



Original Article

# Cell Therapy With Mesenchymal Stem Cells Induces an Innate Immune Memory Response That Attenuates Experimental Colitis in the Long Term

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## Abstract

**Background and Aims:** Mesenchymal stem cells [MSCs] are used in preclinical and clinical studies for treatment of immune-mediated disorders, thanks to their immunomodulatory properties. Cell therapy with MSCs induces multiple effects in the immune system which ultimately lead to increase in the number of immune cells with regulatory phenotype. In this study, we investigated whether the beneficial effects of MSC therapy are maintained in the long term in a clinically relevant mouse model of colitis.

**Methods:** A single dose of adipose-derived MSCs [aMSCs] was infused into dextran sulphate sodium [DSS]-induced colitic mice during the induction phase of the disease. Following a latency period of 12 weeks, mice were re-challenged with a second 7-day cycle of DSS.

**Results:** DSS-induced colitic mice treated with aMSCs showed significant reduction in their colitic disease activity index during the second DSS challenge when compared with non-aMSC treated DSS-induced colitic mice. Strikingly, the long-term protection induced by aMSC therapy was also observed in Rag-1<sup>-/-</sup> mice where no adaptive immune memory cell responses take place. Increased percentages of Ly6G<sup>+</sup>CD11b<sup>+</sup> myeloid cells were observed 12 weeks after the first inflammatory challenge in the peritoneal cavity, spleen, and bone marrow of DSS-induced colitic mice that were infused with aMSCs. Interestingly, upon re-challenge with DSS, these animals showed a concomitant increase in the regulatory/inflammatory macrophage ratio in the colon lamina propria.

**Conclusions:** Our findings demonstrate for the first time that MSC therapy can imprint an innate immune memory-like response in mice which confers sustained protection against acute inflammation in the long term.

**Key Words:** Inflammatory bowel disease; stem cell therapy; sustain protection