MSC extracellular vesicles induce TGF-beta receptor type II clustering in myofibroblasts as a part of anti-fibrotic action

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Differentiation of fibroblasts to myofibroblasts is a central event in pro-fibrotic action of TGF-beta. Previously we showed that extracellular vesicles (EV) secreted by multipotent mesenchymal stromal cells (MSCs) abrogated this TGF-beta effect. Observed anti-fibrotic action of MSCs-derived EVs was mediated by the transfer of specific microRNAs, which caused down-regulation of genes associated with myofibroblast phenotype. We hypothesized that MSC-derived EVs could also directly affect TGF-beta signaling pathway in myofibroblasts.

We tested this using in vitro model of TGF-beta-induced differentiation of human fibroblasts into myofibroblasts. Cells were treated by EVs isolated from the conditioned medium of human MSCs (ASC52telo, ATCC) for 1, 24 or 96 hours. The expression and spatial distribution of TGF-beta signaling pathway components were analyzed by ICC, Western blot and RT-PCR.

TGF-beta caused the increased exposure of TGF-beta receptor type II (TGFbRII) to the cell surface. Unexpectedly, MSC-derived EVs did not suppress this, but rather slightly increased the expression of TGFbRII in myofibroblasts. MSC-derived EVs caused the preservation of the TGF-beta induced intracellular distribution of TGFbRII. Furthermore, MSC-derived EVs led to the formation of large receptor clusters in few days. This was not accompanied by the activation of SMAD 2/3 phosphorylation.

These data suggests that EVs could directly transfer additional copies of TGFbRII, which form large non-signaling clusters, therefore sequestering functional TGF-beta receptors on myofibroblasts and preventing the activation of SMAD 2/3 dependent pro-fibrotic TGF-beta signaling in myofibroblasts.

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