

Mesenchymal stem cell therapy for autoimmune diseases: future Perspectives

Abstract

Mesenchymal Stem Cells (MSC) transplanted into a recipient organism for therapeutic purposes exert their action not only by cell-to-cell contact, but also by secreting soluble factors. Since biological issues and regulatory constraints hamper the use of MSC for clinical purposes, novel approaches should be attempted. In the last years, the feasibility of using MSC-derived micro vesicles as potential mediators carrying tolerogenic molecules has been tested in pre-clinical models of autoimmune diseases.

Keywords: mesenchymal stem cells, exosome, microvesicles, autoimmunity, cell therapy

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Introduction

Mesenchymal Stem Cells, functionally defined as multipotent cells of mesenchymal origin that can be found in disparate tissues and can differentiate into osteoblasts, adipocytes, and chondroblasts under appropriate culture conditions,^{1,2} exert their regenerative and immunosuppressant activity through cell contact and secretion of soluble factors.^{3,4} The repertoire of transmembrane and soluble protein produced by a cell and secreted into the extracellular matrix constitutes the secretome; among the components of the secretome, extracellular vesicles (EVs) should be considered. Extracellular vesicles are defined as spherical membrane-enclosed bodies secreted by cells, consisting of subpopulations characterized by specific size and cellular biogenesis: exosomes (50–150 nm) originating from multivesicular bodies; micro vesicles (150–1,000 nm) originating from the plasma membrane; and apoptotic bodies (>1 μm) originating from the plasma membrane of dying cells.⁵ Exosomes (40–130 nm), constitutively secreted by all cell types, come from endolysosomal pathway, released by exocytosis of multivesicular bodies; their markers are tetraspanins (CD63, CD9, CD81), Alix, TSG101, Hsp60, Hsp70, Hsp90; they contain miRNA and mRNA; lipids (cholesterol, ceramide, sphingomyelin, cytokines receptors, MHC molecules. Microvesicles (100–1000 nm) come from the cell surface, being outward budding of plasma membrane after cell stimulation or a stress such as apoptosis or hypoxia, identified by the expression of integrins, selectins, metalloproteinases, phosphatidyl-serine, and carry mRNA, non-coding RNAs, membrane receptors, cytokines. Apoptotic bodies (50–5000 nm) come from the cell surface, released from cellular blebs during late stage of apoptosis, marked by the presence of phosphatidyl-serine, containing nuclear fractions, cell organelles, DNA, rRNA, mRNA.^{6,7} For their carrier function, EVs contribute to the pathogenesis of autoimmunity or, on the other hand, might be used to control the unregulated activation of the Immune System during autoimmunity. As therapeutic tools, EVs act as the cells they come from; pivotal studies showed MSC-derived EVs that reduce T lymphocyte proliferation, increase the secretion of Interleukin-10 and Tumor Growth Factor (TGF)-β1, promote the generation of CD4+CD25+Foxp3+ regulatory T cells, express Galectin-1, programmed death-ligand 1 and membrane-bound TGF-β1, key factors involved in immunological tolerance.^{8–10} Based on these results, clinical trials using EVs as therapeutic tools for autoimmune diseases have started (www.ClinicalTrials.gov).

The advantage of using EVs as therapeutic tools stands on the ground that issues related with the biology of cells (i.e. autologous vs. allogeneic) and regulatory issues (i.e. *ex-vivo* expansion and storage) might be overcome. The safety of this procedure, however, is still to be assessed. In fact, there is the possibility that some potentially immunogenic proteins, such as Major Histocompatibility Complex molecules or tissue factors, could also be transferred via EVs that might induce allo-immune responses, anti-donor immune responses, or have detrimental procoagulant activity.¹¹

Conclusion

The clinical application of MSC-derived EVs is still at the beginning, but the procedure appears promising. Further studies are needed to assess the mechanism of action, the efficacy, and safety of the procedure.

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Conflict of interest

The author declares there is no conflict of interest.

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