Human Dental Pulp Stem Cells Suppress Alloantigen-induced Immunity by Stimulating T Cells to Release Transforming Growth Factor Beta

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Abstract

Introduction: Human dental pulp stem cells (hDPSCs) are ideal candidates for regenerating damaged dental tissue. To examine the possibility that hDPSCs may be used to regenerate pulp, we tested their *in vitro* effects on acute allogeneic immune responses. **Methods:** A peripheral blood mononuclear cell (PBMC) proliferation assay and immunoglobulin (Ig) production assay were performed to evaluate the immunosuppressive properties of hDPSCs. **Results:** The mixed lymphocyte reaction was suppressed by incubation with hDPSCs. Transforming growth factor beta (TGF-β) was the major soluble factor responsible for inhibiting the allogeneic proliferation of PBMCs. The production of IgM and IgG by allogeneic activation of responder B lymphocytes was also completely abrogated by TGF-β released from hDPSCs via interferon gamma in response to activation of the responder T lymphocytes. **Conclusions:** hDPSCs inhibit acute allogeneic immune responses by their release of TGF-β as a result of allogeneic stimulation of T lymphocytes. This study provides an insight into the potential clinical use of hDPSCs for allogeneic transplantation. *(J Endod 2016;■:1–9)*

Key Words

Allogeneic transplantation, human dental pulp stem cells, immunosuppression, pulp regeneration, transforming growth factor beta

Significance

hDPSCs have the potential to regenerate damaged pulp. This study shows that they are nonimmunogenic and have an immunosuppressive effect. It provides an insight into the potential clinical use of hDPSCs for pulp regeneration using allogeneic transplantation.

Mesenchymal stem cells (MSCs), which originate from the mesoderm, are self-renewing and multipotent and are found in a variety of adult tissues (1–7). Cultured MSCs express CD105, CD73, and CD90 on their surface but lack hematopoietic cell markers like CD11 b, CD19, CD34, CD45, and human leukocyte antigen D related (5). They are capable of differentiating into osteoblasts, chondrocytes, and adipocytes (2, 8). MSCs have been extensively studied because of their potential value in tissue regeneration as well as their immunosuppressive properties (6). MSCs exert their immunosuppressive actions mainly by releasing factors such as transforming growth factor beta (TGF-β), indoleamine 2,3-dioxygenase (IDO), interleukin (IL)-6, nitric oxide and prostaglandin E2, and human leukocyte antigen-G, which modulate the function of various immune cells and activate regulatory T cells (Treg) (9–14). Reciprocal interactions between MSCs and immune cells are required for optimal MSC-induced immunosuppression but can inhibit MSC-based tissue regeneration (7, 15, 16).

Dental tissues contain a variety of MSC-like cells including dental pulp stem cells (DPSCs), stem cells from apical papillae, progenitor cells from dental follicles, stem cells from periodontal ligaments, and stem cells from human exfoliated deciduous teeth (17–22). DPSCs are ideal candidates for regenerating damaged dental tissue because of their ready availability, high proliferation rate, multipotency, and resistance to freezing (17, 18, 22, 23). Importantly, they are nonimmunogenic and do not produce allogeneic immune reactions because they have potent immunosuppressive properties (23). Their easy availability and lack of alloimmunogenicity make them a suitable allogeneic cell source for tissue engineering and regeneration of pulp (24, 25). It is feasible that donor DPSCs could be transplanted to human leukocyte antigen-mismatched recipient patients for regenerative endodontics.

A thorough understanding of the molecular and cellular mechanisms by which DPSCs suppress allogeneic immunity is essential to support their use in allografts and optimize conditions of transplantation. Murine DPSCs have been shown to suppress the activation of allogeneic T lymphocytes by inducing apoptosis via the Fas/Fas ligand

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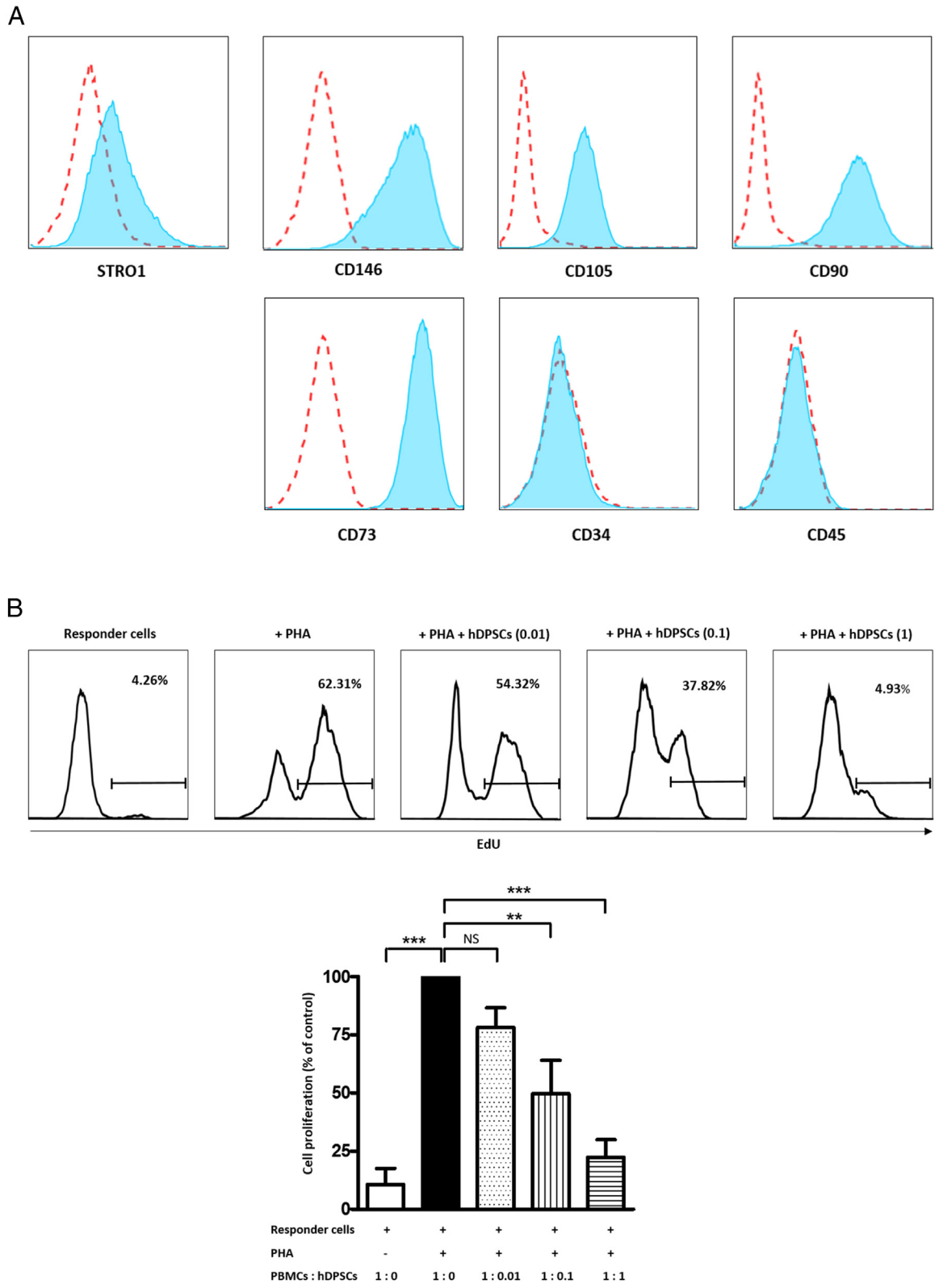

Figure 1. Human dental pulp stem cells (hDPSCs) inhibit allogeneic peripheral blood mononuclear cell (PBMC) proliferation. (*A*) hDPSCs were stained with antibodies against STRO-1, CD146, CD105, CD90, CD73, CD34, and CD45 and analyzed using flow cytometry. (*B*) PBMCs were incubated with 12.5 μg/mL phytohemagglutinin in the presence or absence of mitomycin C–treated hDPSCs at ratios of 0.01:1, 0.1:1, and 1:1 hDPSCs to PBMCs for 5 days. (*C*) Responder PBMCs were incubated with mitomycin C–treated stimulator PBMCs in the presence or absence of mitomycin C–treated hDPSCs at ratios of 0.01:1, 0.1:1, and 1:1 hDPSC to PBMC for 7 days. (*D*) $CD8^+$ T lymphocytes were incubated with mitomycin C–treated stimulator PBMCs in the presence or absence of mitomycin C–treated hDPSCs at ratios of 0.01:1, 0.1:1, and 1:1 hDPSC to PBMC for 7 days. For the proliferation assay, cells that had incorporated EdU were counted by flow cytometry. Data are presented as the means ± standard deviations of 3 experiments performed in triplicate. *P < .05, **P < .01, ***P < .001, or not significant (NS). Similar results were obtained in 4 independent experiments.