Marrow Stromal Cells (MSCs) Potently Inhibit the Primary Induction of T-Helper 17 (Th17) Cells Through Cell-Cell Contact

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Introduction: MSCs are immunosuppressive with the potential to treat autoimmune/inflammatory disease and to promote tissue repair. Pro-inflammatory Th17 cells are pathogenic in some inflammatory diseases. In this study the interactions between mouse MSCs and CD4+ T-cells undergoing primary Th17 induction in vitro were examined.

Materials and Methods: Th17 induction was performed with anti-CD3 and autologous APCs in the presence of IL-6, TGFβ1, anti-IFNγ and anti-IL-4. Analyses included ELISA, surface/intracellular flow cytometry, cell division analysis by CFSE dilution and RT-PCR. MSC effects on flow-sorted naïve (CD4+/CD62Lhi/CD25-) and memory (CD4+/CD62Llo/CD25-) T-cells were separately examined in some experiments.

Results: MSCs potently inhibited primary Th17 induction in co-culture at T-cell:MSC ratio as low as 400:1 ratio (Figure 1). This effect was characterised by preserved T-cell viability, reduced proliferation, suppression of CD25 up-regulation and decreased production of IL-17 upon re-stimulation in the absence of MSCs. Th17 inhibition occurred when either naïve or memory T-cells were induced in the presence of MSCs (Figure 2). Skewing to other T-helper phenotypes was not observed although an IFNγ-secreting component was preserved among memory T-cells. Th17 suppression was not mediated by fibroblasts. The effect was maintained when APCs were replaced by antiCD3/CD28-coated beads. Transwell experiments and conditioned MSC medium failed to suppress primary Th17 induction however conditioned medium from MSC/Th17 co-cultures partially transferred the inhibitory effect.

Discussion and Conclusions: In the mouse, the capacity of MSCs to modulate T-cell activation extends to primary Th17 induction through a contact- or proximity-dependent mechanism. Of interest, the effect is quite potent in vitro and applies to both naïve and memory-phenotype responders. MSC ability to suppress Th17 cell induction may be of therapeutic benefit in autoimmune and autoinflammatory diseases as well as in reducing tissue responses to autologous or allogeneic cellular transplants.

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