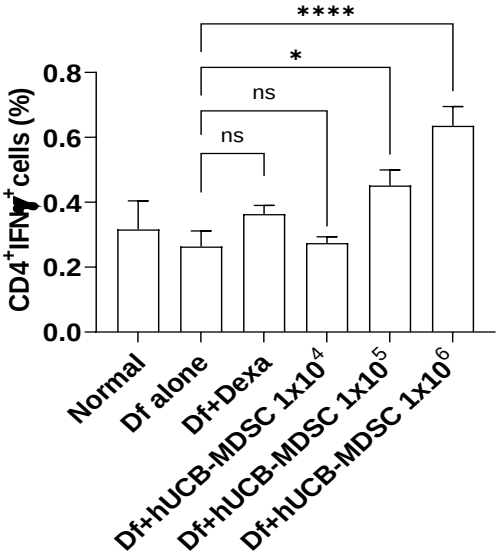

B
Normal LN
AD LN
None
Df
None
Df
Df+hUCB-MDSC
Df+hUCB-MDSC _Transwell
Df+hUCB-MDSC +Nor-NOHA
Df+hUCB-MDSC +1400W
IL-4
IL-17
IL-22
IL-4 0.11
IL-4 0.23
IL-4 0.061
IL-4 3.96
IL-4 2.77
IL-4 4.79
IL-4 3.12
IL-4 2.79
IL-17 0
IL-17 0
IL-17 0.50
IL-17 3.82
IL-17 2.84
IL-17 3.55
IL-17 2.33
IL-17 2.11
IL-22 0
IL-22 0
IL-22 0.50
IL-22 0.97
IL-22 0.61
IL-22 1.03
IL-22 0.58
IL-22 0.74
CD4+IL-4+ (%)
CD4+IL-17+ (%)
CD4+IL-22+ (%)
ns
*
****
stimulation
MDSC co-culture
Normal LN
AD LN
Transwell
Nor-NOHA
1400W

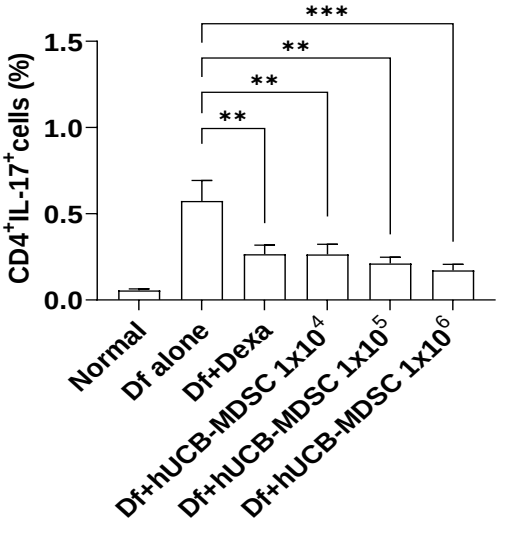
Supplementary Figure 4. Effects of human umbilical cord blood (hUCB)-myeloid-derived suppressor cell (MDSC) therapy on axillary lymph nodes (LNs).

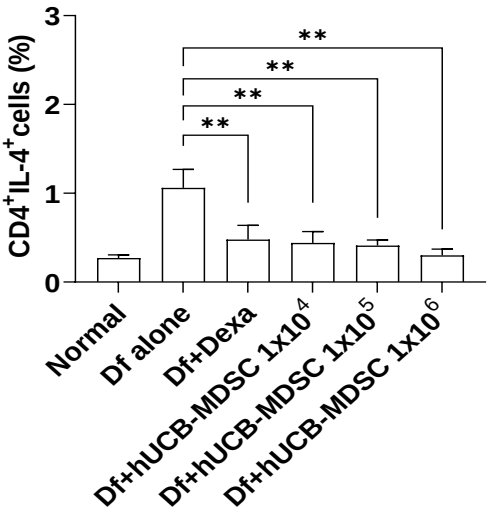
A

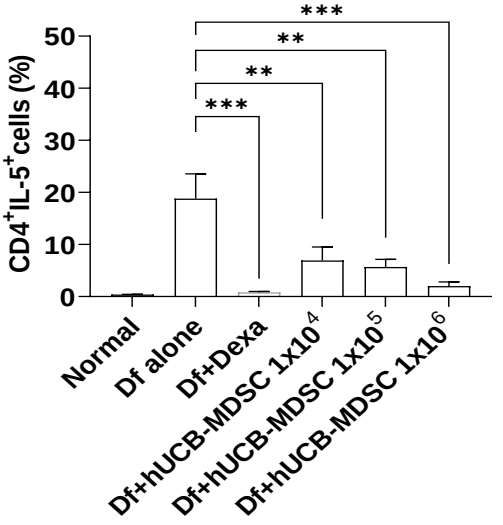


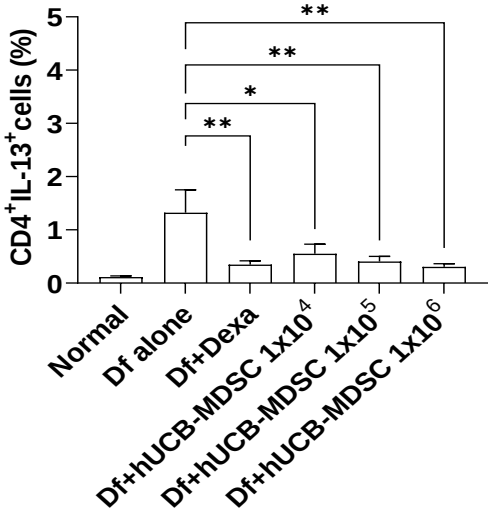
B


CD4+IFNγ+cells (%)
0.0
0.2
0.4
0.6
0.8
****
*
ns
ns
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-17+cells (%)
0.0
0.5
1.0
1.5
***
**
**
**
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-4+cells (%)
0
1
2
3
**
**
**
**
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-5+cells (%)
0
10
20
30
40
50
***
**
**
***
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6


CD4+IL-13+cells (%)
0
1
2
3
4
5
**
**
*
**
Normal
Df alone
Df+Dexa
Df+hUCB-MDSC 1x10^4
Df+hUCB-MDSC 1x10^5
Df+hUCB-MDSC 1x10^6