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Immunological and developmental features of human umbilical cord-derived stem cells

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Immunological aspects of regeneration

Objectives

The use of stem cells is a promising approach for the treatment of degenerative diseases. Extraembryonal tissues, such as umbilical cord, are considered alternative sources of mesenchymal-like stem cells. However, these cells are not fully characterized yet, since large inconsistencies exist among reports concerning their isolation, marker expression, immunomodulatory properties and differentiation capacity. We aim to characterize human umbilical cord matrix-derived stem cells (UCMSCs), and assess their clinical value for neurodegenerative disorders like multiple sclerosis. We hypothesize that UCMSCs differ from classical bone marrow-derived MSCs (BMMSC), show more multipotent characteristics and have a therapeutic effect in experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis.

Materials & methods

UCMSCs were cultured using the explant technique and compared with BMMSCs for growth, morphology and MSC marker expression using phase-contrast microscopy, flow cytometry and immunocytochemistry. In addition, the transcripts of both cell types were compared using Affymetrix GeneChip[®] Human Gene 1.0 microarray chips. Differentially expressed gene sets were generated using R bioconductor, and pathway analysis was performed using DAVID and IPA software. Next, UCMSCs were cocultured with (anti-CD3 activated) peripheral blood mononuclear cells. Proliferation of CD4 and CD8 T cells was measured using CFSE dye dilution with flow cytometry. Cocultures of UCMSCs and monocyte-derived dendritic cells (DCs) were performed after CD14⁺ magnetic selection from PBMCs. Monocytes were differentiated into immature DCs using IL-4 and GM-CSF, and maturation was induced using LPS. monocyte-derived DC phenotype was assessed using flow cytometry. All UCMSC cocultures were performed in contact and transwell setup. Finally, UCMSCs were transplanted in EAE animals. Dark agouti rats were immunized with human recombinant MOG in CFA to induce chronic EAE. UCMSCs were transplanted intravenously, before the onset of symptoms, on day 7. Acute EAE was induced in Lewis rats using guineapig MBP in CFA. UCMSCs were transplanted intravenously at day 10 postinduction. Clinical score was measured daily based on paralysis symptoms during the disease course.

Results

UCMSCs resemble classical MSCs and show a multipotent mesenchymal phenotype. However, microarray analysis demonstrates a distinct transcription profile of UCMSCs compared with BMMSCs. UCMSCs are able to suppress proliferation of activated T cells, and prevent differentiation and maturation of monocyte-derived DCs, both in transwell and contact cocultures, suggesting involvement of soluble mediator(s). The suppressive phenotype is further enhanced after stimulation with proinflammatory cytokines (e.g., IFN- γ), which results in an increased expression of anti-inflammatory molecules, such as IDO-1, HLA-G and PD-L1. Finally, transplantation studies in chronic EAE indicate that UCMSCs delay EAE onset and lower the clinical score at the beginning of the disease course. Transplantation in acute EAE did not alter the clinical course, but markedly reduced lymph node cell proliferation after restimulation with MOG.

Conclusion

Our data indicate that UCMSCs differ from BMMSCs, are able to interact with the immune system and alter immune cell function. In addition UCMSCs have a clinical effect when transplanted into EAE rats. Overall, this developmental and preclinical characterization is a first step in further evaluating UCMSCs potential for multiple sclerosis therapy.