11 Summary

Interferon gamma (IFN$_{\gamma}$) produced by T-helper (Th) cells is key to the defense against intracellular pathogens. Circumstantial evidence, however, suggests that IFN$_{\gamma}$ secreting Th1 cells are also driving autoimmune inflammation such as in Rheumatoid Arthritis (RA). Still, identification of the corresponding IFN$_{\gamma}$-inducing stimuli in the joints of RA patients was not successful so far.

In this study, a T-cell receptor (TCR) independent pathway for induction of IFN$_{\gamma}$ synthesis in human Th cells was identified; IFN$_{\gamma}$ production was induced by proinflammatory cytokines known to be overexpressed in arthritic joints. Interleukin-2 (IL-2) receptor gamma chain ($\gamma_c$) signalling cytokines (IL-2, IL-7 or IL-15) in combination with IL-12 and IL-18 were identified as essential factors promoting IFN$_{\gamma}$ secretion in a peripheral blood derived Th cell subpopulation characterised by IL-18 receptor $\alpha$ chain expression and equipped with functional IL-12 receptors. Analysis of the signalling components involved identified p38 MAPKinase, JanusKinase (JAK) 3 and STAT4 as key molecules mediating cytokine-dependent IFN$_{\gamma}$-production. Besides pharmacological inhibition by p38 or JAK3 blockade, cytokine-driven IFN$_{\gamma}$-synthesis could be efficiently suppressed by CD25$^+$ regulatory T-cells. Differential expression of 4-1BB (CD137), a member of the Tumor Necrosis Factor Receptor superfamily, allowed discrimination of cytokine- from TCR-induced IFN$_{\gamma}$ producers, being only detectable after TCR ligation.

4-1BB expression was then analysed on live IFN$_{\gamma}$-secreting Th cells isolated directly ex vivo from synovial infiltrates of active RA patients. As spontaneous IFN$_{\gamma}$ production was not associated with 4-1BB expression, secretion of the Th1 cytokine must have been induced by the proinflammatory environment rather that by joint-derived (auto-) antigens.

This study allows deduction of new therapeutic options for controlling inflammation in RA: Pharmacological inhibition of p38 MAPKinase could efficiently block cytokine-induced IFN$_{\gamma}$ synthesis in synovial Th cells, thereby eliminating a central mediator within an inflammatory cytokine network in the joint. As IFN$_{\gamma}$-responses after TCR-
ligation are not dependent on p38 signalling, blockade is not expected to result in general immune suppression, as is the case in patients receiving e.g. anti-TNFα therapy. p38 blockade in rodent arthritis models resulted in significant reduction of joint destruction, arguing in favour of future applications in man.