8 FIBROBLASTS AS NEGATIVE REGULATORS OF INFLAMMATION: IMPLICATIONS FOR THE PATHOGENESIS OF RHEUMATOID ARTHRITIS?

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Background and objectives Fibroblasts possess immune regulatory capacities. They are able to suppress the proliferation of T lymphocytes and to modulate the differentiation of dendritic cells (DC). Being ubiquitously present at the sites of lymphocyte priming and restimulation, fibroblasts may have a fundamental role in preventing inappropriate T cell responses or in the termination of immune reactions. A malfunction of fibroblasts could result in an imbalance between immune responses and self tolerance. Such a dysregulation can be observed in rheumatoid arthritis (RA) where pathogenic alterations in the function of synovial fibroblasts result in chronic inflammation and joint destruction. In this study, the authors directly compared the influence of normal dermal and synovial fibroblasts to that of RA synovial fibroblasts (RASf) on T lymphocyte activation and proliferation and on the differentiation, maturation and T cell stimulatory capacity of dendritic cells (DC) in vitro.

Materials and methods Dermal fibroblasts were isolated from the skin of healthy donors, synovial fibroblasts from synovectomy tissue of patients with osteoarthritis (OA) or RA. CD4+T cells were stimulated in the presence or absence of fibroblasts, their proliferation was measured by ³H-Thymidine incorporation and the cytokine secretion was quantified by ELISA. Differentiation of monocytes into DCs was induced in presence or absence of fibroblasts, their phenotype was analysed cytometrically. The T cell stimulatory capacity of DCs was determined in mixed lymphocyte reactions.

Results All fibroblasts prevented the differentiation of monocytes into classical DCs, moreover fibroblast-modulated DCs showed a lower T cell stimulatory capacity. In addition, normal fibroblasts were highly effective in suppressing the proliferation of activated T lymphocytes and in reducing the secretion of T cell effector cytokines such as interferon (IFN)- γ or tumour necrosis factor (TNF)- α . Interestingly, RASf seem to have lost the capability to inhibit the proliferation and cytokine production of activated T cells. Remarkably, in contrast to control fibroblasts, RASf from some patients even stimulated T cells to secrete pro-inflammatory cytokines like IFN γ and Interleukin-17A. The reason and molecular background of this specific phenomenon is currently under investigation.

Conclusions Fibroblasts negatively regulate T cell responses, but these tolerogenic properties are partially lost in RASf. This defect may play a central role in the pathogenesis of RA. So far, treatments with biologics, including anti-TNF α , are often unable to achieve permanent remission. In the future, a reestablishment of the immunosuppressive properties of fibroblasts might enrich the therapeutic armamentarium in the treatment of RA.