Rapid paper

Immunomodulatory effects of dental pulp stem cells on lymphocytes and monocytes from patients with rheumatoid arthritis

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ABSTRACT

Objective. *To investigate the immunomodulatory effects of dental pulp stem cells (DPSCs) on lymphocytes and monocytes from rheumatoid arthritis (RA) patients unresponsive to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs).*

Methods. *Peripheral blood lymphocytes and monocytes were isolated from 12 RA patients unresponsive to csDMARDs. Lymphocytes were activated using anti-CD3/CD28 beads or with CpG ODN 2006, and monocytes with LPS. After 48 hours of co-culture with DPSCs, the expression of 7 immune checkpoints on DPSCs was analysed by flow-cytometry, and 17 cytokines were quantified in the supernatants.*

Results. *Co-culture of DPSCs with CD3/CD28-activated lymphocytes or LPS-activated monocytes increased the expression of PD-L1, PD-L2, CD155, and Galectin-9 on DPSCs. In contrast, lymphocytes activated with ODN 2006 did not alter immune checkpoint expression. CD80, CD86, and 4-1BBL expression was not induced under any condition. Co-culture with DPSCs reduced levels of sFas-L, IFNγ, sIL-6RA, MIP-1β, TNFα in supernatants of CD3/CD28-activated lymphocytes; and BAFF, sFas-L, IL-1β, sIL-6RA, IL-9, IL-17A, IL-18, IL-23, M-CSF, perforin, TNFα in supernatants of LPS-activated monocytes. IL-6 and IP-10 levels increased in all experimental conditions, while IL-9 increased in ODN 2006- and CD3/CD28-stimulated lymphocyte cultures. DPSCs showed differential effects depending on the activation status of lymphocytes and monocytes.*

Conclusion. *The overexpression of inhibitory immune checkpoints by DPSCs may contribute to their immunomodulatory effects. DPSCs modulated a broader range of cytokines in monocyte supernatants compared to lymphocytes.*

Introduction

Rheumatoid arthritis (RA) affects 0.5–1% of European adults, causing joint damage and disability (1). Despite advances in disease-modifying anti-rheumatic drugs (DMARDs) (2), around 30% of patients respond poorly (3), underscoring the need for better treatments. Mesenchymal stem cells (MSCs) are multipotent non-haematopoietic stem cells with regenerative and immunomodulatory abilities, tested in autoimmune disease trials (4). Though generally safe, small sample sizes and inconsistent protocols leave their effectiveness unclear. MSCs modulate innate and adaptive immunity via cell contact and soluble factors, including extracellular vesicles (4,5). This study used dental pulp-derived MSCs: DPSCs (6). Most RA-related MSC research is based on animal models or healthy donor cells, with limited data from RA patients (7). In the collagen-induced arthritis mouse model of RA, MSC administration has been found to increase T lymphocytes hypo-responsiveness, promote the proliferation of regulatory T lymphocytes, modulate fibroblast-like synoviocyte and osteoclast activation, and decrease Th1/Th17 expansion as well as systemic concentrations of inflammatory cytokines (7). Understanding MSC mechanisms could improve their clinical application.

MSC-based therapies may benefit RA patients who are unresponsive to current treatments (8). This study investigated the effects of DPSCs on lymphocytes

and monocytes from conventional synthetic DMARDs (csDMARDs)-refractory RA patients, focusing on immune checkpoint expression on DPSCs and cytokine levels after direct co-culture.

Material and methods

Cohort of patients

We enrolled 12 adult RA patients satisfying the ACR/EULAR 2010 classification criteria (9), who had an inadequate response to csDMARD therapy. Remission was defined according to ACR/EULAR criteria (10) using either a Boolean or an index-based approach. The study was approved by the Local Ethics Committee of Reggio Emilia, Italy (protocol no. 1421/2020/TESS/AUSLRE–RF-2019-12370609), following the Declaration of Helsinki. Written informed consent was obtained from all patients.

DPSCs

Human DPSCs were purchased from CTIBiotech and expanded in alpha-MEM (catalog: 22561) supplemented with 10% heat-inactivated FBS, 100 U/ml penicillin plus 100 mg/ml streptomycin (all from Gibco, ThermoFisher) and routinely cultured at 37°C, 5% CO_2.

Isolation of lymphocytes and monocytes from peripheral blood mononuclear cells

Information regarding the collection of peripheral blood mononuclear cells (PBMCs) is reported in the online Supplementary file. PBMCs were thawed, and manually counted with a haemocytometer. Viability was evaluated by Trypan Blue solution. Lymphocytes and monocytes were isolated from patients' PBMCs using the Miltenyi Biotec's MAgnetic Cell Separation (MACS) technology. Monocytes were isolated by positive cell selection with anti-CD14-MicroBeads (Miltenyi Biotec), following the manufacturer's protocol. Lymphocytes were collected as unlabeled cells in the flowthrough (negative selection). Evaluation of sorting efficiency is reported in the Supplementary file.

Co-culture system

In order to evaluate DPSC immunomodulatory properties, direct co-cultures were performed between DPSCs and lymphocytes or monocytes that were unstimulated or activated with different stimuli: CD3/CD28 Dynabeads™ (Gibco, ThermoFisher) for T lymphocyte activation; ODN 2006-G5 (InvivoGen) at 1 μM concentration for B lymphocyte activation; LPS (Sigma-Aldrich) at 0.1 ng/mL for monocyte activation. Details are reported in the Supplementary file.

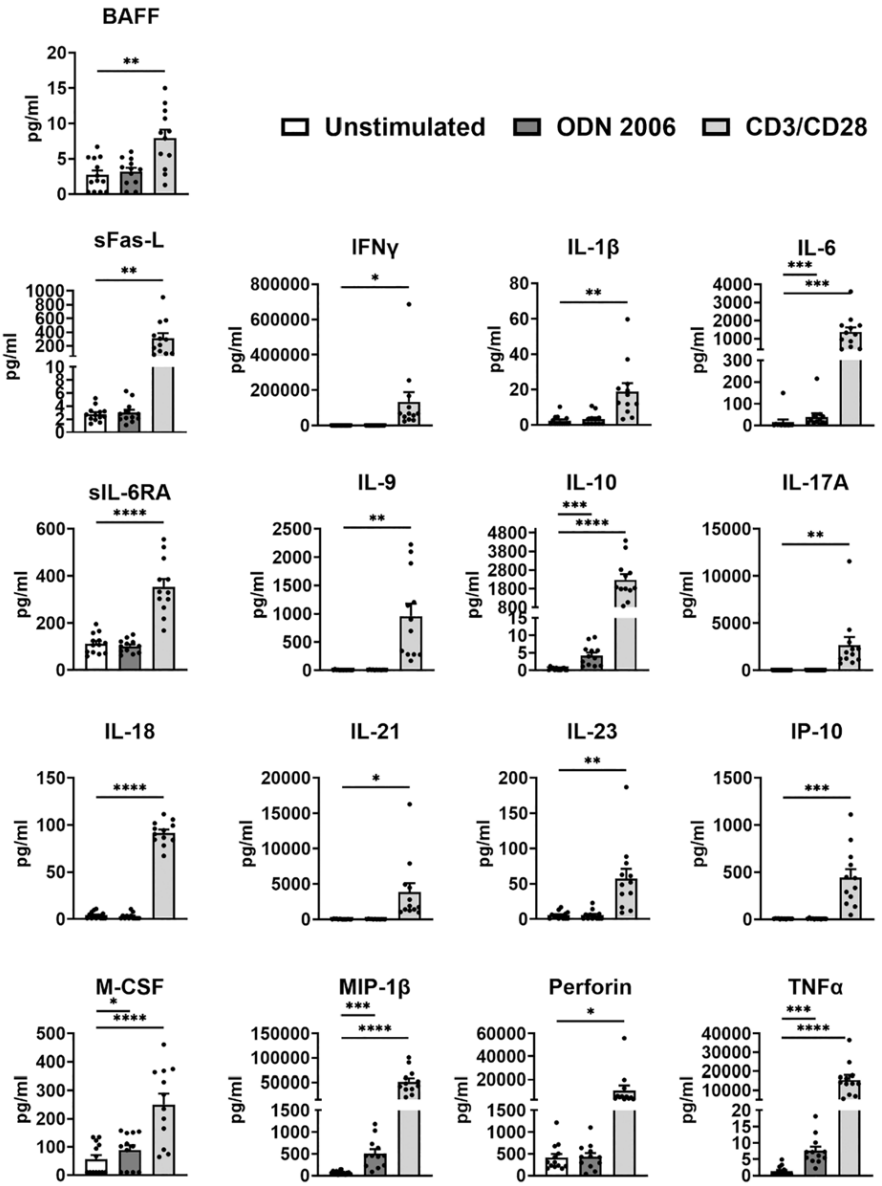

Fig. 1. Effects of lymphocyte stimulation. Concentrations of 17 cytokines were quantified in culture supernatants after 48 hours of treatment of lymphocytes with ODN 2006 and CD3/CD28 antibody-coated beads. Means with SEM are shown. Data were analysed with a paired Student's t-test (stimulated *versus* unstimulated). * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$.

Collection of supernatants and evaluation of immune checkpoint expression on DPSCs

After 48 hours, supernatants were collected for cytokine quantification, and DPSCs were analysed by flow cytometry for the expression of PD-L1, PD-L2, CD155, Galectin-9, CD80, CD86, and 4-1BBL. The protocol of flow cytometry is detailed in the Supplementary file. The gating strategies are shown in Supplementary Figures S1, S2, S3.

Cytokine quantification in supernatants

Concentrations of 16 cytokines were determined using a custom human ProcartaPlex Mix&Match 16-plex (ThermoFisher). IL-6 levels were quantified

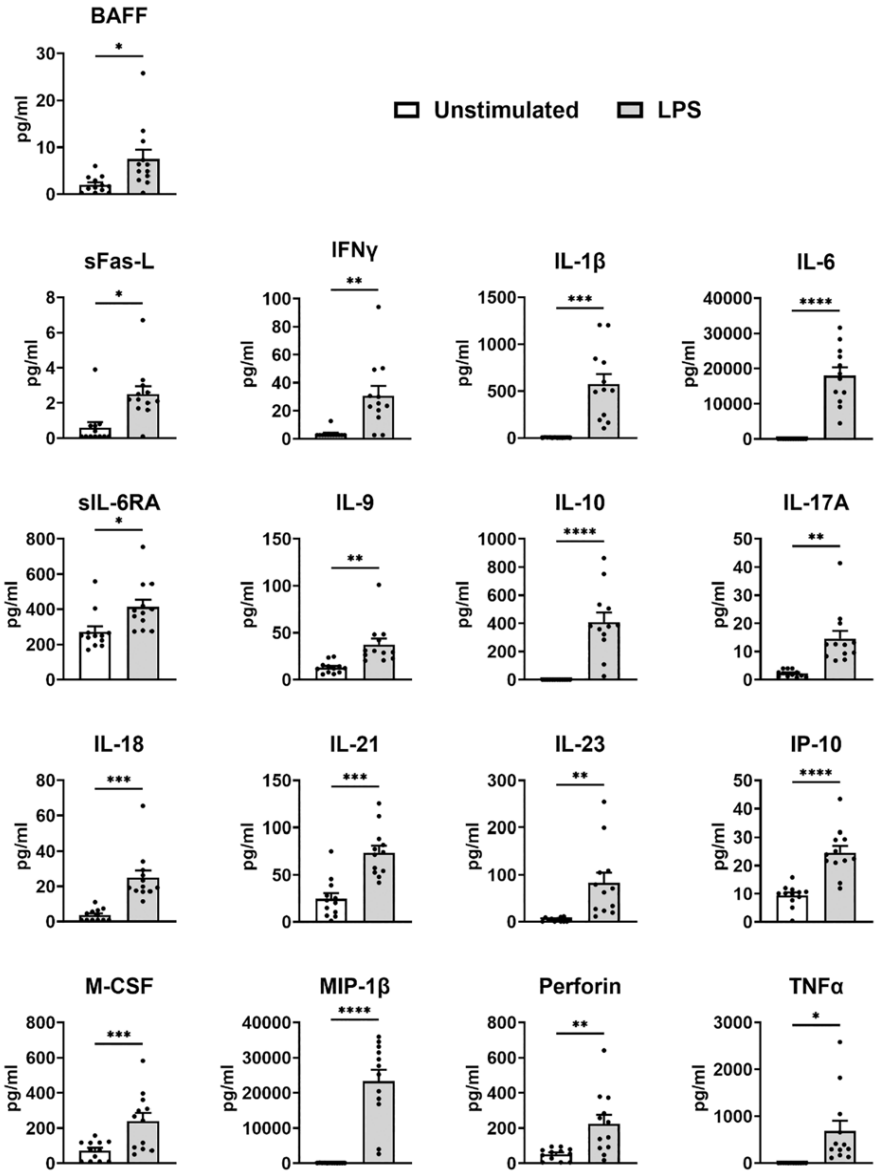

Fig. 2. Effects of monocyte stimulation. Concentrations of 17 cytokines were quantified in culture supernatants after 48 hours of treatment of monocytes with LPS. Means with SEM are shown. Data were analysed with a paired Student's t-test. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$.

with the human IL-6 DuoSet ELISA (R&D Systems). Details are reported in the Supplementary file. Lower detection limits of the assays are as follows: BAFF=1.0 pg/ml; sFas-L=0.5 pg/ml; IFNγ=11.4 pg/ml; IL-1β=2.9 pg/ml; IL-6=2.3 pg/ml; sIL-6RA=0.2 pg/ml; IL-9=2.5 pg/ml; IL-10=0.4 pg/ml; IL-17A=0.9 pg/ml; IL-18=3.8 pg/ml; IL-21=4.9 pg/ml; IL-23=3.3 pg/ml; IP-10=1.6 pg/ml; M-CSF=40.3 pg/ml; MIP-1β=2.4 pg/ml; Perforin=20.0 pg/ml; TNF-α=2.2 pg/ml.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 10. Cytokine concentrations in supernatants were compared using a paired *t*-test. Fold changes induced by co-culture with DPSCs were analysed with a one-sample *t*-test ≠ 1. *p*-values less than 0.05 were considered significant, and fold changes >|1.5| were regarded as biologically significant.

Data repository

The raw data have been deposited in Zenodo (https://zenodo.org/; doi: 10.5281/zenodo.15089978; doi: 10.5281/zenodo.15090064).

Results

Patients

PBMCs were collected from RA patients with active disease who showed inadequate response to csDMARD therapy. Therapy details are in Supplementary Table S1. No patients had infections or cancers at the time of sampling.

Activation of lymphocytes and monocytes in vitro

The mean purity of lymphocytes sorted from PBMCs was 97.2% ± 0.4 standard error of the mean (SEM); that of sorted monocytes was 95.7% ± 0.9 SEM.

To simulate tissue-level inflammation, lymphocytes and monocytes were treated with anti-CD3/CD28 antibody-coated beads, ODN 2006-G5, and LPS. Binding CD3/CD28 activates T lymphocytes. ODN 2006, a synthetic oligonucleotide with unmethylated CpG motifs, binds Toll-like receptor 9 (TLR9), activating B lymphocytes. LPS binds TLR4, activating innate immune cells like monocytes/macrophages and dendritic cells.

Cytokine concentrations in supernatants from unstimulated lymphocytes and monocytes were often low, near the detection limits of the assays. However, sFas-L, sIL-6RA, IL-17A, MIP-1β, and Perforin were detected in all unstimulated lymphocyte supernatants, while sIL-6RA, IL-9, IL-17A, and MIP-1β were detected in all unstimulated monocyte supernatants.

Treatment of lymphocytes with CD3/CD28 beads resulted in a statistically significant up-regulation of all cytokines (Fig. 1), and in increase in forward- and side-scatters of the cells indicating activation (Suppl. Fig. S4).

Treatment of lymphocytes with ODN 2006 resulted in a statistically significant up-regulation of IL-10, TNF-α, IL-6, and MIP-1β (Fig. 1). Lymphocyte activation following ODN 2006 treatment was further confirmed by an increase in CD80 expression on CD19+ B lymphocytes, with 723 median fluorescence intensity (MFI) for treated cells compared to 228 MFI for untreated cells.

Treatment of monocytes with LPS resulted in a statistically significant up-regulation of all cytokines (Fig. 2).

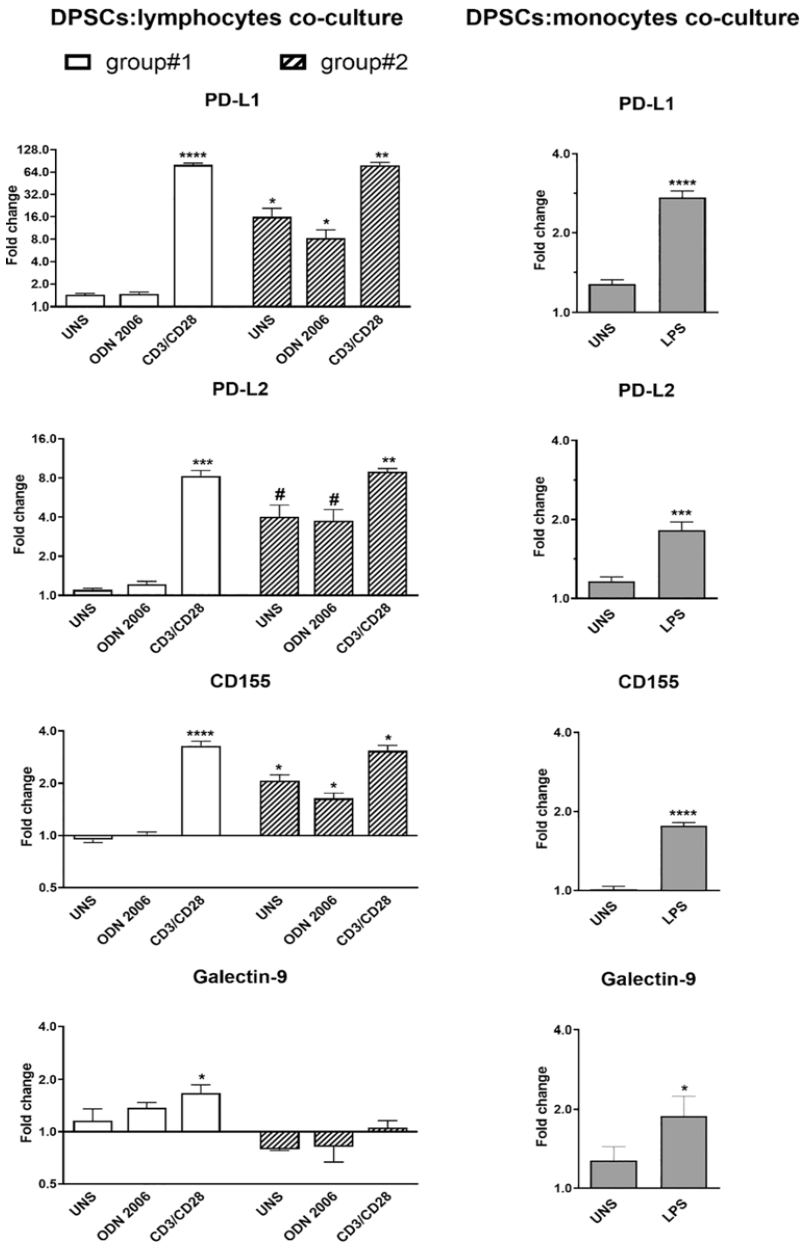

Fig. 3. Effects of the co-culture on immune checkpoint expression by DPSCs. Expression of PD-L1, PD-L2, CD155, and Galectin-9 was determined by flow cytometry on DPSC after co-culture with lymphocytes or monocytes, both unstimulated (UNS) and stimulated. Fold changes = median fluorescence intensities of the markers on DPSCs after co-culture / DPSCs cultured alone. Means with SEM are shown. Data were analysed with one-sample *t*-test ≠ 1.
* $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$. # fold changes > | 1.5 | in all the samples.
Group no.1 includes 8 patients, group no. 2 includes 4 patients.

Expression of immune checkpoints on DPSCs after co-culture

DPSCs expressed PD-L1 (mean MFI = 351±16 SEM), PD-L2 (mean MFI = 3154±217 SEM), CD155 (mean MFI = 1293 ± 40 SEM), and Galectin-9 (mean MFI = 710±190 SEM), but did not express CD80, CD86, and 4-1BBL.

Co-culture with unstimulated lymphocytes showed two patient groups: one with no modulation (n=8, group no. 1 in Fig. 3), and another with increased PD-L1, PD-L2, and CD155 expression on DPSCs (n=4, group no. 2 in Fig. 3). Galectin-9 expression on DPSCs was not modulated by co-culture with unstimulated lymphocytes (Fig. 3).

Co-culture between DPSCs and ODN 2006-stimulated lymphocytes produced results similar to those with unstimulated lymphocytes (Fig. 3).

Co-culture between DPSCs and CD3/CD28-stimulated lymphocytes consistently increased PD-L1 (mean MFI = 27956 ± 1024 SEM), PD-L2 (mean MFI = 24353±1559 SEM), and CD155 (mean MFI = 4139±155 SEM) expression on DPSCs. Galectin-9 expression was only increased following co-culture with CD3/CD28-stimulated lymphocytes from patient group no. 1 (mean MFI = 974±196 SEM) (Fig. 3).

Co-culture between DPSCs and unstimulated monocytes did not affect immune checkpoint expression on DPSCs. However, co-culture with LPS-stimulated monocytes increased PD-L1 (mean MFI = 1024±89 SEM), PD-L2 (mean MFI = 5600±476 SEM), CD155 (mean MFI = 2218±74 SEM), and Galectin-9 (mean MFI = 1359±324 SEM) expression on DPSCs (Fig. 3). Monocytes from all patients showed similar results, so the cohort was not split.

CD80, CD86, and 4-1BBL expression was not induced by any co-culture condition.

Modulation of cytokine concentrations in supernatants by DPSCs co-culture

To determine the effects of DPSCs on cytokine production, we quantified 17 cytokines in supernatants from lymphocytes or monocytes co-cultured with DPSCs, comparing them to those from lymphocytes or monocytes cultured alone (both unstimulated and stimulated). Among the cytokines studied, DPSCs produced only IL-6 (mean = 57.6 pg/ml ± 2.6 SEM) and sIL-6RA (mean = 22.5 pg/ml ± 2.4 SEM).

To interpret the co-culture data between DPSCs and lymphocytes, patients were grouped based on whether their unstimulated lymphocytes induced PD-L1, PD-L2, and CD155 on DPSCs. Supernatants from group no. 2 unstimulated lymphocytes showed higher concentrations of 16/17 cytokines, while those from group no. 1 had higher IL-6 and lower BAFF, sFas-L, IL-21 concentrations (Fig. 4, Suppl. Fig. S5 and S6).

Supernatants from group no. 2 lymphocytes stimulated with ODN 2006 showed higher concentrations of 9/17 cytokines, while those from group no. 1 had higher IL-6, IL-9, IP-10, and lower BAFF concentrations (Fig. 4, Suppl. Fig. S7 and S8).

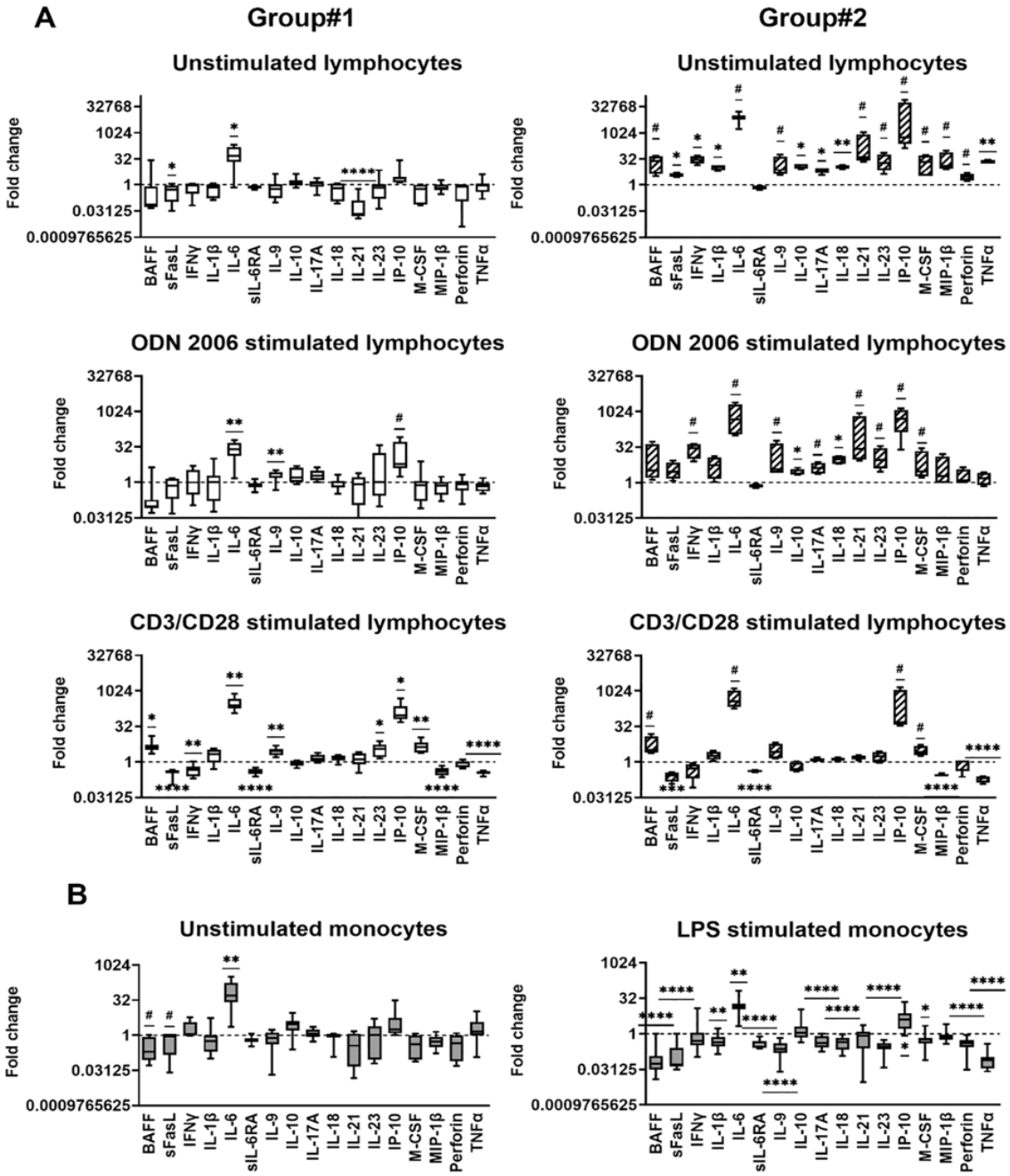

Fig. 4. Effects of the co-culture on cytokine concentrations in supernatants. Fold changes = cytokine concentrations following co-culture / cytokine concentrations by lymphocytes or monocytes cultured alone, both unstimulated and stimulated. Box and whiskers (min to max) are shown. Data were analysed with one-sample *t*-test ≠ 1. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$. # fold changes > | 1.5 | in all the samples where cytokines were detected.
A: Data on lymphocytes from the two groups of patients. Group no. 1 includes 8 patients, group no. 2 includes 4 patients.
B: Data on monocytes from all the patients.

CD3/CD28-stimulated lymphocytes from both patient groups yielded comparable results (Fig. 4). Co-culture with DPSCs led to a decrease in sFas-L, IFNγ, sIL-6RA, MIP-1β, TNF-α, and an increase in BAFF, IL-6, IL-9, IP-10, M-CSF levels (Suppl. Fig. S9).

DPSCs modulated several cytokines in monocytes. Supernatants from both unstimulated and LPS-stimulated monocytes showed consistent decreases in BAFF, sFas-L, IL-1β, sIL-6RA, M-CSF, Perforin, along with an increase in IL-6 after co-culture with DPSCs. Additionally, supernatants from LPS-stimulated monocytes showed decreased IL-9, IL-17, IL-18, IL-23, TNF-α, while IP-10 levels were increased (Fig. 4, Suppl. Fig. S10 and S11).

Discussion

This study aimed to explore the immunomodulatory mechanisms of DPSCs as a potential therapy for RA. Unlike previous studies, we focused on: (i) PBMCs from RA patients rather than healthy donors; (ii) isolated lymphocytes and monocytes instead of whole PBMCs; (iii) both resting and activated immune cells; and (iv) MSCs derived from dental

pulp. T lymphocytes were activated via CD3/CD28, B lymphocytes via TLR9, and monocytes via TLR4. We analysed the expression of 7 immune checkpoints on DPSCs: PD-L1, PD-L2, Galectin-9 with inhibitory effects; CD86, 4-1BBL with activatory effects; CD80, CD155 with dual roles, and quantified cytokines linked to T lymphocyte, B lymphocyte, and monocyte functions in culture supernatants.

DPSCs had different effects on unstimulated *versus* stimulated lymphocytes and monocytes, indicating that systemic MSC administration may yield different outcomes compared to intra-articular delivery, where MSCs directly interact with activated immune cells and the inflammatory microenvironment.

Following co-culture with CD3/CD28-stimulated lymphocytes and LPS-stimulated monocytes, DPSCs upregulated PD-L1, PD-L2, CD155, and Galectin-9. This likely results from inflammatory cytokines (*e.g.* IFNγ and TNFα) induced *in vitro*, known to drive immune checkpoint expression. While our group previously reported PD-L1 upregulation in similar conditions (11), the increased expression of PD-L2, CD155, and Galectin-9 is novel. These markers have also been found on bone marrow-derived MSCs (12-14), highlighting their potential role in DPSC-mediated immunosuppression.

Cytokine profiling of supernatants showed that DPSCs strongly influenced the IL-6 pathway, markedly increasing IL-6 (up to 667,000 pg/ml) while reducing sIL-6RA. This suggests a shift toward IL-6 classical signalling over trans-signalling. We previously reported IL-6 upregulation in DPSCs exposed to activated PBMCs (11,15), and recent studies highlight IL-6 as a key regulator of MSC immunosuppressive properties (16, 17).

DPSC co-culture altered cytokine levels in supernatants from CD3/CD28-activated lymphocytes and LPS-stimulated monocytes, with pronounced effects on monocyte-derived supernatants. This suggests a strong influence of DPSC on monocyte function, consistent with reports that MSCs can reprogram macrophages toward an anti-inflammatory, pro-repair phenotype (18).

To interpret lymphocyte data, we divided patients into two groups because unstimulated lymphocytes from 4 patients triggered immune checkpoint expression on DPSCs and elevated cytokine levels after co-culture. We suspect this was due to DPSC-induced lymphocyte activation, likely driven by the use of allogenic DPSCs. Although MSCs were once considered immune-privileged, studies show immune responses can occur against donor antigens (19). The extent of this allo-immune response likely depends on MHC mismatch, underscoring the need to consider MHC compatibility in allogenic MSC therapies.

We assessed the effects of DPSCs on lymphocytes and monocytes from RA patients unresponsive to csDMARDs, based on the hypothesis that MSC therapies could be applied as second-line treatments. Comparing the effects of DPSCs on samples from patients who are unresponsive *versus* responsive to csDMARDs may reveal differences between these two subsets of patients.

References

1. D'ORAZIO A, CIRILLO AL, GRECO G *et al*.: Pathogenesis of rheumatoid arthritis: one year in review 2024. *Clin Exp Rheumatol* 2024; 42(9): 1707-13. https://doi.org/10.55563/clinexprheumatol/0307ed
2. CONLEY B, BUNZLI S, BULLEN J *et al*.: What are the core recommendations for rheumatoid arthritis care? Systematic review of clinical practice guidelines. *Clin Rheumatol* 2023; 42(9): 2267-78. https://doi.org/10.1007/s10067-023-06654-0
3. LEWIS MJ: Predicting best treatment in rheumatoid arthritis. *Semin Arthritis Rheum* 2024; 64S: 152329. https://doi.org/10.1016/j.semarthrit.2023.152329
4. CHEN B, CHEN Z, HE M, ZHANG L, YANG L, WEI L: Recent advances in the role of mesenchymal stem cells as modulators in autoinflammatory diseases. *Front Immunol* 2024; 15: 1525380. https://doi.org/10.3389/fimmu.2024.1525380
5. QI W, LI F, WANG G *et al*.: The effects of mesenchymal stem cells-derived exosomes in rheumatoid arthritis: a review. *Clin Exp Rheumatol* 2024; 42(7): 1495-506. https://doi.org/10.55563/clinexprheumatol/l49ccg
6. PISCIOTTA A, CARNEVALE G, MELONI S *et al*.: Human dental pulp stem cells (hDPSCs): isolation, enrichment and comparative differentiation of two sub-populations. *BMC Dev Biol* 2015; 15: 14. https://doi.org/10.1186/s12861-015-0065-x
7. PIGNATTI E, MACCAFERRI M, PISCIOTTA A, CARNEVALE G, SALVARANI C: A comprehensive review on the role of mesenchymal stromal/stem cells in the management of rheumatoid arthritis. *Expert Rev Clin Immunol* 2024; 20(5): 463-84. https://doi.org/10.1080/1744666x.2023.2299729
8. LIU R, ZHAO P, TAN W, ZHANG M: Cell therapies for refractory rheumatoid arthritis. *Clin Exp Rheumatol* 2018; 36(5): 911-19.
9. KAY J, UPCHURCH KS: ACR/EULAR 2010 rheumatoid arthritis classification criteria. *Rheumatology* (Oxford) 2012; 51 (Suppl. 6): vi5-9. https://doi.org/10.1093/rheumatology/kes279
10. FELSON DT, SMOLEN JS, WELLS G *et al*.: American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum* 2011; 63(3) :573-86. https://doi.org/10.1002/art.30129
11. DI TINCO R, BERTANI G, PISCIOTTA A *et al*.: Role of PD-L1 in licensing immunoregulatory function of dental pulp mesenchymal stem cells. *Stem Cell Res Ther* 2021; 12(1): 598. https://doi.org/10.1186/s13287-021-02664-4
12. KRUEGER TE, THOREK DLJ, MEEKER AK, ISAACS JT, BRENNEN WN: Tumor-infiltrating mesenchymal stem cells: Drivers of the immunosuppressive tumor microenvironment in prostate cancer? *Prostate* 2019; 79(3): 320-30. https://doi.org/10.1002/pros.23738
13. LIU ZY, DENG L, JIA Y *et al*.: CD155/TIGIT signalling plays a vital role in the regulation of bone marrow mesenchymal stem cell-induced natural killer-cell exhaustion in multiple myeloma. *Clin Transl Med* 2022; 12(7): e861. https://doi.org/10.1002/ctm2.861
14. GIESEKE F, KRUCHEN A, TZARIBACHEV N, BENTZIEN F, DOMINICI M, MÜLLER I: Proinflammatory stimuli induce galectin-9 in human mesenchymal stromal cells to suppress T-cell proliferation. *Eur J Immunol* 2013; 43(10): 2741-49. https://doi.org/10.1002/eji.201343335
15. CROCI S, BONACINI M, DOLCI G *et al*.: Human dental pulp stem cells modulate cytokine production in vitro by peripheral blood mononuclear cells from Coronavirus disease 2019 patients. *Front Cell Dev Biol* 2021; 8: 609204. https://doi.org/10.3389/fcell.2020.609204
16. HUANG P, ZHANG C, DELAWARY M, KORCHAK JA, SUDA K, ZUBAIR AC: Development and evaluation of IL-6 overexpressing mesenchymal stem cells (MSCs). *J Tissue Eng Regen Med* 2022; 16(3): 244-253. https://doi.org/10.1002/term.3274
17. DORRONSORO A, LANG V, FERRIN I *et al*.: Intracellular role of IL-6 in mesenchymal stromal cell immunosuppression and proliferation. *Sci Rep* 2020 14; 10(1): 21853. https://doi.org/10.1038/s41598-020-78864-4
18. BOUCHLAKA MN, MOFFITT AB, KIM J *et al*.: Human mesenchymal stem cell-educated macrophages are a distinct high IL-6-producing subset that confer protection in graft-versus-host-disease and radiation injury models. *Biol Blood Marrow Transplant* 2017; 23(6): 897-905. https://doi.org/10.1016/j.bbmt.2017.02.018
19. GRIFFIN MD, RYAN AE, ALAGESAN S, LOHAN P, TREACY O, RITTER T: Anti-donor immune responses elicited by allogeneic mesenchymal stem cells: what have we learned so far? *Immunol Cell Biol* 2013; 91(1): 40-51. https://doi.org/10.1038/icb.2012.67