3. Stromal cells and fibrosis

A57 SKIN FIBROBLASTS ARE POTENT SUPPRESSORS OF INFLAMMATION IN EXPERIMENTAL ARTHRITIS

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Background and objectives Fibroblasts possess in vitro immunomodulatory properties that are similar to those of multipotent mesenchymal stromal cells (MSC) but their role has been poorly investigated in vivo. Here, we compared the effect of MSC or skin fibroblast injection on the host immune response in the collagen-induced arthritis model.

Materials and methods Fibroblasts were isolated from the skin of DBA1 mice and immunophenotyped by flow cytometry. Their capacity to differentiate into chondrocytes, adipocytes and osteoblasts was evaluated after culture in specific inducing conditions. Immunosuppression was evaluated in concanavalin A-induced proliferative assay. In the CIA model, 10⁶ fibroblasts were intravenously injected at day 18 and 24 after collagen II immunisation. Arthritis was evaluated by the measure of clinical signs (paw swelling and inflammation) and immunological parameters (dosage of collagen II-specific immunoglobulins, inflammatory cytokines and proliferation of T lymphocytes).

Results We first confirm that skin fibroblasts isolated from DBA1 mice lack the capacity to differentiate into osteoblasts or chondrocytes but possess the capacity to differentiate into adipocytes. We also report that fibroblasts inhibit the proliferation of T lymphocytes in a concanavalin A-induced proliferative assay and secrete modulatory molecules, in particular PGE2 and NO. To assess their role in vivo, 10⁶ fibroblasts were intravenously injected at day 18 and 24 after collagen II immunisation of DBA1 mice. We show that similar to MSCs, the intravenous injection of fibroblasts efficiently suppress the clinical signs of arthritis and delay the disease onset. This effect is associated with a reduced inflammation and notably, increased levels of interleukin (IL) -5, IL-10 and IL-13 in the spleens of treated mice. To further characterise the mechanism of immunosuppression, we performed phenotypic analyses and could not detect any induction of CD4⁺CD25⁺Foxp3⁺ Treg cells whereas a population of CD4⁺IL-10⁺ T cells is slightly increased after fibroblast injection and significantly upregulated after MSC administration.

Conclusion Our study shows the therapeutic efficacy of systemic injection of syngeneic fibroblasts to reduce the clinical signs of arthritis and strongly suggests that fibroblasts induce

a Th2 immune profile although we cannot exclude that IL-10 secreting Treg cells may be generated.