

## OPPOSING EFFECT OF MESENCHYMAL STEM CELLS ON TH1 AND TH17 CELL POLARIZATION ACCORDING TO THE STATE OF CD4+ T CELL ACTIVATION.

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Mesenchymal stem cells (MSCs) are multipotent progenitors with broad immunosuppressive properties. However, their therapeutic use in autoimmune disease models has shown dissimilar effects when applied at different stages of disease. We therefore investigated the effect of the addition of MSCs on the differentiation of Th1, Treg and Th17 cells in-vitro, at different states of CD4+ T cell activation.

Methods: CD4+ T lymphocytes purified by negative selection from mouse C57BL/6 splenocytes were cultured under Th1, Th17 and Treg inducing conditions with IL-12, TGF- $\beta$  + IL-6 or TGF- $\beta$  respectively. C57BL/6 bone marrow derived MSCs were added to CD4+ T cell cultures at day 0 or after 3 days of T cell polarizing activation. Intracellular cytokines for Th1, Th17 and Treg T cells were quantitated at day 6 by flow cytometry.

Results: Although baseline (day 0) addition of MSCs suppressed all CD4+ T cell lineages, addition at day 3 solely decreased Th1 cells (64%) ( $p < 0.05$ ) while markedly increasing (50%) Th17 cells ( $p < 0.05$ ) leaving Treg cells unchanged (Figure 1)

Conclusions: MSCs exhibit their typical suppressive phenotype when added early to cell cultures in the presence of Th CD4+ polarizing stimuli. However, once T cell activation has occurred, MSC's show an opposite stimulating effect on Th17 cells while leaving Treg IL-10 producing cells unchanged. These results suggest that the therapeutic use of MSCs in-vivo might exert opposing effects on disease activity, according to the time of therapeutic application and the level of effector T cell activation.

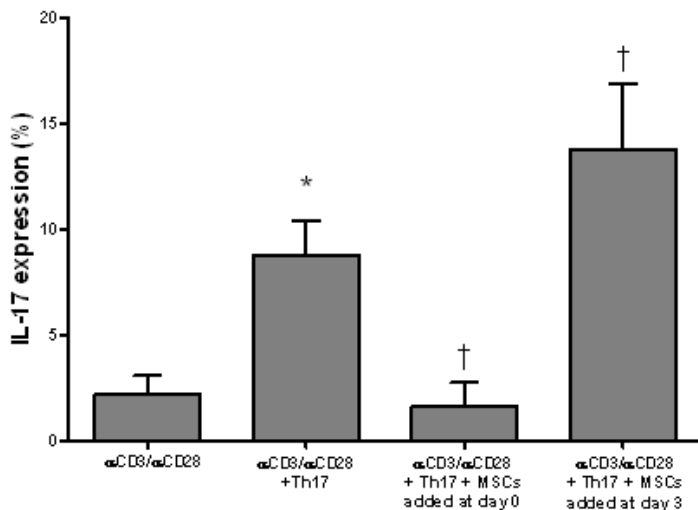


Figure 1: Differential effect of MSCs on IL-17 production by polarized Th17 CD4+ T cells