A108 CD4⁺CD28^{NULL} T CELLS IN RA SHOW DISTINCTIVE PROINFLAMMATORY FEATURES AND IFN- γ PROMOTER DEMETHYLATION

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Background and objectives Approximately one third of rheumatoid arthritis (RA) patients display an expanded T cell subset that lacks the co-stimulatory molecule CD28, often referred to as CD4⁺CD28^{null} T cells. Despite the lack of CD28 expression these cells are not anergic, but oligoclonally expanded, and terminally differentiated with proinflammatory features, for example, rapid secretion of IFN- γ and tumour necrosis factor (TNF). Interestingly, RA patients having an expanded CD28^{null} population are more likely to suffer from extra-articular manifestations and cardiovascular disease. Still, even when CD4⁺CD28^{null} T cells are significantly increased in the circulation, they are usually infrequent in synovial fluid. Here the authors wished to compare the inflammatory capacity of CD28^{null} cells in blood and synovial fluid by studying their cytokine secreting capacity and the postgenomic regulation of the IFN- γ locus.

Materials and methods Mononuclear cells from peripheral blood and synovial fluid were isolated from RA patients. Intracellular cytokine production of cells was investigated by multiparameter flow cytometry following polyclonal and antigen-specific stimulation. In addition, the IFN- γ producing capacity was further studied by epigenetic analysis of the IFN- γ promoter on pure conventional CD4⁺CD28⁺ or CD4⁺CD28^{null} T cells from both blood and synovial fluid. Furthermore, the extended cytokine environment was studied in cell culture supernatants following polyclonal activation.

Results Conventional T cells obtained from both blood and synovial fluid showed a robust production of IFN- γ , TNF and interleukin-17 following polyclonal stimulation. In contrast, the CD4⁺CD28^{null} T cells consistently failed to make interleukin-17, while producing large amounts of IFN- γ . In agreement with the biased cytokine secretion, the IFN- γ promoter of this T cell subset was highly demethylated in blood (n=3), but the authors' preliminary data indicate that this was less pronounced in synovial fluid (n=3).

Conclusions The CD4⁺CD28^{null} T cells commonly found in the circulation of RA patients are devoted Th1 proinflammatory T cells with high capacity of IFN- γ and TNF secretion. However, these cells are not as common in the affected joints, and may have different effector functions at the site of inflammation. Further studies are needed to reveal whether this is due to a conversion in the local inflammatory milieu or whether joint-homing CD28^{null} T cells represent a less differentiated cell subset.