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Differential effects of mesenchymal stem/stromal cells and of their secreted extracellular vesicles in a murine model of inflammatory bowel disease

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We compared the effects of mesenchymal stem cells (MSC) and of mesenchymal stem cells-extracellular vesicles (MSC-EV) intraperitoneal (i.p.) administration in a dextran sulfate sodium (DSS) colitis model. We analyzed changes in body wt, disease activity index (DAI), colon length and histomorphometric analysis of the whole colon. MSC administration was associated with clinical and histological worsening with respect to controls. However, mice treated MSC-EVs showed clinical improvement (body wt and DAI), even if no significant difference was found in histological/morphometric score with respect to controls. Cytokine expression in colon mucosa showed reduced TNF-alpha and increased IL-10 in mice treated with MSC-EVs. In a second test, since Annexin 5 (An5), a molecule with tolerogenic properties can bind to the surface of EVs, we reasoned that this molecule could affect the immune regulatory properties of MSC-EVs. We then tested the effects of both naive and An5-bound MSC-EVs by local administration (enema). MSC-EVs administered by enema had no effect on clinical and histological parameters. In contrast, An5-MSC-EVs dramatically improved both clinical and morphometric-histological scores. Free (unbound) An5 administration had inconsistent effects. In conclusion, MSCs worsened DSS-induced colitis, confirming that these cells can behave as pro-inflammatory agents depending on the environment. In contrast, MSC-EVs showed a partially beneficial effect, suggesting a more predictable behavior and a safer therapeutic profile with respect to their cells of origin. An5 binding enhanced the anti-inflammatory activity of MSC-EVs administered by enema. A dissimilar pattern of cytokine expression was observed following treatment with MSC-EVs or An5-MSC-EVs, suggesting that An5 binding affects the mechanisms of action of MSC-EVs.

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