

Summary

The pathogenesis of two important inflammatory rheumatic diseases, RA and AS, is not clear. In both diseases an immune response against an unknown putative antigen could play a crucial role. T cell responses to antigens derived from bacteria such as klebsiella or to autoantigens derived from the cartilage such as proteoglycan have been tested, but no convincing evidence for their involvement in the pathogenesis has been obtained so far.

In this study, I applied the more sensitive and more specific technique of antigen-specific cytometry to investigate the T cell response to h-hsp60 and y-19kd as well as various cartilage-derived autoantigens. Taking IFN γ -secretion of CD4+ T cell as primary outcome parameter, I set out to quantify the antigen specific T cell response in peripheral blood and synovial fluid of patients with AS or RA, and controls to answer the questions which antigen-specific T cells are detectable in AS patients and compare this to RA patients and controls.

The results indicate that a similar T cell response to h-hsp60 and y-19kd is present in patients with AS and RA compared to healthy controls, which suggests that these two antigens are not primarily involved in the pathogenesis of AS and RA. For cartilage-derived autoantigens, on the basis of the relative frequency of IFN γ ⁺ cells among CD4+ T cells, the results showed that the G1 domain of the proteoglycan aggrecan is recognized by almost two thirds of patients with AS (61.7%) and half of the investigated patients with RA (54.5%). In contrast, normal healthy individuals showed a reactivity only in a few cases (10%). No T cell responses to HC gp39 and collagen II was observed in AS-patients in the present study. Importantly, the response of synovial fluid CD4+ T cells to the G1-domain was shown to be significantly higher compared to PB. Further analysis indicated that two T cell epitopes of G1 domain were identified to be immunodominant in AS: AA residues 292 to 309 and 252 to 269. These data suggest that the G1 domain of aggrecan could be a target of the immune response in AS.

A further aim of this study was to assess the possible effect of anti-TNF α treatment on the capacity of T cells and macrophages to produce cytokines. Treatment of active ankylosing spondylitis with the monoclonal anti-TNF α antibody infliximab is clinically highly effective. The precise mechanism of action, however, is not known. I investigated the cytokine response in 20 active AS patients during

infliximab therapy. The results indicated that infliximab could downregulate the T cell (but not macrophage) production of the proinflammatory cytokines $IFN\gamma$ and $TNF\alpha$ at week 6 and 12, but no effect on IL4- and IL10-production was seen. This downregulation of the proinflammatory cytokines is probably a relevant mechanism for the clinical efficacy.